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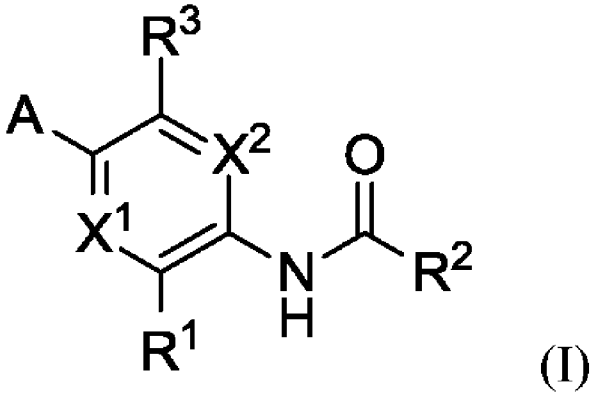
(54) Title: INHIBITORS OF WDR5 PROTEIN-PROTEIN BINDING



(I)

(57) Abstract: The present application is directed to compounds of Formula I: compounds comprising these compounds and their uses, for example as medicaments for the treatment of diseases, disorders or conditions mediated or treatable by inhibition of binding between WDR5 protein and its binding partners.

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TITLE: INHIBITORS OF WDR5 PROTEIN-PROTEIN BINDING

CROSS-REFERENCE TO RELATED APPLICTIONS

[0001] The present application claims the benefit of priority from United States provisional patent application no. 62/301,673 filed on March 1, 2016, the contents of which are incorporated herein by reference in their entirety.

FIELD

[0002] The present application relates to compounds, processes for their preparation, compositions comprising them and their use for the treatment of diseases, disorders and conditions mediated by binding between WDR5 and its binding partners including, but not limited to, MLLl.

BACKGROUND

[0003] Histones, the most basic units for packing DNA into nucleosomes and covalent modifications of histones, such as methylation, acetylation and phosphorylation, play a central role for regulation of gene transcription *[Nat. Rev. Mol. Cell Biol.* **2001,** 2: 422-432; *Cell* **2007,** 128: 693-705]. Epigenetics refers to the heritable changes that control how the genome is accessed in different cell types during embryonic development and cellular differentiation *[Genes. Dev.* **2009;** 23: 781-3]. This capability permits specialization of function between cells without altering the DNA sequence.

[0004] It is now well recognized that misregulation of histone modifications plays a key role in a wide range of human diseases, including but not limited to cancer *[Cell,* **2007,** 10: 693-705; *Nat. Rev. Cancer.,* **2010,** 10:457-469]. Mixed Lineage Leukemia 1 (MLLl) protein is a Histone H3 Lysine 4 (H3K4) methyltransf erase and is frequently misregulated in a subset of acute leukemias *[Trends Mol. Med.,* **2004,** 10: 500-507, *Cell. Stem. Cell,* **2007,** 1:324-337]. MLLl itself has a weak H3K4 methyltransferase activity but its enzymatic activity is dramatically enhanced when MLLl is present in a core complex made up of MLLl, WD repeat domain 5 protein (WDR5), Absent, Small, or Homeotic-2-Like (ASH2L) and Retinoblastoma Binding Protein 5 (RbBP5). Recent studies have clearly shown that the binding between MLLl and WDR5 proteins is optimal for the activity of MLLl but dispensable for the activity of other MLL family members, including MLL2, MLL3 and MLL4 *[Mol.*

Cell, **2014,** 53:247-261]. Hence, blocking the protein-protein binding of MLLl with WDR5 can specifically inhibit the activity of MLLl H3K4 methyltransferase activity, and such inhibition has potential for the treatment of human diseases such as a subset of acute leukemias whose development and progression depend upon MLLl activity.

[0005] WDR5 is a common subunit of all six mammalian histone H3K4 methyltransferases *[Dev. Biol,* **2010**,**339** (2):240-249]. WDR5 has334 amino acids and contains seven typical WD40 repeat domains, each approximately 40 amino acids in length *[Nat. Struct. Mol. Biol,* **2009,** 16 (7):678-680]. Structural studies suggest that the WD40 repeats form a seven-bladed propeller fold, with each blade made up of a four-stranded antiparallel sheet. This structural property suggests that WDR5 has many exposed surfaces making it a useful adaptor to interact with other proteins. Further, pulldown assays indicate that WDR5 prefers to bind dimethylated histone H3K4 peptides *[Nat. Struct. Mol. Biol,* **2009,** 16 (7):678-680].

[0006] Two recent studies suggested an important role of WDR5 in the MLLl complex. The WDR5 interacting (WIN) motif, made up of amino acid residues 3762-3773 next to the SET domain in MLLl protein, was independently discovered to mediate the binding of MLLl with WDR5 *[J. Biol. Chem.,* **2008,** 283(47):32158-32161; *J. Biol. Chem.,* **2008**,283(50):35258-35264] . The crystal structure of the WIN motif peptide with WDR5 shows that the WIN motif, which is the analogue of H3 N-terminal peptide, binds with WDR5 in the central depression of the β-propeller by adopting a 310-helical structure and inserting Arg3765 into the central channel. Hence, the binding between MLLl and WDR5 is mediated by a well-defined pocket in WDR5 and WIN motif (residues 3762-3773) in MLLl. Previous studies have demonstrated that a 3-residue peptide, i.e. Ac-A-R-A-NH_2 (K_i = 0.12 mmol/L) has the same binding affinity as the 12-residue WIN peptide (IQ = 0.16 mmol/L) to WDR5 *[J. Med. Chem.,* **2010,** 53: 5179-5185; *J. Am. Chem. Soc,* **2013,** 135: 669-682].

[0007] Because WDR5 is an essential component of the histone methylation, acetylation, and chromatin remodeling complexes, while not wishing to be limited by theory, WDR5 is believed to serve as an adaptor protein for complex assembly. However, it may also contribute to other physiological phenomena. WDR5 is an important component for assembly or stability of the virus-induced signaling adapter

(VISA) associated complex, which plays a key role in virus-triggered induction of type I interferons (IFNs) and antiviral innate immune response *[Proc. Natl. Acad. Sci. U S A.,* **2010,** 107(2): 815-820]. Previous studies have demonstrated that VISA is located at the outer membrane of mitochondria. Interestingly, this study revealed that WDR5 was not only localized in the nucleus as believed before, but also abundantly localized in the cytoplasm. Viral infection caused translocation of WDR5 from the nucleus to the mitochondria located VISA complex, where it played a role in the assembly and stability of the VISA complex. These studies demonstrate for the first time a cytoplasmic function for WDR5, specifically in virus-triggered signaling resulting in induction of type I IFNs *[Proc. Natl. Acad. Sci. USA.,* **2010,** 107(2): 815-820].

MLL1-WDR5 complex in Leukemogenesis

[0008] Leukemia is characterized by an abnormal increase of white blood cells in the blood or bone marrow. Among all types of cancers, the morbidity of leukemia is the highest for patients below 35 years old. Over 70% of infant leukemia patients bear a translocation involving chromosome 11, resulting in the fusion of the MLL1 gene with other genes *[Nat. Rev. Cancer.,* **2007,** 7(ll):823-833]. MLL1 translocations are also found in approximately 10% of adult acute myeloid leukemia (AML) patients who were previously treated with topoisomerase II inhibitors for other types of cancers *[Nat. Rev. Cancer.,* **2007**,7(1 1):823-833]

[0009] MLL1 is the human homologue of *Saccharomyces cerevisiae* gene *Setl* and the Drosophila gene *Trx.* The genes encode an enzyme to catalyze the methylation of H3K4 *[Nat. Rev. Cancer.,* **2007,** 7(ll):823-833]. Trimethylation of histone 3 at lysine 4 (H3K4) is a hallmark of active gene transcription, and alteration of this process often causes changes in gene expression partem. MLL1 translocation is also linked to altered transcription of important genes involved in stem cell maintenance and development and, thus, leads to leukemogenesis. The MLL1 gene was first discovered in leukemia patients in 1991 *[Nat. Rev. Cancer.,* **2007,** 7(11):823-833]. cDNA of the MLL1 gene contains -12 kb nucleotides and encodes a peptide over 4000 amino acids in length. In the cell, the premature MLL1 protein is digested by taspase, which results in two peptides: a 300 kDa N-terminal fragment and a 170 kDa C-terminal fragment. The two cleaved peptides form a heterodimer, which is

complexed with other components, including WDR5, RBBP5, ASH2L and DPY30. In some leukemia patients, chromosomal translocation results in fusion of -4.2 kb DNA of the MLL1 N-terminal coding region with some other genes *[Cancer. Cell.,* **2003,** 4(3): 197-207].

[0010] The generation of MLL1 fusion protein is sufficient to induce leukemia, which has been demonstrated in animal models *[Nat. Rev. Cancer.,* **2007,** 7(ll):823-833]. The mechanisms of MLL1 fusion-mediated leukemia have been studied extensively in the past twenty years. The MLL/SET1 family members are most enzymatically active when part of the "core complex" (WRAD2), comprising the catalytic SET-domain-containing subunits bound to a sub-complex made up of the proteins WDR5, RbBP5, Ash2L and a homodimer of DPY-30. The necessity of MLL/SET1 members to bind WRAD2 for full activity is the basis of a particular drug development strategy, which seeks to disrupt the binding between the MLL/SET1 subunits and WDR5. Recent efforts to pharmacologically target the MLL1 catalytic activity has centered on attempts to disrupt the MLL1-WDR5 binding by means of Win-motif mimicking peptides and small-molecule peptidomimetics *[J. Med. Chem.,* **2010,** 53: 5179-5185; *J. Am. Chem. Soc,* **2013,** 135: 669-682; *Mol Cell,* **2014;** 53:247-261]. However, as with most peptide based inhibitors, MLL1-WDR5 peptidic inhibitors exhibit poor cell-based activity and lack oral bioavailability due to poor cell-permeability and peptide chemical liability (e.g. susceptibility to peptidases).

Role of WDR5 in other cancers

Bladder Cancer

[0011] WDR5 also plays a critical role in embryonic stem cell self-renewal *[Cell.* **2011;** 145 (2): 183-97] and epithelial-mesenchymal transition *[Mol. Cell,* **2011;** 43(5):811-22]. A recent study found that the protein H2A.Z is overexpressed in bladder cancer and activates oncogenic transcription by recruiting WDR5 and Bromodomain PHD Finger Transcription Factor (BPTF) to its target genes *[Epigenetics. Chromatin.,* **2013;** 6 (1):34], suggesting that WDR5 may play a role in bladder cancer, though its expression pattern, role and mechanism in bladder cancer remained unclear. WDR5 is upregulated in bladder cancer tissues compared with normal tissues as determined by immunohistochemistry (IHC), and is correlated with

advanced tumor stage and overall survival of bladder cancer patients. A recent study found that WDR5 is overexpressed in prostate cancer tissue compared with normal tissues *[Mol. Cell.,* **2014** May 22; 54 (4): 613-25]. Taken together, high expression levels of WDR5 may serve as a novel molecular marker for bladder cancer.

[0012] WDR5 silencing reduces cell growth in breast cancer and prostate cancer *[Mol. Cell.,* **2014,** 54 (4):613-25; *Cell Rep.,* **2013** 5 (2):302-13], but the detailed mechanism and role *in vivo* is still unknown. Through gain or loss of function, WDR5 was found to promote bladder cancer cell proliferation *in vitro* and tumor growth *in vivo,* and that silencing WDR5 mainly induces the G0/G1 phase cell cycle arrest. The cell cycle is regulated by cyclins and cyclin-dependent kinases. Cyclin E1 and Cyclin E2 regulate the G1 to S-phase transition, while Cyclin B1 regulates the G2 to M-phase transition. Moreover, Cyclin E is associated with high-grade, high-stage and invasive bladder cancer *[Cell. Cycle.,* **2012;** 11(7): 1468-76; *Am. J. Pathol,* **2000**;157(3):787-94]. UHMK1 (also named KIS) is overexpressed in leukemia and promotes the G1 to S-phase transition *[Leuk. Res.,* **2008;** 32 (9): 1358-65]. Mechanistically, WDR5 knockdown inhibited cyclin El, cyclin E2 and UHMK1 leading to G0/G1 phase cell cycle arrest, which might disturb the effect of cyclin B1 downregulation on G2 to M-phase transition. Additional studies showed that knockdown of MLL1, a core component of the MLL/SET1 complexes, suppressed HeLa cell proliferation by reducing the expression of cyclin B and inducing the G2/M phase cell cycle arrest *[Oncogene.* **2013**;32(28):3359-70]. These data suggest that WDR5 promotes bladder cancer cell proliferation *in vitro* and *in vivo* by regulating the cell cycle, but the role and mechanism are not the same as MLL1.

[0013] WDR5 is believed to play a role in cancer stem cells (CSCs). CSCs are a small subpopulation of cells in a tumor that can self-renew and differentiate into multiple lineages, and possess strong tumor-initiating capacity. CSCs have been widely identified in a number of malignancies, and the existence of CSCs in bladder cancer was found by Chan *et al [Proc. Natl. Acad. Sci. USA.,* **2009;** 106 (33): 14016-21]. Several studies have found that sphere culture is an effective way to enrich cancer stem cells *[Cell.* **2007**;131(6): 1109-23; *Urol Oncol.* **2012**;30(3):314-8]. It was observed that WDR5 and pluripotency transcription factors were upregulated in UM-UC-3 and T24 spheres. Through gain or loss of function, it was demonstrated that

WDR5 promoted UM-UC-3 and T24 cells self-renewal *in vitro* and upregulated the homeobox protein transcription factor Nanog. Emerging evidence shows that Nanog is overexpressed in poorly differentiated tumors and correlated with poor survival outcome of patients with various types of cancer, including bladder cancer *[Nat. Genet,* **2008;** 40(5):499-507; *Onco. Targets. Ther.,* **2013;** 6:1207-20]. Moreover, Nanog plays a role in CSCs self-renewal and targeting. Nanog has shown promising therapeutic potential in several types of cancer *[Cell Stem Cell.* **2011**;**9** (l):50-63; *Oncogene.* **2013**;32(37):4397-405]. WDR5 directly activates Nanog by mediating its promoter H3K4me3 level. Taken together, recent findings suggest that WDR5 plays a role in self-renewal of bladder cancer cells by regulating Nanog.

[0014] Further studies have demonstrated that WDR5 silencing increased cell apoptosis and decreased bladder cancer cells resistance to cisplatin. Conversely, overexpression of WDR5 enhanced chemoresistance to cisplatin. Moreover, WDR5 directly regulates important inhibitors of apoptotic proteins, MCL1 *[FEES Lett.* **2010;** 584(14):2981-9; *Sci Rep.* **2014** ;4:6098] and BIRC3 *[Expert Opin Ther Targets.2009* ;13(1 1): 1333-45], by H3K4me3.

[0015] In summary, WDR5 is upregulated in bladder cancer, and promotes bladder cancer cell proliferation, self-renewal and chemoresistance via activating a series of oncogenes by H3K4me3. Therefore, WDR5 is a potential biomarker for bladder cancer and a promising target for drug development *[Sci Rep.* **2015;** 5: 8293, *Genom Data.* **2015** ;5:27-9.].

Acute Myeloid Leukemia (AML)

[0016] The CEBPA gene is mutated in 9% of patients with acute myeloid leukemia (AML). Selective expression of a short (30-kDa) CCAAT-enhancer binding protein-a (C/EBPa) translational isoform, termed p30, represents the most common type of CEBPA mutation in AML. The molecular mechanisms underlying p30-mediated transformation remain incompletely understood. Recent studies have shown that C/EBPa p30, but not the normal p42 isoform, preferentially interacts with WDR5, a key component of SET/MLL (SET-domain/mixed-lineage leukemia) histone-methyltransferase complexes. Accordingly, p30-bound genomic regions are enriched for MLL-dependent H3K4me3 marks. The p30-dependent increase in self-renewal and

inhibition of myeloid differentiation required WDR5, as downregulation of the latter inhibited proliferation and restored differentiation in p30-dependent AML models. Small-molecule inhibitors of WDR5-MLL binding selectively inhibited proliferation and induced differentiation in p30-expressing human AML cells revealing the mechanism of p30-dependent transformation and establish the p30 cofactor WDR5 as a therapeutic target in CEBPA-mutant AML *[Nat Chem Biol.* 2015 ;11(8):571-8].

MYCN-amplified Neuroblastoma

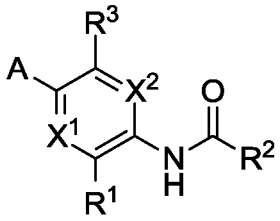
[0017] MYCN gene amplification in neuroblastoma drives a gene expression program that correlates strongly with aggressive disease. Mechanistically, trimethylation of histone H3 lysine 4 (H3K4) at target gene promoters is a prerequisite for this transcriptional program to be enacted. WDR5 is a histone H3K4 presenter that has been found to have an essential role in H3K4 trimethylation. For this reason, in this study, the relationship between WDR5-mediated H3K4 trimethylation and N-Myc transcriptional programs in neuroblastoma cells was investigated. N-Myc upregulated WDR5 expression in neuroblastoma cells. Gene expression analysis revealed that WDR5 target genes included those with MYC-binding elements at promoters such as MDM2. WDR5 was shown to form a protein complex at the MDM2 promoter with N-Myc, but not p53, leading to histone H3K4 trimethylation and activation of MDM2 transcription[Ca«cer *Res* 2015; 75(23); 5143-54]. RNAi-mediated attenuation of WDR5 upregulated expression of wild-type but not mutant p53, an effect associated with growth inhibition and apoptosis. Similarly, a small-molecule antagonist of WDR5 reduced N-Myc/WDR5 complex formation, N-Myc target gene expression, and cell growth in neuroblastoma cells. In MYCN-transgenic mice, WDR5 was overexpressed in precancerous ganglion and neuroblastoma cells compared with normal ganglion cells. Clinically, elevated levels of WDR5 in neuroblastoma specimens were an independent predictor of poor overall survival. Overall, these results identify WDR5 as a relevant cofactor for N-Myc-regulated transcriptional activation and tumorogenesis and as a novel therapeutic target for MYCN-amplified neuroblastomas *[Cancer Res* 2015; 75(23); 5143-54, *Mol Cell.* 2015 ;58(3):440-52.].

SUMMARY

[0018] The structural features as described in the background suggest that the WDR5-MLL binding is a desirable drug target. Hence, agents that bind to the WDR5 protein and compete for binding with WDR5-interacting partners can reverse the transcriptional activities of WDR5 containing complexes. Considering the challenges generally associated with inhibiting protein-protein interactions, along with the current need to treat WDR5-driven tumor types such as leukemia and bladder cancers, complementary approaches including virtual screening, focused library screening and traditional structure activity relationship (SAR) studies were conducted. These studies led to the identification of compounds which inhibit the WDR5 protein-protein binding. In addition, structure-activity relationship studies demonstrated that specific chemical features contribute to longer residence times for the binding of these compounds with WDR5. Studies indicate that longer residence times can be designed into WDR5 inhibitors and contribute to the ligand-induced anti-proliferative effects observed in hematologic and solid tumors.

[0019] A novel class of compounds of Formula (I) have been prepared that show potent disruption of WDR5-MLL1 protein-protein binding and therefore have utility in the treatment of cancers and other WDR5-mediated diseases, disorders and conditions.

[0020] Therefore, in one aspect, the present application includes a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof:



(I)

wherein:

R^1 is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, $_{C\,3}$-iocycloalkyl, OR^4, SR^4, NR^5R^6, Ci-galkyleneOR^4, Ci$_{-6}$alkyleneSR^4 and Ci$_{-6}$alkyleneNR^{5}R^6, provided that R^1 comprises at least one basic nitrogen atom;

R^2 is selected from C_{6}-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^7, SR^7 and NR^8R^9;

R^3 is selected from C_6-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci_ efluoroalkyl, =0, =S, OR^{10}, SR^{10}, $S0_2R^{10}$, $NR^{11}R^{12}$, R^{13}, Ci$_{-6}$alkyleneR^{13}, Ci. salkenyleneR^{13}, OCi$_{-6}$alkyleneR^{13}, SCi$_{-6}$alkyleneR^{13}, C_{1-6}alkyleneNR^{11}R^{12}, Ci. salkyleneOR^{10}, Ci$_{-6}$alkyleneSR^{10}, OC_{1-6}alkyleneNR^{11}R^{12}, SCi$_{-6}$alkyleneNR^{11}R^{12}, OCi. salkyleneOR^{10}, SCi$_{-6}$alkyleneOR^{10}, OCi$_{-6}$alkyleneSR^{10}, SCi$_{-6}$alkyleneSR^{10}, C(0)OR^{10}, C(S)OR^{10}, C(S)NR^{11}R^{12} and C(0)NR^{11}R^{12};

R^4 is selected from H, Ci$_{-6}$alkyl Ci$_{-6}$fluoroalkyl, C(0)Ci$_{-6}$alkyl and C(0)d. $_6$fluoroalkyl;

R^5 and R^6 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci-$_6$fluoroalkyl, C(0)OCi$_{-6}$alkyl, C(0)NHCi_ $_6$alkyl, S02Ci-$_6$alkyl, S02HNCi-$_6$alkyl, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC$_{3-6}$cycloalkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, OH, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fiuoroalkyl, OCi-efluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci.$_6$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)NHCi$_{-6}$alkyl, $S0_2$Ci$_{-6}$alkyl, $S0_2$HNCi$_{-6}$alkyl, Ci-ealkyleneOCi-ealkyl, Ci-salkyleneCs-ioaryl, Ci. $_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC$_{3-6}$cycloalkyl;

R^7 is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$fluoroalkyl and C(0)Ci_ ealkyl;

R^8 and R^9 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci_ $_6$fluoroalkyl and C(0)Ci$_{-6}$alkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, CN, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fluoroalkyl and OCi-$_6$fluoroalkyl;

R^{10} is selected from H, Ci$_{-6}$alkyl, Ci.$_6$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C_{3-}iocycloalkyl, heterocycloalkyl, C_{6-}ioaryl, heteroaryl, Ci$_{-6}$alkyleneC$_3$.iocycloalkyl, Ci$_{-6}$alkyleneC$_6$-ioaryl, Ci$_{-6}$alkyleneheteroaryl and Ci$_{-6}$alkyleneheterocycloalkyl, and is

unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci_{-6}alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci$-$_6$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-$_1$oaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_-$$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{14}, Ci-$_6$alkyleneOR^{14}, Ci-$_6$alkyleneSR^{14} and Ci_{-6}alkyleneNR^{15}R^{16};

R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, $C(0)Ci_{-6}$alkyl, $C(0)Ci_{-6}$fluoroalkyl, $C(O)C_{6}$-$i_0$aryl, $C(O)C_{3}$-$i_0$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, $C(0)OCi_{-6}$alkyl, $C(0)OCi_{-6}$fluoroalkyl, $C(0)OC_{6-}$ioaryl, $C(0)OC_{3-}$iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, $C(0)NHCi_{-6}$alkyl, $C(0)NHCi_{-6}$fluoroalkyl, $C(O)NHC_{6}$-$i_0$aryl, $C(0)NHC_{3-}$$_1$ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, $S0_2Ci_{-6}$alkyl, $S0_2C_1$.$_6$fluoroalkyl, $S0_2C_6$-ioaryl, $S0_2C_3$-iocycloalkyl, $S0_2$heteroaryl, $S0_2$heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl, C_6-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and each of R^{11} and R^{12} are independently unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci_{-6}alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6}-$i_0$aryl, heteroaryl, $C_{3-}$$_1$ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_-$$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{14}, Ci-$_6$alkyleneOR^{14}, Ci-galkyleneSR^{14} and Ci_{-6}alkyleneNR^{15}R^{16}, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci_{-6}alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6}-$i_0$aryl, heteroaryl, C_{3-}iocycloalkyl, heterocycloalkyl, Ci_{-6}alkyleneC$_6$-ioaryl, Ci_{-6}alkyleneC$_3$.iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneR^{14}, Ci-$_6$alkyleneOR^{14}, Ci-$_6$alkyleneSR^{14} and Ci$_-$$_6$alkyleneNR^{15}R^{16};

R^{13} is selected from $C(0)Ci_{-6}$alkyl, $C(0)Ci_{-6}$fluoroalkyl, $C(O)C_{6}$-$i_0$aryl, $C(0)C_{3-}$$_1$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl and C_{6-}ioaryl, and R^{13} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$,

Ci-galkyl, C(0)R^{14}, C(0)OR^{14}, C(0)NR^{15}R^{16}, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{14}, Ci-galkyleneOR^{14}, Ci$_{-6}$alkyleneSR^{14} and Ci$_{-6}$alkyleneNR^{15}R^{16},

R^{14} is selected from H, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl, and R^{14} is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-galkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi_salkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci$_{-6}$alkyleneC$_6$-$_1$oaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci_$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci_salkyleneNiCi-galkyOiCi-galkyl);

R^{15} and R^{16} are each independently selected from H, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci_$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_6$-i$_0$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci$_{-6}$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci_$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fiuoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci.

salkyl), C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(0)OH, C(0)OCi $_{-6}$alkyl, C(0)NH $_2$, C(0)NHCi $_{-6}$alkyl, C(0)N(Ci. $_6$alkyl)(Ci $_{-6}$alkyl), S0 $_2$Ci $_{-6}$alkyl, S(0)Ci $_{-6}$alkyl, C_6-ioaryl, heteroaryl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneC $_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi- $_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi- $_6$alkyl, Ci-$_6$alkyleneNH $_2$, Ci_ $_6$alkyleneNHCi- $_6$alkyl and Ci $_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci- $_6$alkyl);

X^1 and X^2 are each independently selected from CR^{17} and N;

R^{17} is selected from H, F, Ci-$_6$alkyl and Ci-$_6$fiuoroalkyl;

A is F, and

all alkyl and alkylene groups are optionally fluorosubstituted.

[0021] In another aspect, the present application includes a composition comprising one or more compounds of the application and a carrier.

[0022] In another aspect, the present application includes a method for inhibition of binding of WDR5 to its binding partners in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of the application to the cell.

[0023] The present application also includes a method of treating a disease, disorder or condition that is mediated or treatable by inhibition of binding between WDR5 protein and its binding partners comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. In an embodiment of the present application, the disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners is cancer.

[0024] Other features and advantages of the present application will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating embodiments of the application, are given by way of illustration only and the scope of the claims should not be limited by these embodiments, but should be given the broadest interpretation consistent with the description as a whole.

DRAWINGS

[0025] The embodiments of the application will now be described in greater detail with reference to the attached drawings in which:

[0026] Figure 1 illustrates WDR5 as an adaptor protein in multiple complexes and related biological processes.

DETAILED DESCRIPTION

I. Definitions

[0027] Unless otherwise indicated, the definitions and embodiments described in this and other sections are intended to be applicable to all embodiments and aspects of the present application herein described for which they are suitable as would be understood by a person skilled in the art.

[0028] The term "compound of the application" or "compound of the present application" and the like as used herein refers to a compound of Formula I, including compounds of la, lb, Ic and Id, and pharmaceutically acceptable salts and/or solvates thereof.

[0029] The term "composition of the application" or "composition of the present application" and the like as used herein refers to a composition, such a pharmaceutical composition, comprising one or more compounds of Formula I, including compounds of Formula la, lb, Ic and/or Id or pharmaceutically acceptable salts and/or solvates thereof.

[0030] The term "and/or" as used herein means that the listed items are present, or used, individually or in combination. In effect, this term means that "at least one of or "one or more" of the listed items is used or present. The term "and/or" with respect to pharmaceutically acceptable salts and/or solvates thereof means that the compounds of the application exist as individual salts and hydrates, as well as a combination of, for example, a salt of a solvate of a compound of the application.

[0031] As used in the present application, the singular forms "a", "an" and "the" include plural references unless the content clearly dictates otherwise. For example, an embodiment including "a compound" should be understood to present certain aspects with one compound, or two or more additional compounds.

[0032] In embodiments comprising an "additional" or "second" component, such as an additional or second compound, the second component as used herein is chemically different from the other components or first component. A "third" component is different from the other, first, and second components, and further enumerated or "additional" components are similarly different.

[0033] As used in this application and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "include" and "includes") or "containing" (and any form of containing, such as "contain" and "contains"), are inclusive or open-ended and do not exclude additional, unrecited elements or process steps.

[0034] The term "consisting" and its derivatives as used herein are intended to be closed terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, and also exclude the presence of other unstated features, elements, components, groups, integers and/or steps.

[0035] The term "consisting essentially of, as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers, and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of these features, elements, components, groups, integers, and/or steps.

[0036] The term "suitable" as used herein means that the selection of the particular compound or conditions would depend on the specific synthetic manipulation to be performed, the identity of the molecule(s) to be transformed and/or the specific use for the compound, but the selection would be well within the skill of a person trained in the art.

[0037] In embodiments of the present application, the compounds described herein may have at least one asymmetric center. Where compounds possess more than one asymmetric center, they may exist as diastereomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present application. It is to be further understood that while the stereochemistry of the compounds may be as shown in any given compound listed herein, such compounds may also contain certain amounts (for example, less than

20%, suitably less than 10%, more suitably less than 5%) of compounds of the present application having an alternate stereochemistry. It is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the present application.

[0038] The compounds of the present application may also exist in different tautomeric forms and it is intended that any tautomeric forms which the compounds form, as well as mixtures thereof, are included within the scope of the present application.

[0039] The compounds of the present application may further exist in varying polymorphic forms and it is contemplated that any polymorphs, or mixtures thereof, which form are included within the scope of the present application.

[0040] The present description refers to a number of chemical terms and abbreviations used by those skilled in the art. Nevertheless, definitions of selected terms are provided for clarity and consistency.

[0041] The terms "about", "substantially" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least ±5% of the modified term if this deviation would not negate the meaning of the word it modifies or unless the context suggests otherwise to a person skilled in the art.

[0042] The expression "proceed to a sufficient extent" as used herein with reference to the reactions or process steps disclosed herein means that the reactions or process steps proceed to an extent that conversion of the starting material or substrate to product is maximized. Conversion may be maximized when greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100% of the starting material or substrate is converted to product.

[0043] The term "basic nitrogen" as used herein refers to a nitrogen atom that has a lone pair of electrons available to participate in an interaction with a hydrogen atom. In an embodiment, the interaction is a hydrogen bond, an ionic bond or a covalent bond. In general, the basic nitrogen atom will be either a primary, secondary

or tertiary alkyl amine nitrogen atom, either in a linear, branched or cyclic group. In some embodiments, the pKa of the conjugate acid of the basic nitrogen atom will be greater than about 8-10.

[0044] The term "alkyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, saturated alkyl groups. The number of carbon atoms that are possible in the referenced alkyl group are indicated by the prefix "C_{nl-n2}". For example, the term Ci.i $_0$alkyl means an alkyl group having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms.

[0045] The term "alkylene", whether it is used alone or as part of another group, means straight or branched chain, saturated alkylene group, that is, a saturated carbon chain that contains substituents on two of its ends. The number of carbon atoms that are possible in the referenced alkylene group are indicated by the prefix "C_ni_{-n2}". For example, the term C_{2-6}alkylene means an alkylene group having 2, 3, 4, 5 or 6 carbon atoms.

[0046] The term "alkenyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, unsaturated alkyl groups containing at least one double bond. The number of carbon atoms that are possible in the referenced alkylene group are indicated by the prefix "C_ni_{-n2}". For example, the term C_{2-6}alkenyl means an alkenyl group having 2, 3, 4, 5 or 6 carbon atoms and at least one double bond.

[0047] The term "fluoroalkyl" as used herein refers to an alkyl group wherein one or more, including all of the hydrogen atoms are replaced by a fluorine atom. In an embodiment, the fluoroalkyl comprises at least one -CHF_2 group. In another embodiment, the fluoroalkyl comprises at least one -CF_3 group.

[0048] The term "fluorosubstituted" as used herein refers to a chemical group wherein one or more, including all of the hydrogen atoms, are replaced by a fluorine atom.

[0049] The term "cycloalkyl," as used herein, whether it is used alone or as part of another group, means a saturated carbocyclic group containing a number of carbon atoms and one or more rings. The number of carbon atoms that are possible in

the referenced cycloalkyl group are indicated by the numerical prefix "**$C_ni_{-n}2$**". For example, the term $_{C\ 3}$-iocycloalkyl means a cycloalkyl group having 3, 4, 5, **6,** 7, 8, **9** or 10 carbon atoms.

[0050] The term "aryl" as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing from **6** to 20 carbon atoms and at least one aromatic ring. In an embodiment of the application, the aryl group contains from **6, 9** or 10 carbon atoms, such as phenyl, indanyl or naphthyl.

[0051] The term "heterocycloalkyl" as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing 3 to 20 atoms, suitably 3 to 10 atoms, and at least one non-aromatic, ring in which one or more of the atoms are a heteromoiety selected from **O,** S, **S(O),** $S0_2$, N, NH and NCi_{-6}alkyl, suitably **O,** S, N, NH and NCi_{-6}alkyl. Heterocycloalkyl groups are either saturated or unsaturated (i.e. contain one or more double bonds) and contain one or more than one ring (i.e. are polycyclic). When a heterocycloalkyl group contains more than one ring, the rings may be fused, bridged, spirofused or linked by a bond. When a heterocycloalkyl group contains the prefix $C_ni_{-n}2$ this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteromoiety as defined above.

[0052] A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms there between.

[0053] The term "heteroaryl" as used herein refers to cyclic groups containing from 5 to 20 atoms, suitably 5 to 10 atoms, at least one aromatic ring and at least one a heteromoiety selected from **O,** S, **S(O),** $S0_2$, N, NH and NCi_{-6}alkyl, suitably **O,** S, N, NH and NCi_{-6}alkyl. Heteroaryl groups contain one or more than one ring (i.e. are polycyclic). When a heteroaryl group contains more than one ring, the rings may be fused, bridged, spirofused or linked by a bond. When a heteroaryl group contains the prefix **C_ni_{-n2}** this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteromoiety as defined above.

[0054] The term "available", as in "available hydrogen atoms" or "available atoms" refers to atoms that would be known to a person skilled in the art to be capable of replacement by a substituent.

[0055] The terms "halo" or "halogen" as used herein, whether it is used alone or as part of another group, refers to a halogen atom and includes fluoro, chloro, bromo and iodo.

[0056] The term "amine" or "amino," as used herein, whether it is used alone or as part of another group, refers to groups of the general formula NRR', wherein R and R' are each independently selected from hydrogen and an alkyl group, such as C_{1-6}alkyl.

[0057] The term "atm" as used herein refers to atmosphere.

[0058] The term "MS" as used herein refers to mass spectrometry.

[0059] The term "aq." as used herein refers to aqueous.

[0060] DCM as used herein refers to dichloromethane.

[0061] DIPEA as used herein refers to N,N-diisopropyl ethylamine

[0062] DMF as used herein refers to dimethylformamide.

[0063] DMSO as used herein refers to dimethylsulfoxide.

[0064] EtOAc as used herein refers to ethyl acetate.

[0065] HATU as used herein refers to l-[Bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate.

[0066] MeOH as used herein refers to methanol.

[0067] MeCN as used herein refers to acetonitrile.

[0068] HC1 as used herein refers to hydrochloric acid.

[0069] TFA as used herein refers to trifluoroacetic acid.

[0070] TBAF as used herein refers to tetra-n-butyl ammonium fluoride.

[0071] CsF as used herein is cesium fluoride.

[0072] μwave as used herein refers to a microwave reaction vessel.

[0073] SnAr as used herein represents nucleophilic aromatic substitution.

[0074] LCMS as used herein refers to liquid chromatography-mass spectrometry.

[0075] The term "protecting group" or "PG" and the like as used herein refers to a chemical moiety which protects or masks a reactive portion of a molecule to prevent side reactions in those reactive portions of the molecule, while manipulating or reacting a different portion of the molecule. After the manipulation or reaction is complete, the protecting group is removed under conditions that do not degrade or decompose the remaining portions of the molecule. The selection of a suitable protecting group can be made by a person skilled in the art. Many conventional protecting groups are known in the art, for example as described in "Protective Groups in Organic Chemistry" McOmie, J.F.W. Ed., Plenum Press, 1973, in Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis", John Wiley & Sons, 3rd Edition, 1999 and in Kocienski, P. Protecting Groups, 3rd Edition, 2003, Georg Thieme Verlag (The Americas).

[0076] The term "subject" as used herein includes all members of the animal kingdom including mammals, and suitably refers to humans. Thus the methods of the present application are applicable to both human therapy and veterinary applications. In an embodiment, the subject is a mammal. In another embodiment, the subject is human.

[0077] The term "pharmaceutically acceptable" means compatible with the treatment of subjects, for example humans.

[0078] The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to a subject.

[0079] The term "pharmaceutically acceptable salt" means either an acid addition salt or a base addition salt which is suitable for, or compatible with, the treatment of subjects.

[0080] An acid addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic acid addition salt of any basic

compound. Basic compounds that form an acid addition salt include, for example, compounds comprising an amine group. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acids, as well as acidic metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include mono-, di- and tricarboxylic acids. Illustrative of such organic acids are, for example, acetic, trifluoroacetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, mandelic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid and other sulfonic acids such as methanesulfonic acid, ethanesulfonic acid and 2-hydroxyethanesulfonic acid. In an embodiment, the mono- or di-acid salts are formed, and such salts exist in either a hydrated, solvated or substantially anhydrous form. In general, acid addition salts are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection criteria for the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts such as but not limited to oxalates may be used, for example in the isolation of compounds of the application for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

[0081] A base addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic base addition salt of any acidic compound. Acidic compounds that form a basic addition salt include, for example, compounds comprising a carboxylic acid group. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium or barium hydroxide as well as ammonia. Illustrative organic bases which form suitable salts include aliphatic, alicyclic or aromatic organic amines such as isopropylamine, methylamine, trimethylamine, picoline, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine,

dicyclohexylamine, choline, and caffeine. [See, for example, S. M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.* **1977,** *66,* 1-19]. The selection of the appropriate salt may be useful, for example, so that an ester functionality, if any, elsewhere in a compound is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

[0082] The term "solvate" as used herein means a compound, or a salt or prodrug of a compound, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate". The formation of solvates of the compounds of the application will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions. The selection of suitable conditions to form a particular solvate can be made by a person skilled in the art.

[0083] The term "treating" or "treatment" as used herein and as is well understood in the art, means an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission (whether partial or total), whether detectable or undetectable. "Treating" and "treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. "Treating" and "treatment" as used herein also include prophylactic treatment. For example, a subject with early cancer can be treated to prevent progression, or altematively a subject in remission can be treated with a compound or composition of the application to prevent recurrence. Treatment methods comprise administering to a subject a therapeutically effective amount of one or more of the compounds of the application and optionally consist of a single administration, or altematively comprise a series of administrations. For example, the compounds of the application are administered at least once a week. However, in another embodiment, the compounds are administered to the

subject from about one time per two weeks, three weeks or one month. In another embodiment, the compounds are administered about one time per week to about once daily. In another embodiment, the compounds are administered 2, 3, 4, 5 or 6 times daily. The length of the treatment period depends on a variety of factors, such as the severity of the disease, disorder or condition, the age of the subject, the concentration and/or the activity of the compounds of the application, and/or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration is required. For example, the compounds are administered to the subject in an amount and for duration sufficient to treat the subject.

[0084] "Palliating" a disease, disorder or condition means that the extent and/or undesirable clinical manifestations of a disease, disorder or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to not treating the disorder.

[0085] The term "prevention" or "prophylaxis", or synonym thereto, as used herein refers to a reduction in the risk or probability of a patient becoming afflicted with a disease, disorder or condition or manifesting a symptom associated with a disease, disorder or condition.

[0086] The "disease", "disorder" or "condition" as used herein refers to a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners, in particular MLLl, and in particular using a WDR5 protein inhibitor, such as a compound of the application herein described.

[0087] The term "mediated or treatable by inhibition of binding between WDR5 protein and its binding partners" as used herein means that the disease, disorder or condition to be treated is affected by, modulated by and/or has some biological basis, either direct or indirect, that includes WDR5 binding, in particular, increased WDR5 binding, to its binding partners, such as MLLl. Such biological basis includes, for example, WDR5 and/or MLLl gene overexpression or WDR5 and/or MLLl protein over-accumulation or over-expression of proteins that are products of or precursors to WDR5-mediated and/or MLLl gene expression. In a

refined context, "mediated or treatable by inhibition of binding between WDR5 protein and its binding partners" refers to an effect mediated through inhibition of binding between WDR5 and MLL1. In a broader context, "mediated or treatable by inhibition of binding between WDR5 protein and its binding partners" can include the large number of diseases that are caused by aberrant methylation of histone 3 lysine 4 (H3K4) residues, as results from aberrant WDR5 and/or MLL1 activity. As used herein, WDR5 refers to the protein identified as GenBank Accession number NM_017588 *[J. Biol. Chem.* **2001,** 276 (49), 46515-46522] and isoforms that include this sequence, and shorter versions. Similarly, the other WDR5 proteins are characterized and described in any of the protein databases. As used herein, MLL1 refers to the protein identified as GenBank Accession number NM_005933 *[Proc. Natl. Acad. Sci. U.S.A.* **1991,** 88 (23), 10735-10739; *DNA Cell Biol.* **1995,** 14 (6), 475-483] and isoforms that include this sequence, and shorter versions. Similarly, the other MLL1 proteins are characterized and described in any of the protein databases.

[0088] The term "binding" as used herein refers to any interaction between two entities, such as two proteins, that leads to a functional effect.

[0089] As used herein, the term "effective amount" or "therapeutically effective amount" means an amount of one or more compounds of the application that is effective, at dosages and for periods of time necessary to achieve the desired result. For example in the context of treating a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners, an effective amount is an amount that, for example, increases said inhibition compared to the inhibition without administration of the one or more compounds. In an embodiment, effective amounts vary according to factors such as the disease state, age, sex and/or weight of the subject. In a further embodiment, the amount of a given compound or compounds that will correspond to an effective amount will vary depending upon factors, such as the given drug(s) or compound(s), the pharmaceutical formulation, the route of administration, the type of condition, disease or disorder, the identity of the subject being treated, and the like, but can nevertheless be routinely determined by one skilled in the art.

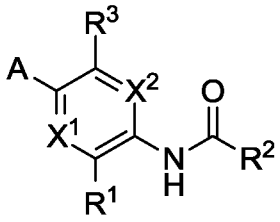
[0090] The term "administered" as used herein means administration of a therapeutically effective amount of one or more compounds or compositions of the application to a cell, tissue, organ or subject.

[0091] The term "neoplastic disorder" as used herein refers to a disease, disorder or condition characterized by cells that have the capacity for autonomous growth or replication, e.g., an abnormal state or condition characterized by proliferative cell growth. The term "neoplasm" as used herein refers to a mass of tissue resulting from the abnormal growth and/or division of cells in a subject having a neoplastic disorder. Neoplasms can be benign (such as uterine fibroids and melanocytic nevi), potentially malignant (such as carcinoma *in situ)* or malignant (i.e. cancer). Exemplary neoplastic disorders include the so-called solid tumours and liquid tumours, including but not limited to carcinoma, sarcoma, metastatic disorders (e.g., tumors arising from the prostate), hematopoietic neoplastic disorders, (e.g., leukemias, lymphomas, myeloma and other malignant plasma cell disorders), metastatic tumors and other cancers.

[0092] The term "cancer" as used herein refers to cellular-proliferative disease states.

II. Compounds and Compositions of the Application

[0093] The present application includes a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof:



(I)

wherein:

R^1 is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, C_{i-6}alkyl, C_{i-6}fiuoroalkyl, C_{3}-iocycloalkyl, OR^4, SR^4,

NR^5R^6, Ci-galkyleneOR4, Ci_{-6}alkyleneSR4 and Ci_{-6}alkyleneNR5R6, provided that R1 comprises at least one basic nitrogen atom;

R2 is selected from C_{6}-ioaryl and heteroaryl, and R2 is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR7, SR7 and NR^8R^9;

R3 is selected from C_6-ioaryl, heteroaryl and heterocycloalkyl, and R3 is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci_{-}efluoroalkyl, =0, =S, OR10, SR10, $S0_2R^{10}$, $NR^{11}R^{12}$, R13, Ci_{-6}alkyleneR13, Ci. salkenyleneR13, OCi_{-6}alkyleneR13, SCi_{-6}alkyleneR13, C_{1-6}alkyleneNR11R12, Ci. salkyleneOR10, Ci_{-6}alkyleneSR10, OC_{1-6}alkyleneNR11R12, SCi_{-6}alkyleneNR11R12, OCi. salkyleneOR10, SCi_{-6}alkyleneOR10, OCi_{-6}alkyleneSR10, SCi_{-6}alkyleneSR10, C(0)OR10, C(S)OR10, C(S)NR11R12 and C(0)NR11R12;

R4 is selected from H, Ci_{-6}alkyl C^fluoroalkyl, C(0)Ci_{-6}alkyl and C(0)d.$_6$fluoroalkyl;

R5 and R6 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl, C(0)Ci_{-6}alkyl, C(0)Ci-$_6$fluoroalkyl, C(0)OCi_{-6}alkyl, C(0)NHCi$_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, $S0_2HNCi_{-6}$alkyl, Ci-ealkyleneOCi-ealkyl, Ci_{-6}alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC$_{3-6}$cycloalkyl, or R5 and R6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, OH, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fiuoroalkyl, OCi-efluoroalkyl, C(0)Ci_{-6}alkyl, C(0)Ci.$_6$fluoroalkyl, C(0)Ci_{-6}alkyl, C(0)NHCi$_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, $S0_2HNCi_{-6}$alkyl, Ci-ealkyleneOCi-ealkyl, Ci-ealkyleneCe-ioaryl, Ci.$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC$_{3-6}$cycloalkyl;

R7 is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$fluoroalkyl and C(0)Ci-ealkyl;

R8 and R9 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$fluoroalkyl and C(0)Ci-$_6$alkyl, or R8 and R9 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or

substituted with one or more substituents selected from halo, OH, CN, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fluoroalkyl and OCi-$_6$fluoroalkyl;

R^{10} is selected from H, Ci$_{-6}$alkyl, Ci.$_6$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, heteroaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and is unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci$_{-6}$alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, S(0)Ci $_{-6}$alkyl, S0 $_2$Ci-$_6$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_6$-$_1$oaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR ^{14}, Ci-$_6$alkyleneOR ^{14}, Ci-$_6$alkyleneSR ^{14} and Ci$_{-6}$alkyleneNR ^{15}R^{16};

R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(O)C$_{6-i0}$aryl, C(O)C$_{3-i0}$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi $_{-6}$alkyl, C(0)OCi $_{-6}$fluoroalkyl, C(0)OC $_{6}$-ioaryl, C(0)OC $_{3-}$iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi $_{-6}$alkyl, C(0)NHCi $_{-6}$fluoroalkyl, C(O)NHC$_{6-i0}$aryl, C(0)NHC $_{3-}$$_1$ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0 $_2$Ci$_{-6}$alkyl, S0 $_2$C$_1$.$_6$fluoroalkyl, S0 $_2$C $_6$-ioaryl, S0 $_2$C$_3$-iocycloalkyl, S0 $_2$heteroaryl, S0 $_2$heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl, C_6-ioaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and each of R^{11} and R^{12} are independently unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci$_{-6}$alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, S(0)Ci $_{-6}$alkyl, S0 $_2$Ci$_{-6}$alkyl, C$_{6-i0}$aryl, heteroaryl, C$_{3-}$$_1$ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR ^{14}, Ci-$_6$alkyleneOR ^{14}, Ci$_{-6}$alkyleneSR ^{14} and Ci$_{-6}$alkyleneNR ^{15}R^{16}, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci$_{-6}$alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, S(0)Ci $_{-6}$alkyl, S0 $_2$Ci$_{-6}$alkyl, C$_{6-i0}$aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl,

Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneR^{14}, Ci-$_6$alkyleneOR^{14}, Ci-$_6$alkyleneSR^{14} and Ci$_6$alkyleneNR^{15}R^{16};

R^{13} is selected from C(0)Ci$_6$alkyl, C(0)Ci$_6$fluoroalkyl, C(O)C$_{6-10}$aryl, C(0)C$_{3-10}$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, heteroaryl and C$_6$-ioaryl, and R^{13} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, NR^{15}R^{16}, Ci$_6$alkyl, C(0)R^{14}, C(0)OR^{14}, C(0)NR^{15}R^{16}, S(0)Ci$_6$alkyl, S0$_2$Ci$_6$alkyl, C$_{6-10}$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_{3-10}$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{14}, Ci-galkyleneOR^{14}, Ci$_6$alkyleneSR^{14} and Ci$_6$alkyleneNR^{15}R^{16},

R^{14} is selected from H, Ci$_6$alkyl, Ci$_6$fluoroalkyl, C(0)Ci$_6$alkyl, C(0)Ci$_6$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_{3-10}$ocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl, and R^{14} is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-galkyl, OCi$_6$fluoroalkyl, SCi$_6$alkyl, SCi$_6$fluoroalkyl, NH$_2$, NHCi$_6$alkyl, N(Ci.$_6$alkyl)(Ci$_6$alkyl), C(0)Ci$_6$alkyl, C(0)Ci$_6$fluoroalkyl, C(0)OH, C(0)OCi$_6$alkyl, C(0)NH$_2$, C(0)NHCi$_6$alkyl, C(0)N(Ci$_6$alkyl)(Ci$_6$alkyl), S0$_2$Ci$_6$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6-10}$oaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci$_6$salkyleneNiCi-galkyOiCi-galkyl);

R^{15} and R^{16} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_6$alkyl, SCi$_6$fluoroalkyl, NH$_2$, NHCi$_6$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_6$alkyl, C(0)Ci$_6$fluoroalkyl, C(0)OH, C(0)OCi$_6$alkyl, C(0)NH$_2$, C(0)NHCi$_6$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_6$alkyl), S0$_2$Ci$_6$alkyl, S(0)Ci$_6$alkyl, C$_{6-10}$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-

$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci$_-$$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-i0}aryl, heteroaryl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci$_-$$_6$alkyleneNHCi-$_6$alkyl and Ci$_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

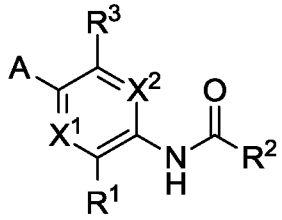
X^1 and X^2 are each independently selected from CR^{17} and N;

R^{17} is selected fromH, F, Ci-$_6$alkyl and Ci-$_6$fiuoroalkyl;

A is F, and

all alkyl and alkylene groups are optionally fluorosubstituted.

[0094] The present application also includes a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof:



(I)

wherein:

R^1 is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci$_{-6}$alkyl, Ci$_{-6}$fiuoroalkyl, OR^4, SR^4, NR^5R^6, Ci$_-$

$_6$alkyleneOR^4, Ci-$_6$alkyleneSR^4 and Ci-$_6$alkyleneNR^{5}R^6, provided that R^1 comprises at least one basic nitrogen atom;

R^2 is selected from $_{C\,6}$-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^7, SR^7 and NR^{8}R^9;

R^3 is selected from $_{C\,6}$-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci$_-$sfiuoroalkyl, OR^{10}, SR^{10}, NR^{11}R^{12}, R^{13}, Ci$_-$$_6$alkyleneR^{13}, OCi$_-$$_6$alkyleneR^{13}, SCi.salkyleneR^{13}, Ci$_-$$_6$alkyleneNR^{11}R^{12}, Ci$_-$$_6$alkyleneOR^{10}, Ci$_-$$_6$alkyleneSR^{10}, OCi.$_6$alkyleneNR^{11}R^{12}, SCi$_-$$_6$alkyleneNR^{11}R^{12}, OCi$_-$$_6$alkyleneOR^{10}, SCi$_-$$_6$alkyleneOR^{10}, OCi$_-$$_6$alkyleneSR^{10}, SCi$_-$$_6$alkyleneSR^{10}, C(0)OR^{10}, C(S)OR^{10}, C(S)NR^{11}R^{12} and C(0)NR^{11}R^{12};

R^4 is selected from H, C$_{1-6}$alkyl Ci$_-$$_6$fluoroalkyl, C(0)Ci$_-$$_6$alkyl and C(0)d.$_6$fluoroalkyl;

R^5 and R^6 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl, C(0)Ci-$_6$alkyl and C(0)Ci-$_6$fluoroalkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, Ci-galkyl OCi$_-$$_6$alkyl, Ci$_-$$_6$fluoroalkyl, OC^fluoroalkyl, C(0)Ci$_-$$_6$alkyl and C(0)Ci$_-$$_6$fluoroalkyl;

R^7 is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$fluoroalkyl and C(0)Ci$_-$$_6$alkyl;

R^8 and R^9 are independently selected from H, Ci$_-$$_6$alkyl, Ci$_-$$_6$fiuoroalkyl, C(0)Ci.$_6$fluoroalkyl and C(0)Ci-$_6$alkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fluoroalkyl and OCi-$_6$fluoroalkyl;

R^{10} is selected from H, Ci$_-$$_6$alkyl, Ci$_-$$_6$fluoroalkyl, C(0)Ci$_-$$_6$alkyl, C(0)Ci$_-$$_6$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, $_{C\,6}$-ioaryl, heteroaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and is

unsubstituted or substituted with one or more substituents selected from halo, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci-galkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_{3-10}cycloalkyl, heterocycloalkyl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl, Ci_{-6}alkyleneheteroaryl, Ci_{-6}alkyleneheterocycloalkyl, Ci_{-6}alkyleneR^{14}, Ci_{-6}alkyleneOR^{14}, Ci_{-6}alkyleneSR^{14} and Ci_{-6}alkylene$NR^{15}R^{16}$;

R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, $C(0)Ci_{-6}$alkyl, $C(0)Ci_{-6}$fluoroalkyl, C_{3-10}cycloalkyl, heterocycloalkyl, heteroaryl, C_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneheteroaryl and Ci_{-6}alkyleneheterocycloalkyl, and each of R^{11} and R^{12} are independently unsubstituted or substituted with one or more substituents selected from halo, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci-galkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_{3-10}cycloalkyl, heterocycloalkyl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl, Ci_{-6}alkyleneheteroaryl, Ci_{-6}alkyleneheterocycloalkyl, Ci_{-6}alkyleneR^{14}, Ci-galkyleneOR^{14}, Ci_{-6}alkyleneSR^{14} and Ci_{-6}alkylene$NR^{15}R^{16}$, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci_{-6}alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_{3-10}cycloalkyl, heterocycloalkyl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl, Ci_{-6}alkyleneheteroaryl, Ci_{-6}alkyleneR^{14}, Ci_{-6}alkyleneOR^{14}, Ci_{-6}alkyleneSR^{14} and Ci_{-6}alkylene$NR^{15}R^{16}$;

R^{13} is selected from $C(0)Ci_{-6}$alkyl, $C(0)Ci_{-6}$fluoroalkyl, C_{3-10}cycloalkyl, heterocycloalkyl, heteroaryl and C_{6-10}aryl, and R^{13} is unsubstituted or substituted with one or more substituents independently selected from halo, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci_{-6}alkyl, $C(0)R^{14}$, $C(0)OR^{14}$, $C(0)NR^{15}R^{16}$, $S(0)Ci_{-6}$alkyl, $S0_2Ci_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_{3-10}cycloalkyl, heterocycloalkyl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl, Ci_{-6}alkyleneheteroaryl, Ci_{-6}alkyleneheterocycloalkyl, Ci_{-6}alkyleneR^{14}, Ci-galkyleneOR^{14}, Ci_{-6}alkyleneSR^{14} and Ci_{-6}alkylene$NR^{15}R^{16}$,

R^{14} is selected from H, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, $C(0)Ci_{-6}$alkyl, $C(0)Ci_{-6}$fluoroalkyl, C_{3-10}cycloalkyl, heterocycloalkyl, C_{6-10}aryl, Ci_{-6}alkyleneC_{6-10}aryl, Ci_{-6}alkyleneC_{3-10}cycloalkyl and Ci_{-6}alkyleneheterocycloalkyl, and R^{14} is unsubstituted or substituted

with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi.$_6$fluoroalkyl, SCi$_{-6}$alkyl, SCi-$_6$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci-$_6$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)d.$_6$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

R^{15} and R^{16} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, Ci$_{-6}$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci$_{-6}$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-sfiuoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, NCCi-salkylXCi-salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci$_{-6}$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci$_{-6}$alkyleneNHCi-$_6$alkyl and Ci$_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

X^1 and X^2 are each independently selected from CR^{17} and N;

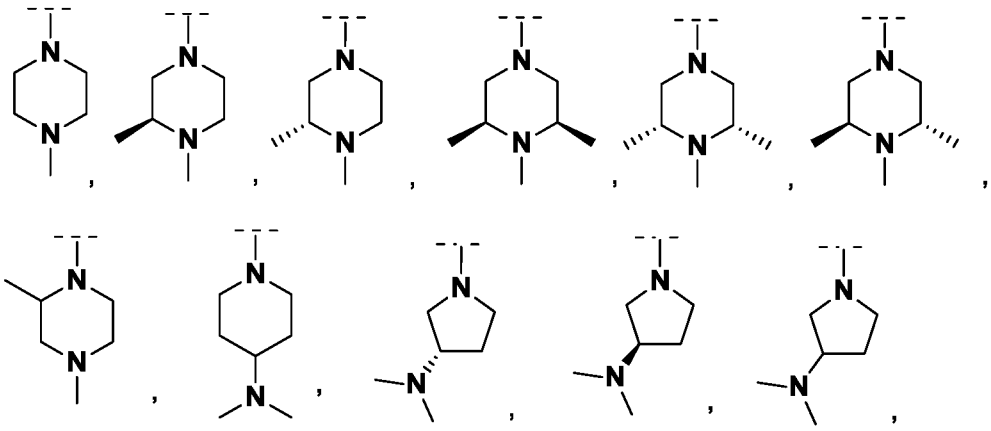
R^{17} is selected froniH, Ci-$_6$alkyl and Ci-$_6$fluoroalkyl;

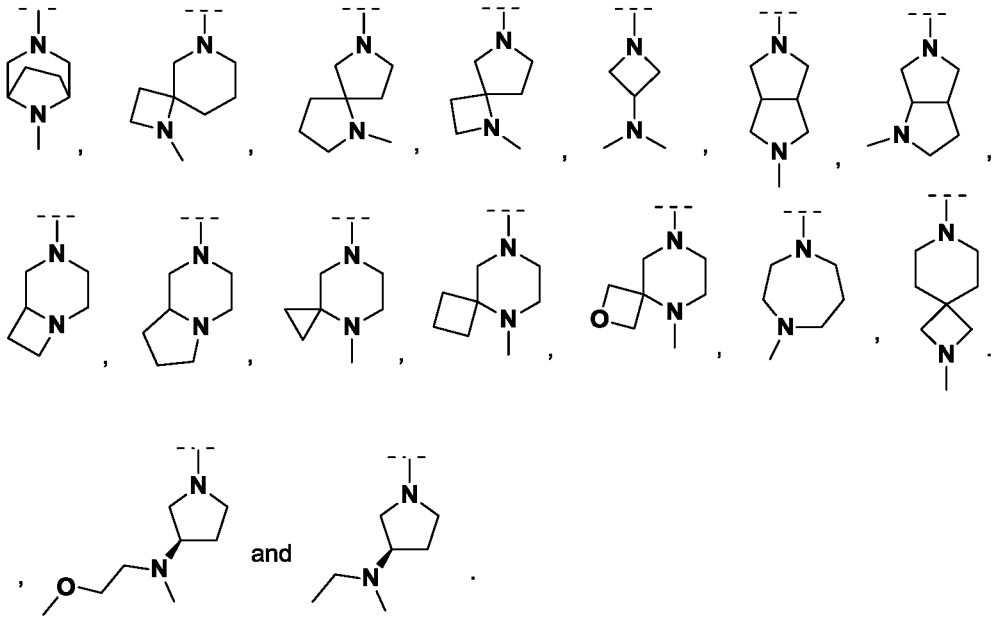
A is F; and

all alkyl and alkylene groups are optionally fluorosubstituted.

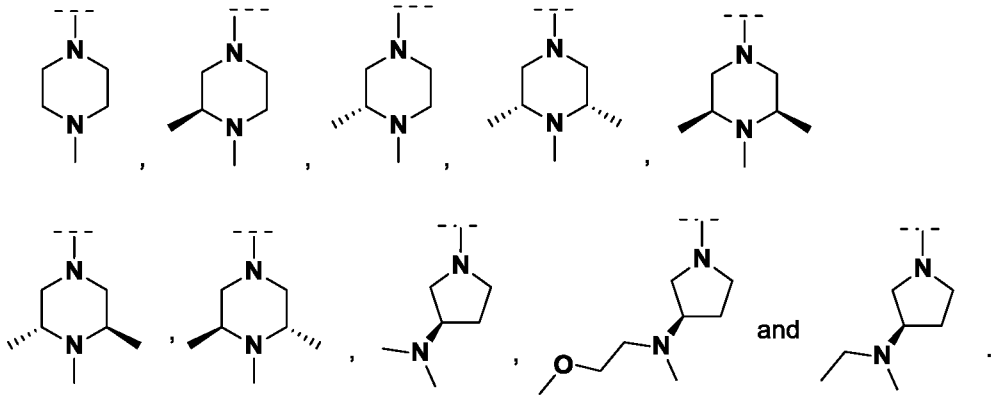
[0095] In some embodiments, R^1 is a heterocycloalkyl that is unsubstituted or substituted with one, two or three substituents selected from halo, Ci-$_6$alkyl, Ci_$_6$fluoroalkyl, NR^5R^6 and Ci-$_6$alkyleneNR^5R^6, provided that R^1 comprises at least one basic nitrogen atom. In some embodiments, R^1 is a heterocycloalkyl that is substituted with one or two substituents selected from halo, Ci-$_6$alkyl and NR^5R^6, provided that R^1 comprises at least one basic nitrogen atom. In some embodiments, R^1 is a heterocycloalkyl that is substituted with one or two substituents selected from Ci-$_6$alkyl and NR^5R^6, provided that R^1 comprises at least one basic nitrogen atom. In some embodiments, R^1 is a Cs-eheterocyclalkyl comprising one or two nitrogen atoms at least one of which is basic.

[0096] In some embodiments, R^1 is selected from:

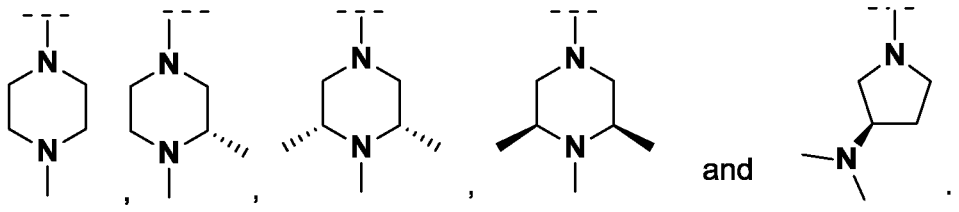




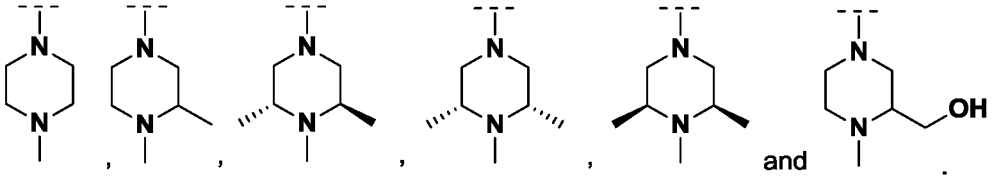
[0097] In some embodiments, R^1 is selected from:



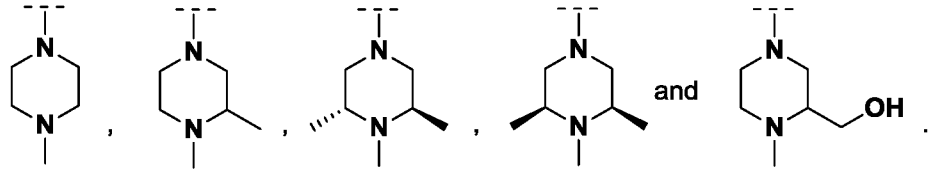
[0098] In some embodiments, R^1 is selected from:



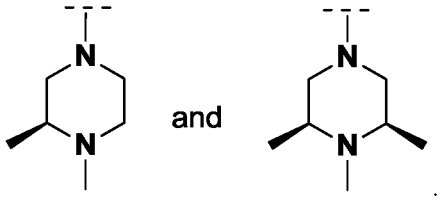
[0099] In some embodiments, R^1 is selected from:



[00100] In some embodiments, R^1 is selected from:

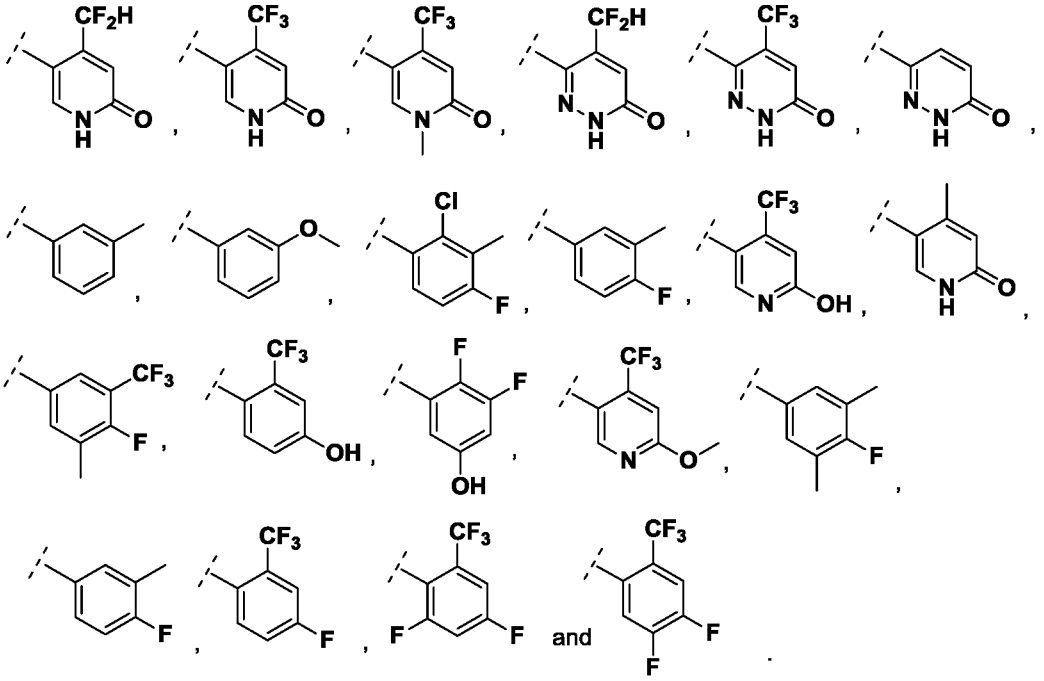


[00101] R^1 is selected from:

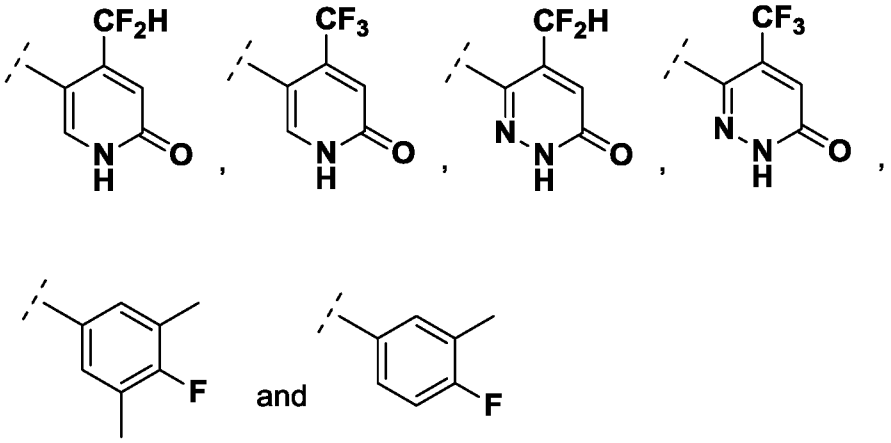


[00102] In some embodiments, R^2 is selected from C_6-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one, two or three substituents selected from halo, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, **=0,** OR^7, SR^7 and NR^8R^9. In some embodiments, R^2 is selected from $_{C\,6}$-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one, two or three substituents selected from halo, $Ci\text{-}_6$alkyl, $Ci\text{-}_6$fiuoroalkyl, **=0** and NR^8R^9. In some embodiments, R^2 is selected from $_{C\,6}$-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one or two substituents selected from halo, $Ci\text{-}_6$alkyl, $Ci\text{-}_6$fiuoroalkyl and **=0.** . In some embodiments, R^2 is selected from phenyl and C_6-heteroaryl, and R^2 is substituted with one to three substituents selected from F, CF_2H, CF_3 and **=0.**

[00103] In some embodiments, R^2 is selected from:

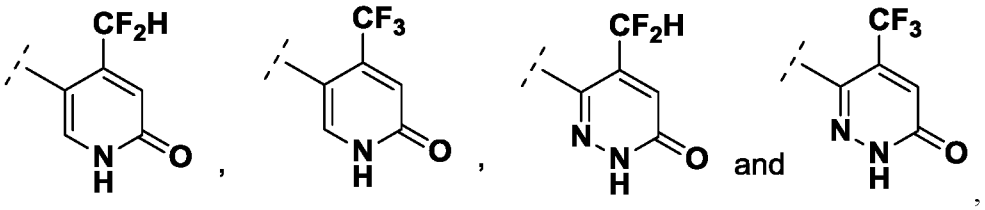


[00104] In some embodiments, R^2 is selected from

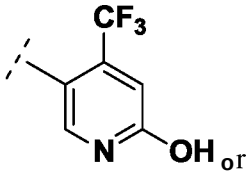
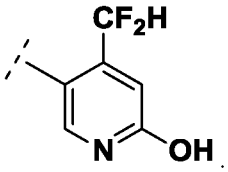


or a tautomer thereof.

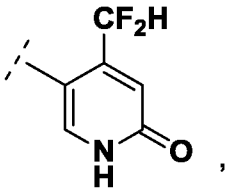
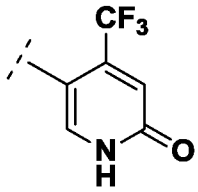
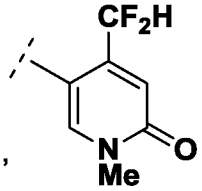
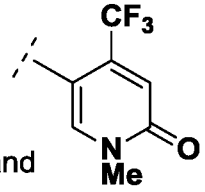
[00105] In some embodiments, R^2 is selected from:

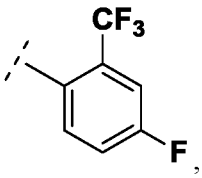


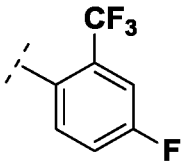
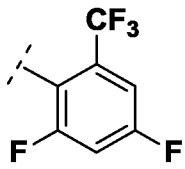
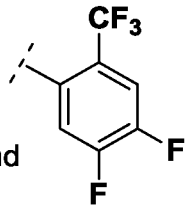
or a tautomer thereof.

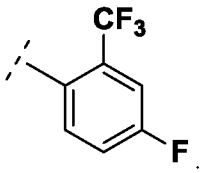
[00106] In an embodiment, the tautomer of the R^2 group is  or  .

[00107] In some embodiments, R^2 is selected from:

 ,  ,  and  , or a tautomer thereof.

[00108] In some embodiments, R^2 is selected from:  ,

 ,  and  .

[00109] In some embodiments, R^2 is  .

[00110] In some embodiments, R^3 is selected from C_{6}-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is substituted with one, two or three substituents selected from halo, CN, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, OR^{10}, $NR^{11}R^{12}$, R^{13}, Ci_{-6}alkyleneR^{13}, OCi. salkyleneR^{13}, Ci_{-6}alkyleneNR^{11}R^{12}, Ci_{-6}alkyleneOR^{10}, OCi_{-6}alkyleneNR^{11}R^{12}, OCi. salkyleneOR^{10}, C(0)OR^{10} and C(0)NR^{11}R^{12}. In some embodiments, R^3 is selected from C_{6}-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is substituted with one or two

substituents selected from halo, CN, Ci_6alkyl, Ci.6fluoroalkyl, OR^{10}, $NR^{11}R^{12}$, R^{13}, Ci_6alkyleneR 13, OCi_6alkyleneR 13, C_{1-6}alkyleneNR11R12, Ci_6alkyleneOR 10, OCi. salkyleneNR^R 12 and OCi_6alkyleneOR 10. In some embodiments, R^3 is selected from C 6-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is unsubstituted or substituted with one or two substituents selected from halo, CN, C_{1-6}alkyl, OR^{10}, $NR^{11}R^{12}$, R^{13} and OCi-6alkyleneR 13. In some embodiments, R^3 is heteroaryl, and R^3 is substituted with one substituent selected from halo, CN, Ci_6alkyl, OR^{10}, $NR^{11}R^{12}$, R^{13} and OCi. 6alkyleneR 13. In some embodiments, R^3 is heteroaryl, and R^3 is substituted with one substituent selected from R^{13}. In some embodiments, R^3 is phenyl. In some embodiments, R^3 is selected from monocyclic Cs-eheterocycloalkyl and monocyclic C_5. 6heteroaryl. In some embodiments, R^3 is selected from phenyl, pyrimidinyl, pyridinyl, dihydropyridine, dihydropyrrolyl, aziridinyl, oxiranyl, furanyl, thienyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl. In some embodiments, R^3 is selected from phenyl, pyridinyl, pyrimidinyl and dihydropyridinyl.

[00111] In some embodiments, R^5 and R^6 are independently selected from H, Ci_6alkyl and heterocycloalkyl. In some embodiments, R^5 and R^6 are independently selected from H and Ci-6alkyl. In some embodiments, R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one, two or three substituents selected from halo and Ci-6alkyl. In some embodiments, R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

[00112] In some embodiments, R^{10} is selected from H, Ci-6alkyl, Ci_ 6fiuoroalkyl, C(0)Ci- 6alkyl, C_3-iocycloalkyl, heterocycloalkyl, C 6-ioaryl, heteroaryl, Ci_ 6alkyleneC 3-iocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneheteroaryl and Ci_ 6alkyleneheterocycloalkyl. In some embodiments, R^{10} is selected from H, Ci-6alkyl, Ci_ 6fluoroalkyl, C_3_iocycloalkyl, heterocycloalkyl, Ci-ealkyleneCs-iocycloalkyl and Ci.

$_{6}$alkyleneheterocycloalkyl. In some embodiments, R^{10} is selected from H, **Ci**-$_{6}$alkyl, **Ci**-$_{6}$fluoroalkyl, heterocycloalkyl and **Ci**-$_{6}$alkyleneC $_{3}$-iocycloalkyl. In some embodiments, R^{10} is selected from **Ci**-$_{6}$alkyl and **Ci**-$_{6}$fluoroalkyl. In some embodiments, R^{10} is an unsubstituted or substituted monocyclic heterocycloalkyl selected from dihydropyridinyl, pyridinyl, pyrimidinyl, aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl In some embodiments, R^{10} is morpholinyl.

[00113] In some embodiments, R^{11} and R^{12} are each independently selected from H, **Ci**-ioalkyl, **Ci**-iofluoroalkyl, **C(0)Ci** -$_{6}$alkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, heteroaryl, $_{C\ 6}$-ioaryl, **Ci**-$_{6}$alkyleneC $_{3}$-iocycloalkyl, **Ci**-$_{6}$alkyleneC $_{6}$-ioaryl, **Ci**-$_{6}$alkyleneheteroaryl and **Ci**-$_{6}$alkyleneheterocycloalkyl. In some embodiments, R^{11} and R^{12} are each independently selected from H, **Ci**-ioalkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, **Ci**-$_{6}$alkyleneC $_{3}$-iocycloalkyl and **Ci**-$_{6}$alkyleneheterocycloalkyl. In some embodiments, R^{11} and R^{12} are each independently selected from H, **Ci**-ioalkyl and $_{C\ 3}$-iocycloalkyl. In some embodiments, R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

[00114] In some embodiments, R^{13} is selected from **C(0)Ci** -$_{6}$alkyl, $_{C3-}$ $_{1}$ocycloalkyl, heterocycloalkyl, heteroaryl and $_{C\ 6}$-ioaryl. In some embodiments, R^{13} is selected from $_{C\ 3}$-iocycloalkyl and heterocycloalkyl. In some embodiments, R^{13} is heterocycloalkyl. In some embodiments, R^{13} is an unsubstituted or substituted monocyclic heterocycloalkyl selected from aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl,

4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl. In some embodiments, R^{13} is morpholinyl.

[00115] In some embodiments, X^1 and X^2 are each independently selected from CR^{17} and N, in which R^{17} is selected from H and $Ci-_6$alkyl. In some embodiments, both of X^1 and X^2 are CR^{17}, in which R^{17} is H. In some embodiments, one of X^1 and X^2 is CR^{17} and the other of X^1 and X^2 is N, in which R^{17} is H.

[00116] In some embodiments, the compound of Formula I is selected from:

4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholin-4-ylpyrirnidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(6-morpholin-4-ylpyridin-3-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(l ,3-benzodioxol-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3R)-3,4-dimethylpiperazin-l-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(mfluoromethyl)-lH^yriine-3-carboxamide;

N-[2-[(3S)-3,4-dimethylpiperazin-l-yl]-4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(mfluoromethyl)-lH^yriine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrirmώn-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2^yrrolidin-l-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(mfluoromethyl)-lH^yriine-3-carboxamide;

N-[5-[2-(cyclohexylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-ethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-methylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclohexylamino)pyridin-3-yl]-4-fluoro-2-(4-me1hylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-hydroxypyrimidin-5-yl)-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[2-(2,2,2-trifluoroe1hoxy)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-pyrimidin-5-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,4-dime1hoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[2-[3-(dimethylamino)pyrrolidin-l-yl]-4-fluoro-5-(2-mo ϕ holin-4-ylpyrimiώn-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methylbenzamide;

6-acetamido-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin- 1-yl]phenyl] -4-(tafluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

N-[4-fluoIO-5-(4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(oxan-4-yloxy)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-3-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-me%lpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-pyridin-3-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5^yridin-4-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3R)-3-(dimethylamino)pyrrolidin- 1-yl] -4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3S)-3-(dimethylamino)pynOlidin^yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(dimethylamino)pyrimidin-5-yl] -4-fluoro-2-(4-methylpiperazin- 1-yl)phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(morpholin-4-ylmethyl)pyridin-3-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)-lH-pyrazole-4-carboxamide;

N-(2',6-difluoro-4-(4-methylpiperazin-1-yl)-5'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(3'-((cyclopentylamino)methyl)-6-fluoro-4-(4-methylpiperazin- 1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-mo rpholinopyridin-4-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(mo ϕ holinomethyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(((tetrahydro-2H-pyran-4-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

(R)-N-(4-fluoro-2-(4-methylpiperazin- 1-yl)-5-(5-(((tetrahydrofuran-3-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

(R)-N-(4-(3,4-dimethylpiperazin- 1-yl)-6-fluoro-3'-(moϕ holinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

(S)-N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

N-(6-fluoro-3'-(moϕ holinomethyl)-4-((3R,5 S)-3,4,5-trimethylpiperazin- 1-yl)-[1,Γ-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-(3-(dimethylamino)pyrrolidin- 1-yl)-6-fluoro-3'-(moϕ holinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-mo ϕ holin-4-ylpyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2<difluorome%l)-N-(5<2<(2S,6R)-2,6-dime%lmo rpholino)pyrimidin-5-yl)-2-((S)-3,4-dime1hylpiperazin-l-yl)-4-fluorophenyl)-4-fluorobenzamide;

N-[5-(l,3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-4-methoxy-6-oxo-1H-pyridine-3-carboxamide;

N-[5-[2-(cyclopropylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-[(cyclohexylamino)methyl]phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-cWoro-4-moϕ holin-4-ylphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[5-(3,4-dihydro-2H-l,5-benzodioxepin-7-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-l,4-benzodioxin-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-methyl-2,3-dihydro-l,4-benzoxazin-7-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-acetamidopyrimidin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-phenyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]benzamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-methoxybenzamide;

3,5-dichloro-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridazine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]furan-2-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyridin-4-yl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(3-mo ϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrirmdin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-methoxybenzamide;

2-c^lloro-4-fluoro-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

5-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrirnidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methoxybenzamide;

N-[4-fluoro-544<2-methoxyethoxy)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-chloro-6-(2-methylpropoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[3-chloro-4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yljphenyl] -3-(tafluoromethyl)- 1H-pyrazole-4-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

N-[5-(3-chloro-5-cyano-4-hydroxyphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-cyano-6-phenylmethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-cyanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-cyanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-

oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5,6-dime1hoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-1,3-benzodioxole-4-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-4-methoxybenzamide;

4-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(3-fluoro-5-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-chloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

2-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-methoxybenzamide;

3,4-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(4-methoxyphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-pyrrolidin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-acetanlido-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-

yl]phenyl]-l-methylindazole-3-carboxamide;

N-[4-fluoro-5-(4-moϕholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-1-methylindazole-3-carboxamide;

N-[4-fluoro-5434[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[3-[(4-fluoropiperidin-l-yl)methyl]phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-(3,4,6,7,9,9a-hexahydro-lH-pyrazino[2, 1-c][1,4]oxazin-8-yl)-4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methylpyrazole-4-carboxamide;

N-[4-fluoro-5-(4-moϕholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-1-methylpyrazole-4-carboxamide;

N-[5-(5-cyano-6-hydroxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-moϕholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3-carboxamide;

N-[5-[3-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3<dime%lamino)-N-[4-fluoro-5<2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-oxazole-4-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(4-moϕholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-

l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trime1hylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(6-cyanopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(6-cyano-5-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-methoxy-6-(trifluoromethyl)pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-methoxy-6-methylpyridin-4-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-cyano-N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxypyridine-3-carboxamide;

3-chloro-N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

2,6-dichloro-N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

3-chloro-2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

tert-butyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(trifluoromethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(tafluoromethoxy)phenyl] phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-phenyl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<4-cWorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(4-methoxyphenyl)methyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<6-me%lpyridazin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-methylpropyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(cyclopropylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin^-yl]-541<3,3,3-trifluoropropyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[(4-fluorophenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[4-fluoro-541-^yridin-3-ylme1hyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-541<thiophen-3-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazm-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-5-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

3.5-difluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmorpholin-4-yl]pyrirnidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]-541<l,3-tliiazol-2-ylme1hyl)-3.6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(2-methyl- 1,3-oxazol-5-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(1-methylpyrazol-4-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-

pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(4-moϕ holin-4-ylphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[[4-(4-methylpiperazin-l-yl)phenyl]methyl]-3,6-dihydro-2H-pyridin-4-yl]-24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(oxan-4-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3,5-dichloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]benzamide;

3,5-dichloro-N-[4-fluoro-5-(4-moϕ holin-4-ylphenyl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]benzamide;

N-[5-(5-cyano-6-moϕ holin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(5-methyl-6-morpholin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-lH-pyrrolo[2,3-b]pyridin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]-545<trifluoromethyl)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-(tert-butylcarbamoyl)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

3-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(4-mo ϕ holin-4-ylphenyl)-2-[(3R)-3-(dimethylan^ino)pyn·olidin-l-yljphenyl] -1H-pyrazole-4-carboxamide;

N-[4-fluoro-5-(5-methylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-carbamoylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-545<trifluoromethyl)pyridin-3-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-methyl-l,3-thiazole-2-carboxamide;

2-[(dimethylamino)methyl]-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -1,3-thiazole-4-carboxamide;

4-chloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -lH-pyrazole-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dime1hylamino)pyrrolidi^ - 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrirnidin-5^ -2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl] -3-(trifluoromethyl)- lH-pyrazole-4-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -3-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -4-(trifluoromethyl)- 1,3-thiazole-5 -carboxamide;

2-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

3-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-methoxybenzamide;

3,5-dichloro-N-[4-fluoro-5-(4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methylpyrazole-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-lH-pyrazole-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-4-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-5-carboxamide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-4-(trifluoromethyl)-l,3-thiazole-5-carboxamide;

3,5-dichloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2<4-me1hyl-l,4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoIO-5-(4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(5-cyanopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-chloropyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyclohexyloxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[2-(4-methoxyphenyl)acetyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2^yrrolidin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)thiophene-2-carboxamide;

3,5-dichloro-4-fluoro-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrin^idin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,3-dichloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[5-(5-ethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-

4-(difluoromethyl)- 1-methyl-6-oxopyridine-3 -carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)- 1-methyl-6-oxopyridine-3 -carboxamide;

N-[5-[6-(dimethylarrdno)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpipera^ in-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[545-cyano-6<dime%larnino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(dimethylamino)-5-fluoropyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-(5-chloro-6-mo ϕ holin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-[l,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

2<difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-((S)-2-methylmo ϕ holino)pyrimidin-5-yl)phenyl)-4-fluorobenzamide;

N-[4-fluoro-5 -(2-moϕ holin-4-ylpyrimidin-5 -yl)-2-(3,3,4-trimethylpiperazin- 1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyridin-4-yl)-24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5<4^yrrolidin-l-ylphenyl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fl^ oro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

2,3-difluoro-N-[4-fluoro-5<2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

2-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-(l-cyclopentyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[1-(4-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(l-butan-2-yl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-L· yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5^iperidin-4-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3-(dimethylarrino)pyrrolidin-l-yl] phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2^ropan-2-yloxypyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-[l,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-

carboxamide;

N-[4-fluoro-541<l-methylpiperidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2,2-dimethylpropanoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<l-pyrirnidin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(l-methylsulfonyl-2,5-dihydropyrrol-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3,5-dichloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

2-chloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluorobenzamide;

N-[5-(l-acetyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

ethyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

2-methylpropyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[5-[1-(3,3-dimethylbutanoyl)-3,6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-fluoropyridin-3-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[244-(dimethylamino)piperidin^^ -4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[4-[2-(dimethylan^ino)ethyl]piperazin-l-yl]-4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5 -yl)phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[2-[2-[(dimethylan^ino)methyl]mo rpholin-4-yl]-4-fluoro-5-(2-mo rpholi^ -4-ylpyrimidin-5 -yl)phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(6^yrrolidin-l-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-cyano-6-pyrrolidin-l-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,2-difluoro-l,3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-4-azetidin-N-[4-azetidin-5-(2-oxo-1H-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-methoxybenzamide;

3-chloro-2,4-diazetidin-N-[4-azetidin-5-(2-oxo-1H-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-(6-cyano-4-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(1-pyridin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(5-methylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-(5-chloropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

ethyl 2-[4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridin-l-yl]pyrimidine-4-carboxylate;

N-[4-fluoro-2-[3-(methylan^ino)pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[3-[(dimethylamino)methyl]pyrrolidin- 1-yl]-4-fluoro-5-(2-mc^holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3-hydroxy-5-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-3-hydroxybenzamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-3-hydroxyquinoline-4-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dime1hylamino)pyrroliώn-1-yl]phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[5-[l-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(pyrrolidine-l-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(4-methylpiperazine- 1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-

[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

phenyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-5-[l-[(2R,6S)-2,6-dimethyloxan-4-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-hydroxy-2-(trifluoromethyl)benzamide;

2,3-difluoro-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-hydroxybenzamide;

N-[5-[2-(cyclobutylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylpropoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(diethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpipera^ n-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

3-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

3,4,5-trifluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

2-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-6-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-

dimethylpiperazin- 1-yl] phenyl] -2-(trifluoromethyl)benzamide;

3,5-dichloro-N-[4-fluoro-2-[3-(methylamino)pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl] benzamide;

N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl] phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[4-(4-methylpiperazin-l-yl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

3,5-dichloro-N-[4-fluoro-2-[3-[methyl (propyl)amino]pyn·olidin-l-yl]-5-(2-mo rpholin-4-ylpyrimidin-5-yl)phenyl]benzamide;

N-[5-[l-[2-(dime%lamino)acetyl]-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-[4-[5-[2-fluoro-5-[[6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]pyrimidin-2-yl]piperazin-l-yl]-4-oxobutanoic acid;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-(dime1hylan^ino)-4-fluoropyrrolidin- 1-yl] phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,4R)-3-(dime1hylamino)-4-fluoropyrrolidin- 1-yl] phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-2-mo ϕ holin-4-yl-5-(2-piperazin-l-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-(dime1hylan^ino)-4-fluoropyrrolidin- 1-yl] phenyl] -6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,4R)-3-(dime1hylamino)-

4-fluoropyn olidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

tert-butyl 4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-4-(difluoromethyl)-6-oxo- 1H-pyridine-3-carboxamide;

l-ethyl-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

2,3-dichloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-2-[(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-(2,2,6,6-tetramethylmo ϕ holin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[2-(2,2,6,6-tetramethylmo rpholin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)-lH-pyrazole-3-carboxamide;

tert-butyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carbonyl]amino]-4-[(3R,5 S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carbonyl]amino]-4-

[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate;

tert-butyl 5-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]armno]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-ihydro-2H - pyridine- 1-carboxylate;

tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin^-yl]-5<l,2,3,64etrahydropyridin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carboxarnide;

N-[5<2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carboxarnide;

N-[5<8-azabicyclo[32J]oct-2-en-3-yl)-4-fluoro-24(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

4<difluorome%l)-N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-6-oxo- 1H-pyridine-3-carboxamide;

N-[5<2-butan-2-yloxypyriin-4-yl)-4-fluoro-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyriine-3-carboxarnide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrirniώn-5-yl)-24(3R,4R)-3<dime%lan^ino)-4-methoxypyrrolidin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(l-pyrirnidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-pyrimidin-2-yl-2,5-dihydropyrrol-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<8-pyrirnidin-2-yl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluo ro-2-[(3R)-3,4-dimethylpipe Γazin-l-yl]-5-[2-[(3R)-3-methylmo ϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide;

N-[4-fluoro-5-[2-[(3R)-3-methylmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-yl4,4,5,64etrahydropyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmo ϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl] phenyl] - 1-methyl-6-oxopyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(lR,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-24(3R,4R)-34e%l(me%l)an^ino]-4-fluoropyn olidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[e1hyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-

3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-24(3R,4R)-34e%l(me%l)amino]-4-fluoropyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-24(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-[(2R)-2-propan-2-ylmo ϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R)-2-propan-2-ylmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylmo ϕ holin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-7-(trifluoromethyl)-[l,2,4]triazolo[4,3-a]pyridine-6-carboxamide;

N-[5-[2-(7-azabicyclo[2.2.1]heptan-7-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluorθ-5-(3-fluorθ-4^ oφHo 1iη-4^1 ph^1)-2-[(3 R,5R)-3,4,5-rimethy1piperaζiη-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5<2-moφ holin-4-ylpyrimidin-5-yl)-24(3R,4R)-34e%l(me%l)an^ino]-4-methoxypyrrolidin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmorpholin-4-yl]pyrirnidin-5-yl]-2-[(3S,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424me%l-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[me%l-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo φ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,5-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-fluoropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[1-(4,6-dimethylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[methyl(oxan-4-yl)amino]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[methyl(oxan-4-yl)amino]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541<dime%lcarbamoyl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

ethyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-5-[l-(pyrrolidine-l-carbonyl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-me%lpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fluoropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[2<4-me%lpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[542<dime%lamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]pyrimidin-5 -yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-me1hylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridazin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-

yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<l^yrirnidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 - carboxamide;

N-[4-fluoro-5-[4-[(4-fluorophenyl)methyl]piperazin-l-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-pyr midin-2-ylpiperazin-1-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylnK^holin-4-yl] pyrimidin-5 -yl]phenyl] -6-oxo- lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmo ϕ holin-4-yl] pyrimidin-5 -yl]phenyl] -6-oxo- lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-methylsulfonylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-methyl-l,4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-(difluoromethyl)-N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxamide;

N-[5-[l-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl^ -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(mo ϕ holin-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-methylpropyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(Muo Гѳmethyl)-N-[4-fluo ro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxarnide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxarnide;

N-[4-fluoro-5-[l-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-

[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-[5-[(dimethylarrino)methyl]pyri midin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N -[4-fluorθ-5-[1-[5-^ oφ holίη-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2^ -pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3S)-3<dime%lamino)pyrrolidin-l-yl]-5-[2-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[^[(21^6S)-2,6-dinie%lmor^ olin-4-yl]pyrimidin-5-yl]-2-[(3S)-3-[ethyl(methyl)amino]pyrrolidin-l-yl]ph^ nyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo φ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo φ holin-4-ylpyrin^idin-5-yl)-2-[(3R)-3-[methyl(propan-2-y^aminolpyn-olidin-l-ylJphenylJ -e-oxo^-^rifluoromethy^-lH-pyridine-S-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo φ holin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo φ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo φ holin-4-yl]pyridin-3-yl]-2-[(3R)-

3,4-dime1hylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-542<4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-542<4½droxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3S)-3<dime%lamino)pyrrolidin-l-yl]-5-[2-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyrin^idin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3S)-3-[ethyl(methyl)amino] pyrrolidin- 1-yljphenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyr midin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-5-yl)-2-[(3R)-3-[methyl(propan-2-y^aminolpyn-olidin-l-yllphenyll-l-methyl -e-oxo^-^fluoromethy^pyridine-S-carboxamide;

4-fluoro-N-[4-fluoro-5 -[24(2R,6S)-2,6-dime%lmoϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5 -[24(2R,6S)-2,6-dime%lmoϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluorome1hyl)benzamide;

4-fluoro-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluorome1hyl)benzamide;

N-[4-fluoro -24(3R)-3,4-dime%lpiperazin-l-yl]-5-[6-[(2R)-2-methylmoϕ holin-4-yl]pyridin-3 -yl]phenyl] -6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[4-fluoro-541<5-methoxypyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-me%lpyrirnidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fluoropyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(pyrrolidine-l-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(pyrazine-2-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-methylpropyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylpyrazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<4-cyano-l,3-thiazol-2-yl)-4-fluoro -24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<5-cyano-l,3-thiazol-2-yl)-4-fluoro -24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxopyridine-3 -carboxamide;

N-[4-fluoro -24(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmo ϕ holin-4-yl] pyrimidin-5 -yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-[(2R)-2-me1hylmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[l-[5-[(dimethylaniino)methyl]pyrirnidin-2-yl]-2,5-dihydropyn -ol-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[5-(mo ϕ holin-4-ylmethyl)pyrimidin-2-yl] -2,5-dihydropyrrol-3-yl] -2-

[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmc^holin-4-yl] pyrimidin-5-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-piperazin- 1-ylpyrirnidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxarnide;

4-fluoro-N-[4-fluoro-5-[2-(4^ropan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)berizarnide;

N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmo rpholin-4-yl]pyrirmdin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxainide;

N-[4-fluoro-5-[2-[(3R)-3-methylmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(1-methylcyclobutyl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(1-methylcyclobutyl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyriώn-2-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyrazin-2-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(3R)-3-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-l-propyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-l-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,4,5-tetramethylpiperazin-4-ium-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl] pyrimidin-5 -yl]phenyl] - 1-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-4-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-4-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-4-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-4-carboxamide;

N-[4-fluoro-5-[4-(moϕ holine-4-carbonyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-544<4-me%lpiperazine-l-carbonyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(3-methyloxetan-3-yl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

(3-methyloxetan-3-yl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

(3-methyloxetan-3-yl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-2-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-3-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-5-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-5-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-5-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(tafluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-5-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]arruno]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,^-thiazole-5-carboxamide;

N-[4-fluoro-5-[5-(morpholine-4-carbonyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH^yridine-3-

carboxamide;

N-[4-fluoro-545<4-me%lpiperazine-l-carbonyl)4,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

5-amino-4-fluoro-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[l-(6-cyclopropylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(6-ethylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-6-oxo-lH ϕ yridine-3-carboxan^ide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-6-oxo-lH ϕ yridine-3-carboxan^ide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

5-amino-4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-l-ethyl-2,3,3a,4,6,6a-hexahydropyn-oloP^-cJpyrrol-S-ylJphenylJ -e-oxo^-^fluoromethy^-lH-pyridine-S-carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl] -2-[(3 S)-3,4-dimethylpiperazin- 1-yl] phenyl] -6-oxo- lH-pyridine-3 -carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-l-me1hyl-6-oxopyridine-3-carboxan^ide;

4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-l-me1hyl-6-oxopyridine-3-carboxan^ide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(2,2,2-trifluoroethyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(3R)-3-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxarnide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-

carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-[4-fluoro-5-[2-(moϕ holine-4-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-542<4-me%lpiperazine-l-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(6-piperazin-l-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-

thiazole-2-carboxamide;

N-[4-fluoro-5-[2-(mo ϕ holine-4-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-542<4-me%lpiperazine-l-carbonyl)4,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(cyclohexylamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(methylamino)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiper^ n-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[5-(2-cyanopyrimidin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[542<dime%lamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[4-(methylamino)piperidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro -24(3S)-3,4-dimethylpiper^-1-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide ;

4-fluoro-N-[4-fluoro-5-[24(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(6-piperazin-l-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

2-fluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

2-fluoro-5-[2-fluoro-54[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[5-[2-(4-tert-butylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-[4-(cyclopropylmethyl)piperazin-l-yl]pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[2-(4-cyclopropylpiperazin-l-yl)-4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(5-fluoro-6-oxo-lH-pyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3 -carboxamide;

benzyl N-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]pyridin-3-yl]carbamate;

N-[4-fluoro-5-(5-fluoro-l-methyl-6-oxopyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(4-methoxybenzoyl)-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5 S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-oxo-l,3-dihydropyrrolo[2,3-b]pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<l-me%l-2-oxopyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methyl-6-oxopyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541<cyclohexanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

tert-butylN-[l-[2-[(3,5-dicWorobenzoyl)amino]-5-fluoro-4-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl]pyrrolidin-3 -yl] -N-methylcarbamate;

3,5-dichloro-N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l-yl]-5-(2-moϕ holin-4-ylpyrimidin-5-yl)phenyl]benzan^ide;

N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(pyrazine-2-carbonyl)-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5 S)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-methoxy-4-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] - 1-methyl -6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] - 1-methyl -6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(6-methylsulfonylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(methanesulfonamido)pyrirnidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylsulfonyl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(5-cyanopyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-543-fluoro-4<methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-544-fluoro-3<methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-moϕ holin-4-ylpyrimidin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

propan-2-yl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

propan-2-yl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl] pyrimidin-5 -yl]phenyl] - 1-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dime%lpiper^ -1-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxami de;

N-[4-fluoro-5-(6-fluoropyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-(trifluoromethyl)pyridin-2-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5 -[24(2R)-2-me%lmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

4-(Difluoromethyl)-N-(4-fluoro-5 -(1 -(pyrrolidine- 1-carbonyl)-2,5 -dihydro- 1H-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-me1hylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dime1hylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)berizarnide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorornethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-t^liazol-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-t^liazol-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(Muo Гomethyl)-N-[4-fluo ro-5-(2-mo ϕ holin-4-yl-l,3-1hiazol-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-(Muo Гomethyl)-N-[4-fluo ro-5-(2-mo ϕ holin-4-yl-l,3-1hiazol-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(ta^uoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

N-[542,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[5-[2,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo- 1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylrtK^holin-4-yl] pyrimidin-5 -yl]phenyl]-6-oxo- lH-pyridine-3-carboxamide

(S)-4-(Sifluoromethyl)-N-(2-(3,4-dimethylp^ razin-1-yl)-4-fluoro-5-(1-(pyrrolidine-1-carbonyl)-2,5-dihydro- lH-pyrrol-3-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

1-Methylcyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-2,5-dihydro-lH-pyrrole-1 -carboxylate;

1-Methylcyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-

carboxamido)-4-(3,4-dimethylpiperazin-l-yl)-2-fluorophenyl)-2,5-dihydro-lH-pyrrole- 1-carboxylate;

N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trime1hylpiperazin-1-yl]phenyl] -4-(difluoromethyl)-6-oxo- 1H-pyridine-3-carboxamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-me1hylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluorome1hyl)benzamide;

3,3-Difluorocyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-2,5-dihydro-lH-pyrrole-1 -carboxylate;

3,3-Difluorocyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-l-yl)-2-fluorophenyl)-2,5-dihydro-lH-pyrrole- 1-carboxylate;

(S)-N-(5-(l-(2-cyanopyrimidin-5-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[5-[l-(4-cyano-l,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[4-fluoro-5-[l-(l,3-oxazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-tamethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide

4-(difluoromethyl)-N-[4-fluoro-5-(l-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2 -[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-541<5-fonnylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

ethyl 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

4-fluoro-N-[4-fluoro-5-(l-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2<difluorome%l)-4-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrin^idin-5-yl)-2-[(3R)-

3,4-dimethylpiperazin-1-yl]phenyl]benzamide;

2<difluorome%l)-4-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrin^idin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide;

2,6-difluoro-442-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,6-difluoro-442-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmoϕ holin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,3-difluoro-442-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-[2,3-Muoro-4-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-2,3-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate;

N-[4-fluoro-5-(l-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-5-(l-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[5<l,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5<l,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5<l,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[541-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[1-(5-cyano-1,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(tafluoromethyl)benzamide;

N-[5-[1-(5-cyano-1,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(tafluoromethyl)benzamide;

N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-

1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmo rpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(oxan-4-yloxy)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyrimidin-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-

2H-pyridine- 1-carboxylate;

(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]arruno]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin- 1-yljphenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

(3,3-difluorocyclobutyl) 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)berizoyl]arnino]-4-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

(3,3-difluorocyclobutyl) 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)berizoyl]arnino]-4-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-4-(difluoromethyl)-6-oxo- lH-pyridine-3 -carboxamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclohexylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[(2,2-dimethylcyclohexyl)carbamoyl]-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(mo ϕ holin-4-ylmethyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-mo ϕ holin-4-ylethyl)pyrazol-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[l-(2-mo ϕ holin-4-ylethyl)pyrazol-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-mo ϕ holin-4-ylethyl)pyrazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorornethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(2-mo ϕ holin-4-yle1hyl)pyrazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

4-(difluorome%l)-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrin^idin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzarnide;

propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]arnino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate;

propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]arnino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl] -4-fluoro-2-[(3R,5 S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclohexylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[cyclopropylmethyl(methyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[(4,4-difluorocyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[24(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yljphenyl]-2-(trifluoromethyl)benzamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4-((1iAυoΓoηethy1)-N-[4-fluoΓθ-5-[4-(ηιoϕ ho1iη-4^1η6%1)-1,3-thiaζo1-2^1]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(6-piperazin-l-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[5-[4-[(2,2-dimethylcyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-((lii1υoΓoηethy1)-N-[4-fluoΓθ-5-[5-(ηιoϕ ho1iη-4^1η6%1)-1,3-thiaζo1-2^1]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-(ώ ΑυοΓοηethyl)-N-[4-fluoΙθ-5-[2-(ηιοφ 1ho1iη-4^1η16%1)-1,3-i1iaζo1-4^1]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoΙθ-5-[4-(ηιοφ 1ho1iη-4^1η16%1)-1,3-thiaζo1-2^1]-2-[(3R,58)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoΙθ-5-[5-(ηιοφ 1ho1iη-4^1η16%1)-1,3-thiaζo1-2^1]-2-[(3R,58)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2<difluorome%l)-N-(5<2<(2S,6R)-2,6-dime%lmo rpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluorobenzamide;

2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((S)-2-methylmoφ holino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)benzamide; and

2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmoφ holino)pyr imidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)benzamide,

3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide;

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;

(S)-3-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-moφ holinopyrimidin-4-yl)phenyl)-5-fluoropicolinamide;

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmo rpholino)pyrimidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;

3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide;

N-(4'-(cyclohexyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)- [1,1'-biphenyl] -3-yl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

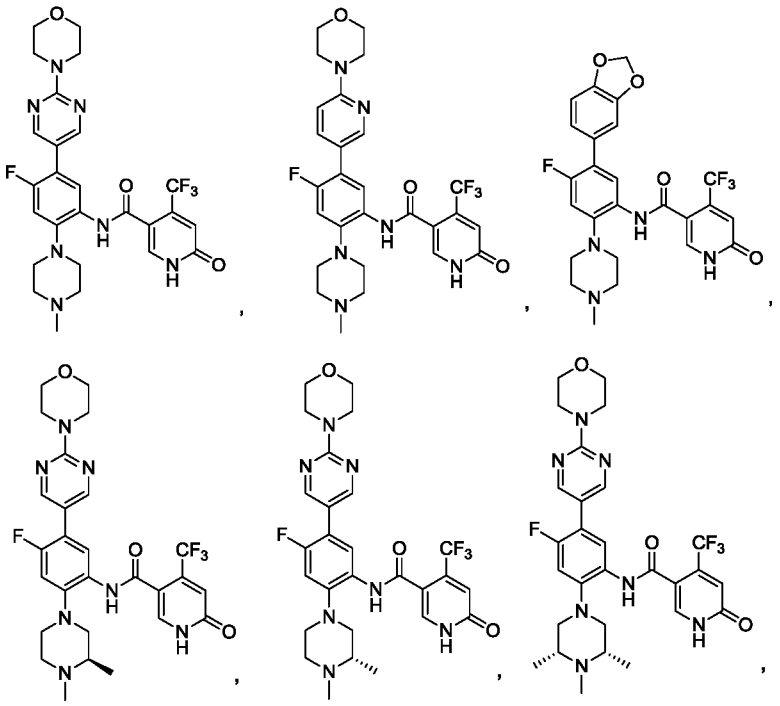
N-(4'-(cyclopentyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)- [1,1'-biphenyl] -3-yl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

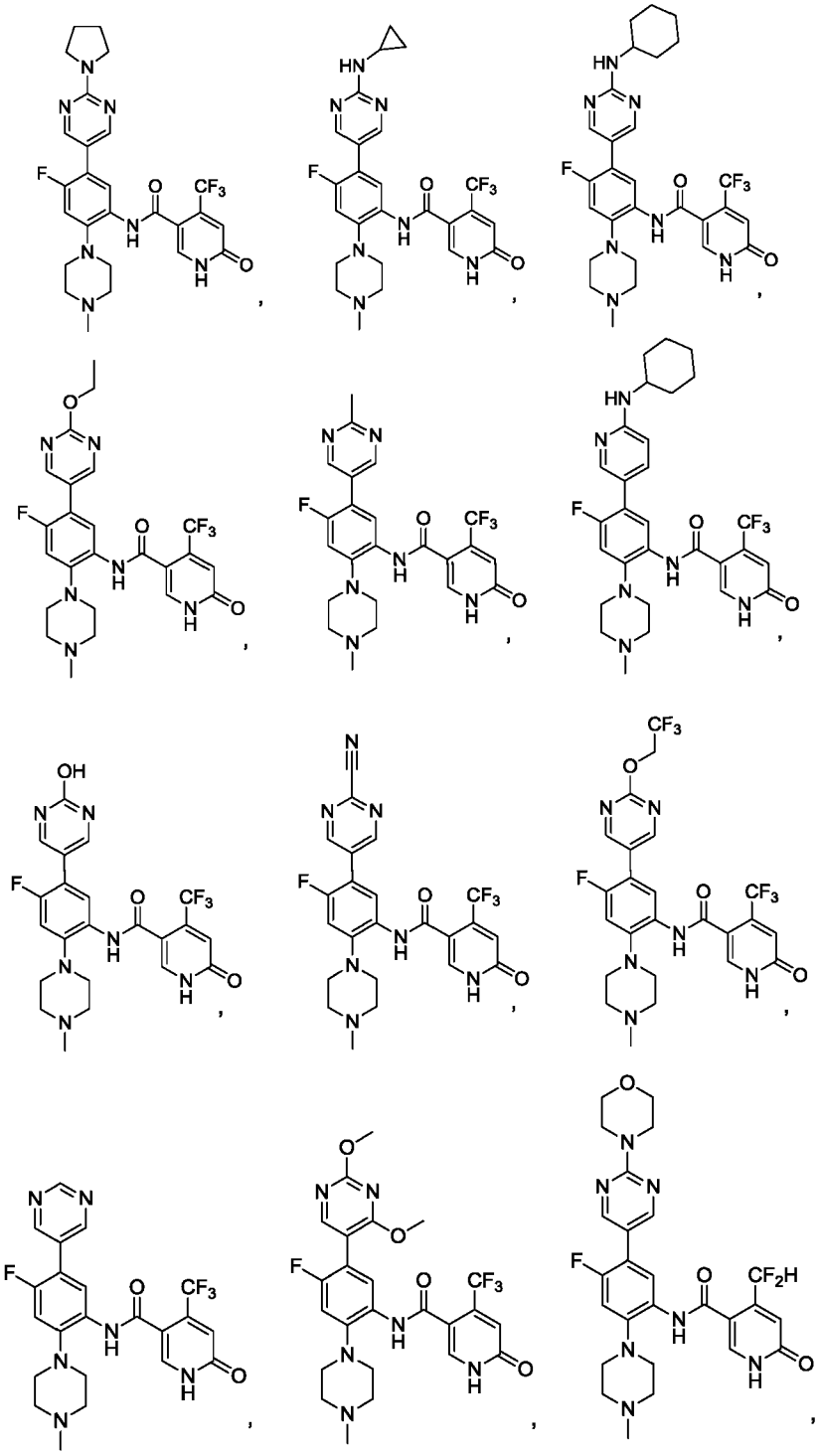
6-oxo-N-(3',5',6-trifluoro-4'-(((R)-tetrahydrofuran-3-yl)carbamoyl)-4-((3S,5R)-3,4,5 -trimethylpiperazin- 1-yl)-[1,1'-biphenyl] -3-yl)-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

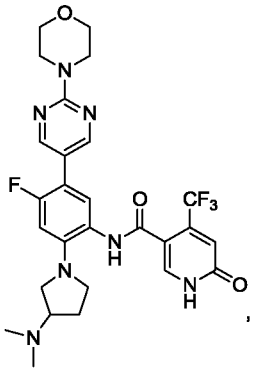
3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide; and

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

[00117] In some embodiments, the compound of Formula I is selected from,:



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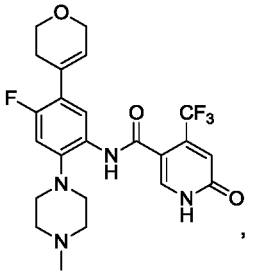
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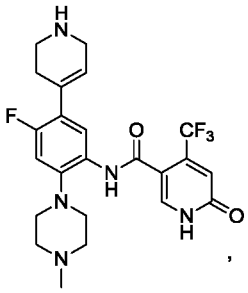
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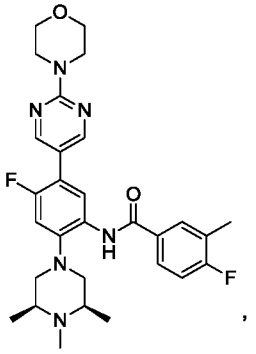
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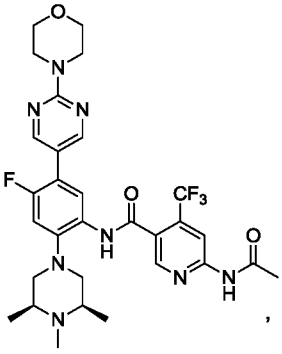
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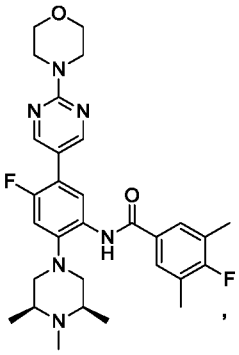
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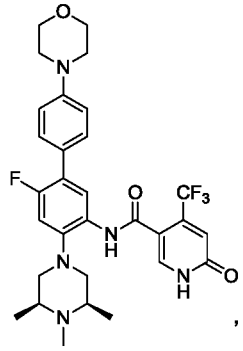
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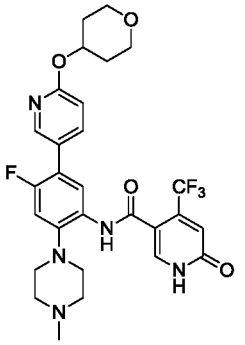
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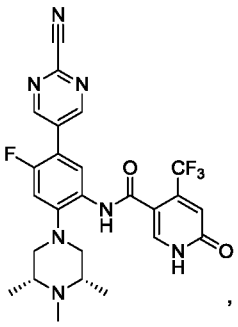
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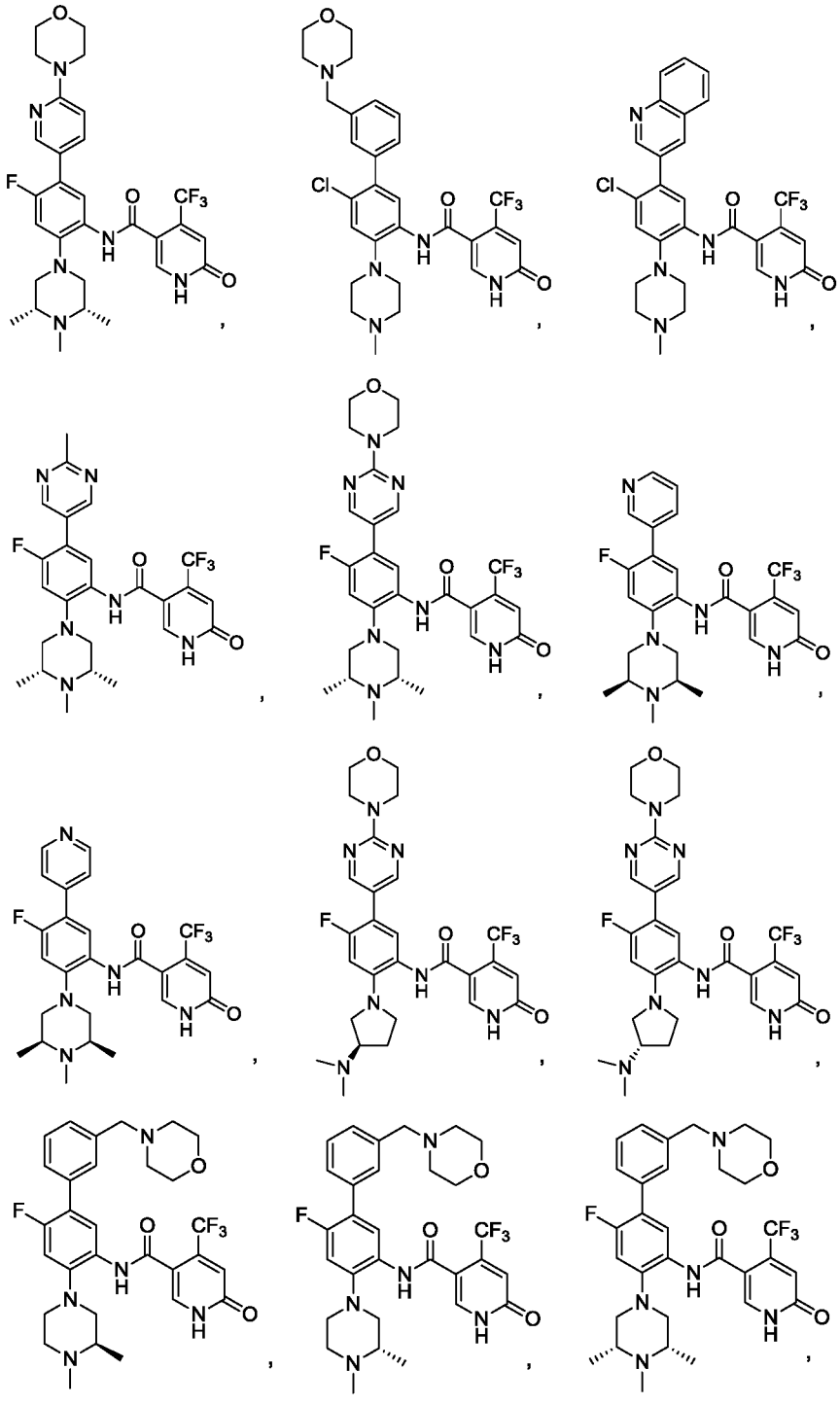

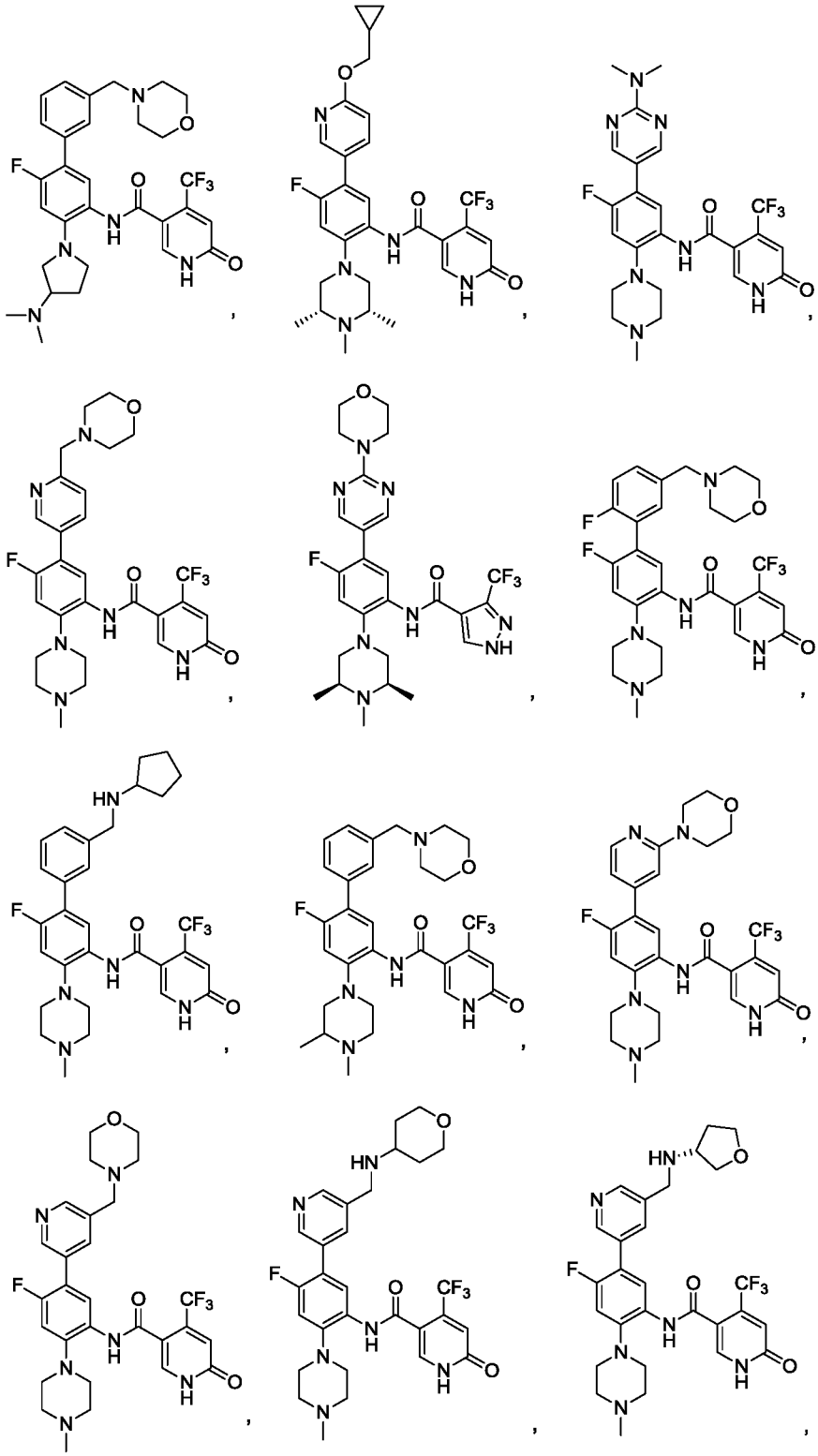

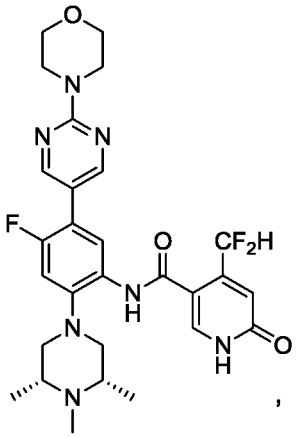
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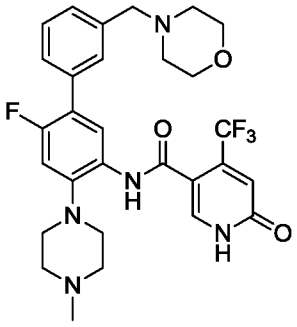
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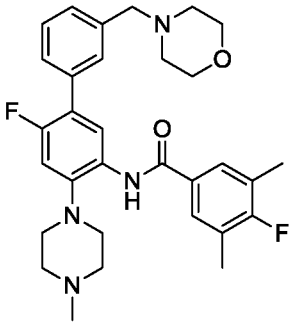
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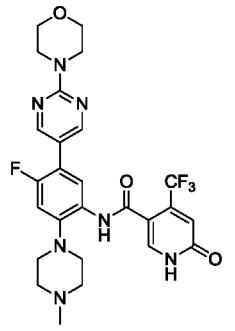
or a pharmaceutically acceptable salt and/or solvate thereof

[00118] In some embodiments, the compound of Formula I is selected from,: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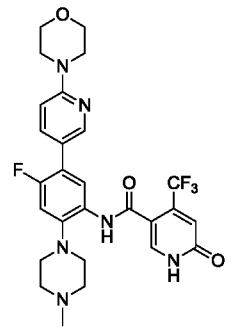
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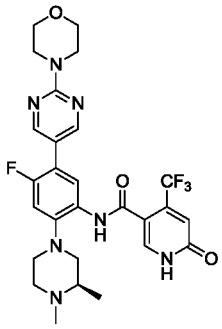
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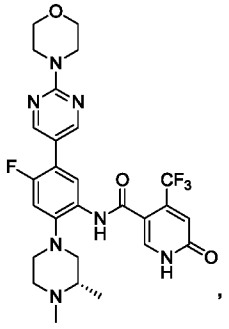
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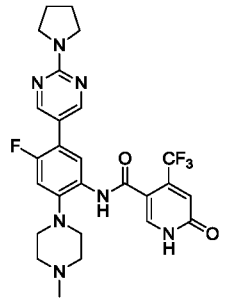
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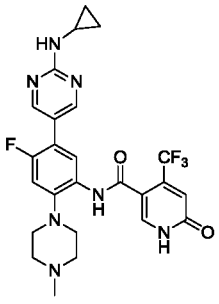
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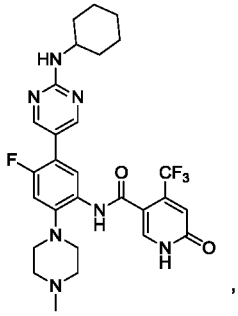
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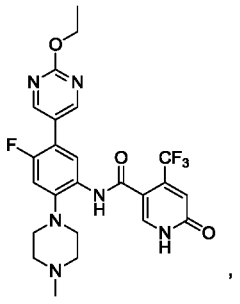
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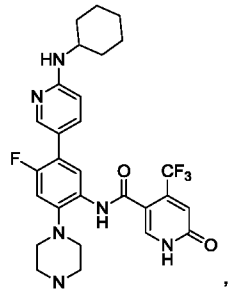
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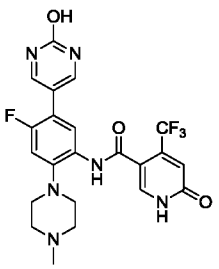
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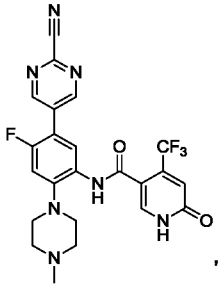
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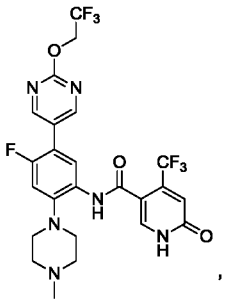
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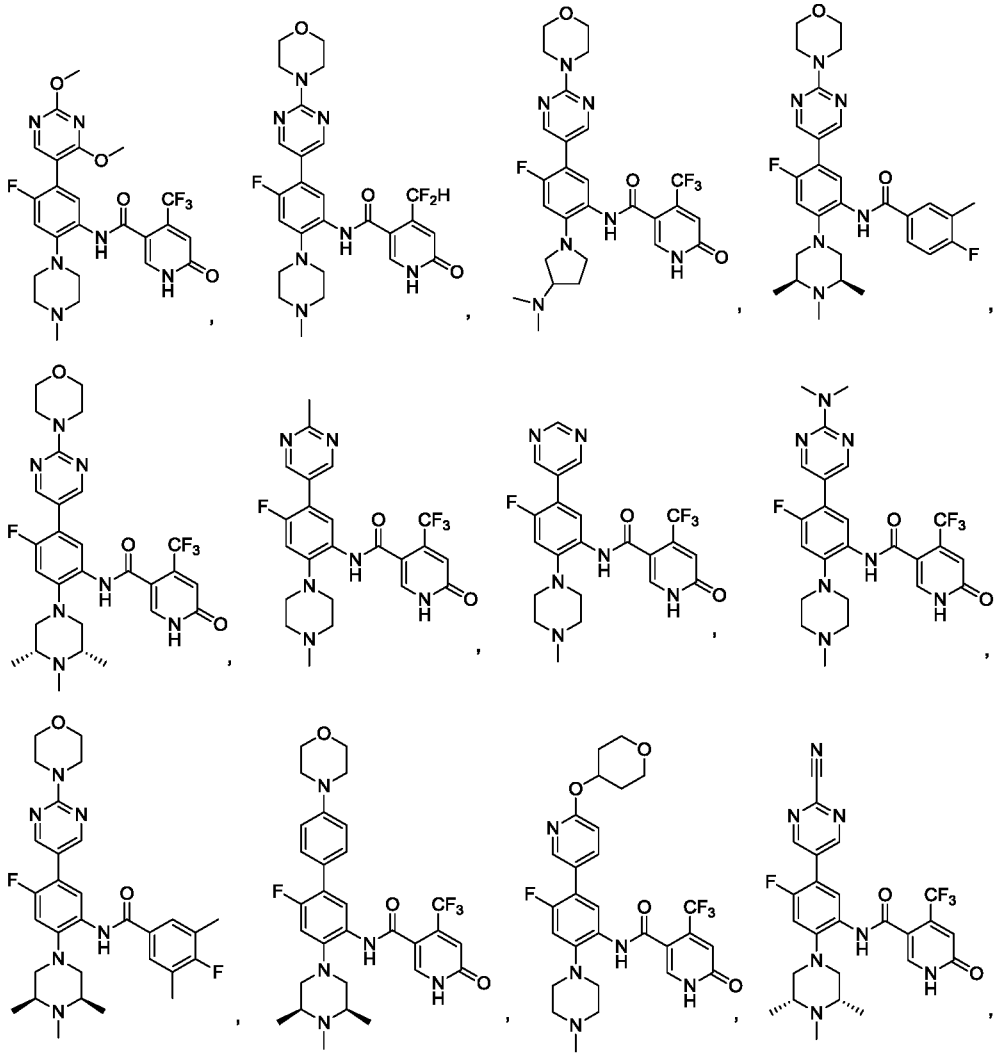
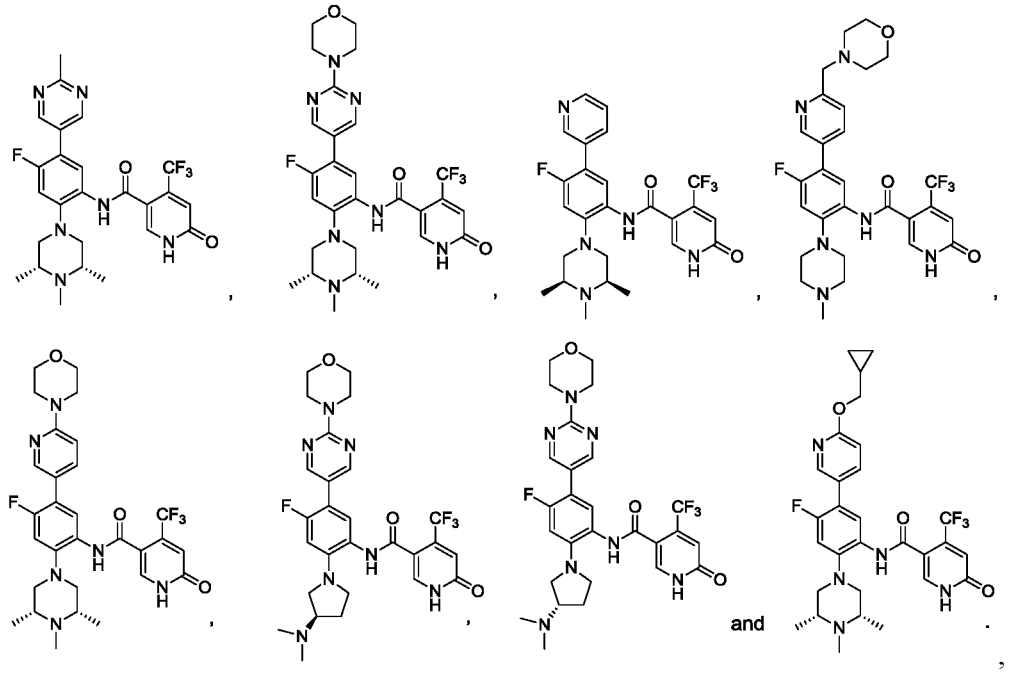
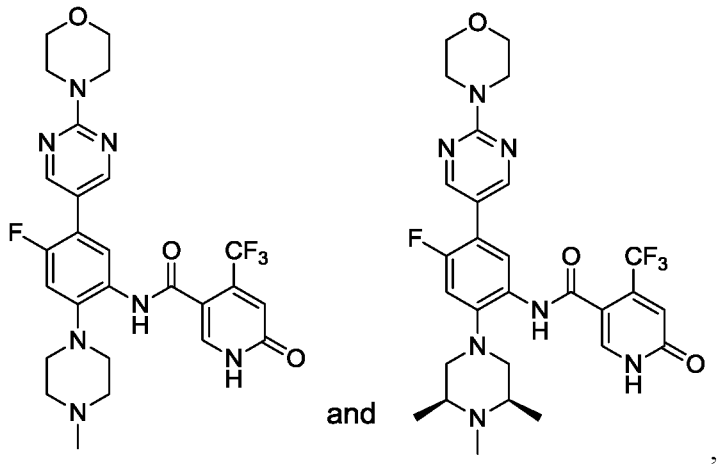


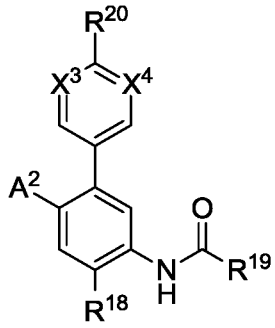


or a pharmaceutically acceptable salt and/or solvate thereof.

[00119] In some embodiments, the compound of Formula I is selected from, a pharmaceutically acceptable salt and/or solvate thereof:



[00120] The present application also includes a compound of Formula (la) or a pharmaceutically acceptable salt and/or solvate thereof:



(Ia)

wherein:

R^{18} is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, C_{3-}iocycloalkyl, OR^{21}, SR^{21}, $NR^{22}R^{23}$, Ci-galkyleneOR^{21}, Ci_{-6}alkyleneSR^{21} and Ci_{-6}alkyleneNR^{22}R^{23}, provided that R^{18} comprises at least one basic nitrogen atom;;

R^{19} is selected from $_{C\,6}$-ioaryl and heteroaryl, and R^{19} is unsubstituted or substituted with one or more substituents selected from halo, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, =0, =S, OR^{24}, SR^{24} and $NR^{25}R^{26}$;

R^{20} is selected from H, halo, CN, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, OR^{27}, SR^{27}, $S0_2R^{27}$, $NR^{28}R^{29}$, R^{30}, Ci_{-6}alkyleneR^{30}, Ci_{-6}alkenyleneR^{30}, OCi_{-6}alkyleneR^{30}, SCi_{-6}alkyleneR^{30}, Ci_{-6}alkyleneNR^{28}R^{29}, Ci_{-6}alkyleneOR^{27}, Ci_{-6}alkyleneSR^{27}, OCi_{-6}alkyleneNR^{28}R^{29}, SCi_{-6}alkyleneNR^{28}R^{29}, OCi_{-6}alkyleneOR^{27}, SCi_{-6}alkyleneOR^{27}, OCi_{-6}alkyleneSR^{27}, SCi_{-6}alkyleneSR^{27}, C(0)OR ^{27}, C(S)OR^{27}, C(S)NR^{28}R^{29} and C(0)NR ^{28}R^{29};

R^{21} is selected from H, Ci_{-6}alkyl Ci_{-6}fluoroalkyl, C(0)Ci_{-6}alkyl and C(0)Ci_{-6}fluoroalkyl;

R^{22} and R^{23} are independently selected from H, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, heterocycloalkyl, C(0)Ci_{-6}alkyl, C(0)Ci_{-6}fluoroalkyl, C(0)OCi_{-6}alkyl, C(0)NHCi_{-6}alkyl, $S0_2Ci_{-6}$alkyl, $S0_2HNCi_{-6}$alkyl, Ci_{-6}alkyleneOCi_{-6}alkyl, Ci_{-6}alkyleneC$_{6}$-ioaryl, Ci_{-6}alkyleneheteroaryl, Ci_{-6}alkyleneheterocycloalkyl and Ci_{-6}alkyleneC$_{3-6}$cycloalkyl, or R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, OH, Ci_{-6}alkyl OCi_{-6}alkyl, Ci_{-6}fiuoroalkyl, OCi-sfiuoroalkyl, C(0)Ci_{-6}alkyl, C(0)Ci_{-6}fluoroalkyl, C(0)Ci_{-6}alkyl, C(0)NHCi_{-6}alkyl,

S0 2Ci-6alkyl, S0 2HNCi -6alkyl, Ci.6alkyleneOCi -6alkyl, Ci-ealkyleneCe-ioaryl, Ci.6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl and Ci-6alkyleneC 3-6cycloalkyl;

R24 is selected froniH, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci- 6alkyl;

R25 and R26 are independently selected from H, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci_6alkyl, or R25 and R26 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, CN, Ci-6alkyl OCi-6alkyl, Ci-6fiuoroalkyl and OCi-6fluoroalkyl;

R27 is selected from H, Ci-6alkyl, Ci-6fluoroalkyl, C(0)Ci- 6alkyl, C 3-iocycloalkyl, heterocycloalkyl, C 6-ioaryl, heteroaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci-ealkyleneCe-ioaryl, Ci-6alkyleneheteroaryl and Ci_6alkyleneheterocycloalkyl, and is unsubstituted or substituted with one or more substituents selected from halo, OR31, SR31, NR32R33, Ci-6alkyl, C(0)R 31, C(0)OR 31, C(0)NR 32R33, S(0)Ci -6alkyl, S0 2Ci-6alkyl, C6-i0aryl, heteroaryl, C3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-1ocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 31, Ci-galkyleneOR31, Ci-6alkyleneSR31 and Ci-6alkyleneNR32R33;

R28 and R29 are each independently selected from H, Ci.i0alkyl, Ci.iofluoroalkyl, C(0)Ci -6alkyl, C(O)C6-i0aryl, C(0)C 3-iocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi -6alkyl, C(0)OCi -6fluoroalkyl, C(O)OC6-i0aryl, C(O)OC3-i0cycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi -6alkyl, C(0)NHCi -6fluoroalkyl, C(O)NHC6-i0aryl, C(0)NHC 3-iocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0 2Ci-6alkyl, S0 2Ci-6fluoroalkyl, S0 2C 6-ioaryl, S0 2C3-iocycloalkyl, S0 2heteroaryl, S0 2heterocycloalkyl, C3-1ocycloalkyl, heterocycloalkyl, heteroaryl, C 6-ioaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci_6alkyleneC 6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and each of R28 and R29 are independently unsubstituted or substituted with one or more substituents selected from halo, CN, OR31, SR31, NR32R33, Ci-6alkyl, C(0)R 31, C(0)OR 31, C(0)NR 32R33, S(0)Ci -6alkyl, S0 2Ci-6alkyl, C6-i0aryl, heteroaryl, C3-1ocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci_6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 31, Ci-6alkyleneOR 31, Ci-galkyleneSR31 and Ci-6alkyleneNR32R33, or

R^{28} and R^{29} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{31}, SR^{31}, $NR^{32}R^{33}$, C_{1-6}alkyl, C(0)R^{31}, C(0)OR^{31}, C(0)$NR^{32}R^{33}$, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneR^{31}, Ci-$_6$alkyleneOR^{31}, Ci-$_6$alkyleneSR^{31} and Ci$_{-6}$alkyleneNR^{32}R^{33};

R^{30} is selected from C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(O)C_6-i$_0$aryl, C(0)C$_{3-10}$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, heteroaryl and C$_6$-ioaryl, and R^{30} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{31}, SR^{31}, $NR^{32}R^{33}$, Ci-galkyl, C(0)R^{31}, C(0)OR^{31}, C(0)$NR^{32}R^{33}$, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{31}, Ci-galkyleneOR^{31}, Ci$_{-6}$alkyleneSR^{31} and Ci$_{-6}$alkyleneNR^{32}R^{33},

R^{31} is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, Ci$_{-6}$alkyleneC$_6$-ioaryl, Ci$_{-6}$alkyleneC$_3$.iocycloalkyl and Ci.$_6$alkyleneheterocycloalkyl, and R^{31} is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C_3-$_1$ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-ealkyleneNiOi-ealkylXCi-ealkyl);

R^{32} and R^{33} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci$_{-6}$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi$_{-6}$fluoroalkyl, SCi.

salkyl, SC^fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci-$_6$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heteroCycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci$_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{32} and R^{33} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-i0}aryl, heteroaryl, C_{3-l}ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

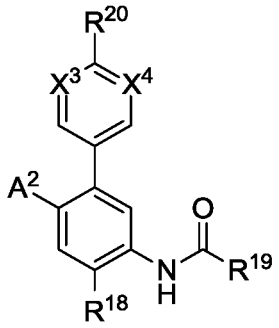
X^3 and X^4 are each independently selected from CR^{34} and N;

R^{34} is selected from H, Ci-$_6$alkyl and Ci-$_6$fluoroalkyl;

A^2 is F; and

alkyl and alkylene groups are optionally fluorosubstituted.

[00121] The present application also includes a compound of Formula (la) or a pharmaceutically acceptable salt and/or solvate thereof:



(la)

wherein:

R^{18} is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci_6alkyl, Ci.6fluoroalkyl, OR^{21}, SR^{21}, $NR^{22}R^{23}$, Ci-6alkyleneOR21, Ci_6alkyleneSR21 and Ci_6alkyleneNR22R23, provided that R^1 comprises at least one basic nitrogen atom;

R^{19} is selected from C6-ioaryl and heteroaryl, and R^{19} is unsubstituted or substituted with one or more substituents selected from halo, Ci-6alkyl, Ci-6fluoroalkyl, =0, =S, OR^{24}, SR^{24} and $NR^{25}R^{26}$;

R^{20} is selected from H, halo, CN, Ci_6alkyl, Ci_6fluoroalkyl, OR^{27}, SR^{27}, $NR^{28}R^{29}$, R^{30}, Ci_6alkyleneR30, OCi_6alkyleneR30, SCi_6alkyleneR30, Ci_6alkyleneNR28R29, Ci.salkyleneOR27, Ci_6alkyleneSR27, OCi_6alkyleneNR28R29, SCi_6alkyleneNR28R29, OCi.salkyleneOR27, SCi_6alkyleneOR27, OCi_6alkyleneSR27, SCi_6alkyleneSR27, C(0)OR27, C(S)OR27, C(S)NR28R29 and C(0)NR28R29;

R^{21} is selected from H, Ci_6alkyl Ci.6fluoroalkyl, C(0)Ci_6alkyl and C(0)d.6fluoroalkyl;

R^{22} and R^{23} are independently selected from H, Ci-6alkyl, Ci-6fluoroalkyl, heterocycloalkyl, C(0)Ci-6alkyl and C(0)Ci-6fluoroalkyl, or R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, Ci-galkyl OCi_6alkyl, Ci_6fluoroalkyl, OC^fluoroalkyl, C(0)Ci_6alkyl and C(0)d.6fluoroalkyl;

R^{24} is selected from H, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci-6alkyl;

R^{25} and R^{26} are independently selected from H, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci_6alkyl, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, Ci-6alkyl OCi-6alkyl, Ci-6fiuoroalkyl and OCi-6fluoroalkyl;

R^{27} is selected from H, Ci-6alkyl, Ci-6fluoroalkyl, C(0)Ci-6alkyl, C3-iocycloalkyl, heterocycloalkyl, Ce-ioaryl, heteroaryl, Ci-6alkyleneC3-iocycloalkyl, Ci-6alkyleneC6-1oaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and is unsubstituted

or substituted with one or more substituents selected from halo, OR^{31}, SR^{31}, $NR^{32}R^{33}$, Ci-galkyl, $C(0)R^{31}$, $C(0)OR^{31}$, $C(0)NR^{32}R^{33}$, $S(0)Ci_{-6}alkyl$, $S0_2Ci_{-6}alkyl$, $C_{6-10}aryl$, heteroaryl, C_{3-10}-iocycloalkyl, heterocycloalkyl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneC_{3-10}$ocycloalkyl, $Ci_{-6}alkyleneheteroaryl$, $Ci_{-6}alkyleneheterocycloalkyl$, $Ci_{-6}alkyleneR^{31}$, Ci-galkyleneOR31, $Ci_{-6}alkyleneSR^{31}$ and $Ci_{-6}alkyleneNR^{32}R^{33}$;

R^{28} and R^{29} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, $C(0)Ci_{-6}alkyl$, C_{3-10}iocycloalkyl, heterocycloalkyl, heteroaryl, C_{6-10}aryl, $Ci_{-6}alkyleneC_{3-10}$ocycloalkyl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneheteroaryl$ and $Ci_{-6}alkyleneheterocycloalkyl$, and each of R^{28} and R^{29} are independently unsubstituted or substituted with one or more substituents selected from halo, OR^{31}, SR^{31}, $NR^{32}R^{33}$, $Ci_{-6}alkyl$, $C(0)R^{31}$, $C(0)OR^{31}$, $C(0)NR^{32}R^{33}$, $S(0)Ci_{-6}alkyl$, $S0_2Ci_{-6}alkyl$, $C_{6-10}aryl$, heteroaryl, C_{3-10}-iocycloalkyl, heterocycloalkyl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneC_{3-10}$ocycloalkyl, $Ci_{-6}alkyleneheteroaryl$, $Ci_{-6}alkyleneheterocycloalkyl$, $Ci_{-6}alkyleneR^{31}$, Ci-galkyleneOR31, $Ci_{-6}alkyleneSR^{31}$ and $Ci_{-6}alkyleneNR^{32}R^{33}$, or

R^{28} and R^{29} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, OR^{31}, SR^{31}, $NR^{32}R^{33}$, $Ci_{-6}alkyl$, $C(0)R^{31}$, $C(0)OR^{31}$, $C(0)NR^{32}R^{33}$, $S(0)Ci_{-6}alkyl$, $S0_2Ci_{-6}alkyl$, $C_{6-10}aryl$, heteroaryl, C_{3-10}-iocycloalkyl, heterocycloalkyl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneC_{3-10}$-iocycloalkyl, $Ci_{-6}alkyleneheteroaryl$, $Ci_{-6}alkyleneR^{31}$, $Ci_{-6}alkyleneOR^{31}$, $Ci_{-6}alkyleneSR^{31}$ and $Ci_{-6}alkyleneNR^{32}R^{33}$;

R^{30} is selected from $C(0)Ci_{-6}alkyl$, C_{3-10}iocycloalkyl, heterocycloalkyl, heteroaryl and C_{6-10}-ioaryl, and R^{30} is unsubstituted or substituted with one or more substituents independently selected from halo, OR^{31}, SR^{31}, $NR^{32}R^{33}$, $Ci_{-6}alkyl$, $C(0)R^{31}$, $C(0)OR^{31}$, $C(0)NR^{32}R^{33}$, $S(0)Ci_{-6}alkyl$, $S0_2Ci_{-6}alkyl$, $C_{6-10}aryl$, heteroaryl, C_{3-10}ocycloalkyl, heterocycloalkyl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneC_{3-10}$-iocycloalkyl, $Ci_{-6}alkyleneheteroaryl$, $Ci_{-6}alkyleneheterocycloalkyl$, $Ci_{-6}alkyleneR^{31}$, $Ci_{-6}alkyleneOR^{31}$, Ci-galkyleneSR31 and $Ci_{-6}alkyleneNR^{32}R^{33}$,

R^{31} is selected from H, $Ci_{-6}alkyl$, $Ci_{-6}fluoroalkyl$, $C(0)Ci_{-6}alkyl$, C_{3-10}-iocycloalkyl, heterocycloalkyl, C_{6-10}-ioaryl, $Ci_{-6}alkyleneC_{6-10}aryl$, $Ci_{-6}alkyleneC_{3-10}$-iocycloalkyl and $Ci_{-6}alkyleneheterocycloalkyl$, and R^{31} is unsubstituted or substituted with one or more

substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-efluoroalkyl, SCi$_{-6}$alkyl, SC^fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci-**6alkyl**)(Ci-$_6$alkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(d.$_6$alkyl)(Ci-$_6$alkyl), S0$_2$Ci-$_6$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

R^{32} and R^{33} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci$_{-6}$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi$_{-6}$fluoroalkyl, SCi.salkyl, SC^fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci-$_6$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci$_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{32} and R^{33} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-sfiuoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, NCCi-salkylXCi-salkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(d.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

X^3 and X^4 are each independently selected from CR^{34} and N;

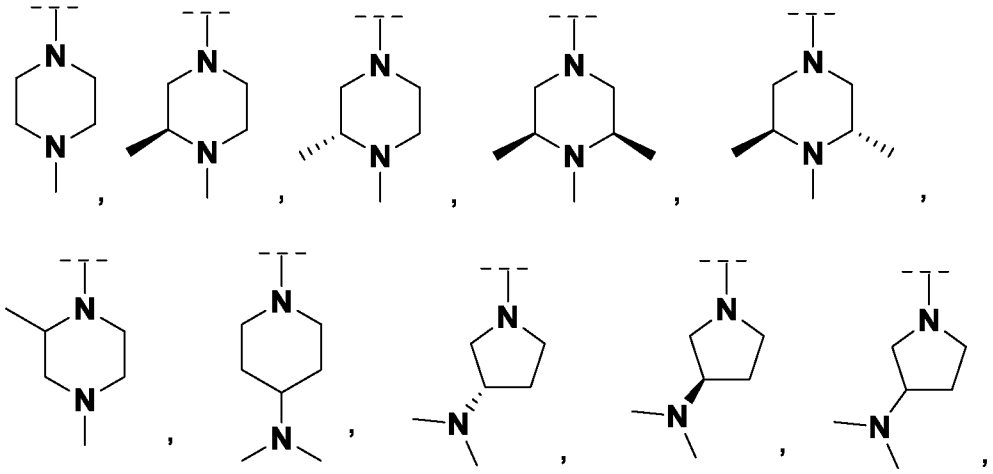
R^{34} is selected from H, **Ci-6**alkyl and **Ci-6**fluoroalkyl;

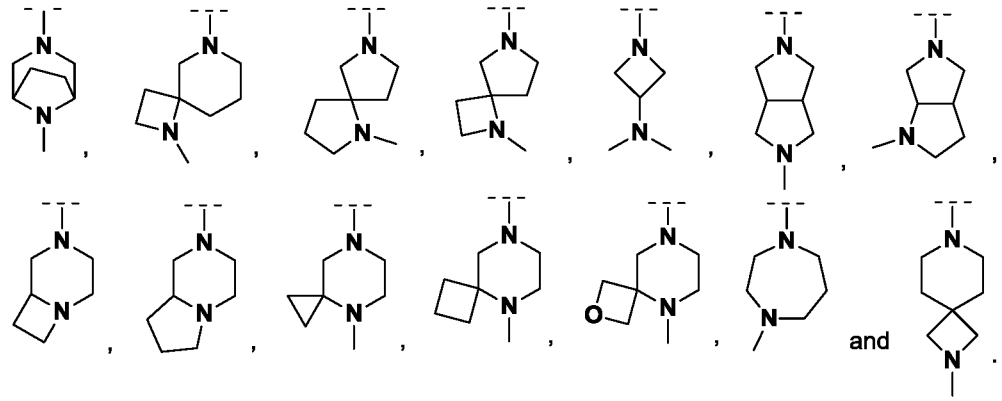
A^2 is F; and

alkyl and alkylene groups are optionally fluorosubstituted.

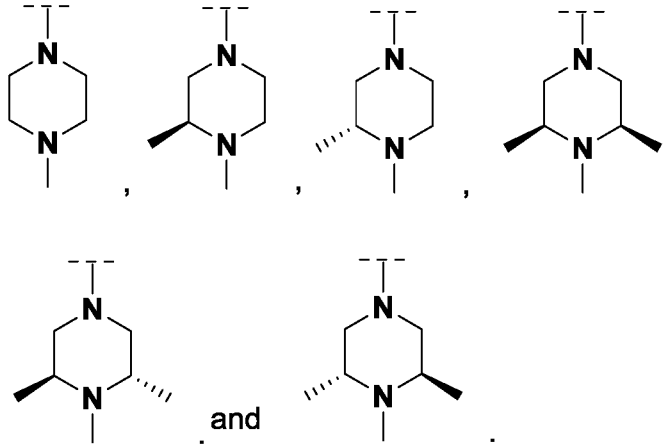
[00122] In some embodiments, R^{18} is a heterocycloalkyl that is unsubstituted or substituted with one, two or three substituents selected from halo, **Ci-6**alkyl, **Ci-6**fluoroalkyl, $NR^{22}R^{23}$ and **Ci-6**alkylene$NR^{22}R^{23}$, provided that R^{18} comprises at least one basic nitrogen atom. In some embodiments, R^{18} is a heterocycloalkyl that is substituted with one or two substituents selected from halo, **Ci-6**alkyl and $NR^{22}R^{23}$, provided that R^{18} comprises at least one basic nitrogen atom. In some embodiments, R^{18} is a heterocycloalkyl that is substituted with one, two or three substituents selected from **Ci-6**alkyl and $NR^{22}R^{23}$, provided that R^{18} comprises at least one basic nitrogen atom. In some embodiments, R^{18} is a **C5**-heterocyclalkyl comprising one or two nitrogen atoms at least one of which is basic.

[00123] In some embodiments, R^{18} is selected from:

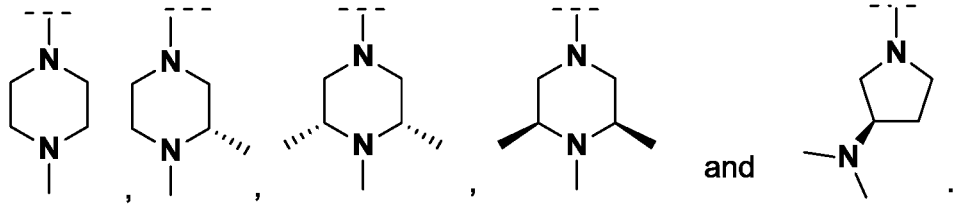




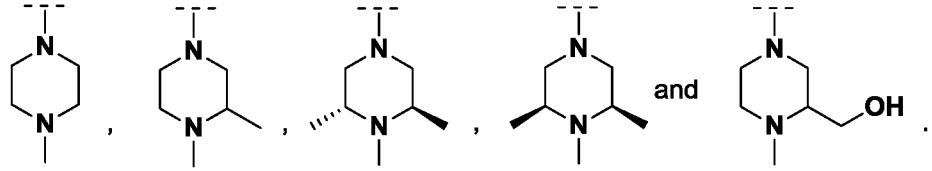
[00124] In some embodiments, R^{18} is selected from:



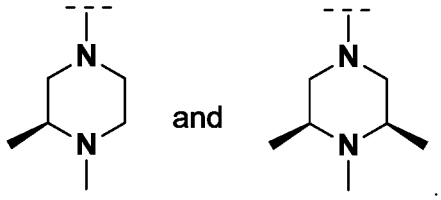
[00125] In some embodiments, R^{18} is selected from:



[00126] R^{18} is selected from:

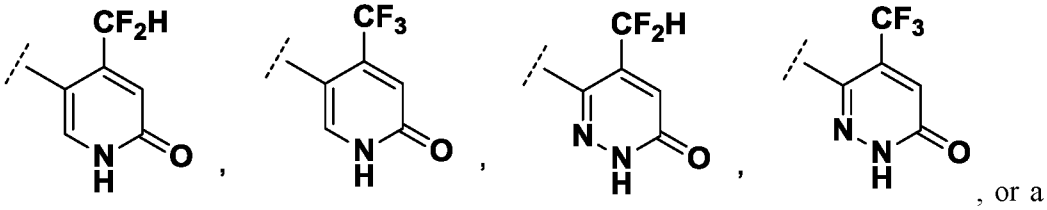


[00127] R^{18} is selected from:

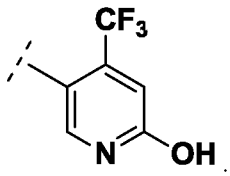


[00128] In some embodiments, R^{19} is selected from C_{6-10}aryl and heteroaryl, and R^{19} is unsubstituted or substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl, **=0,** OR^{24}, SR^{24} and $NR^{25}R^{26}$. In some embodiments, R^{19} is selected from C_{6-10}aryl and heteroaryl, and R^{19} is unsubstituted or substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl, **=0** and $NR^{25}R^{26}$. In some embodiments, R^{19} is selected from C_{6-10}aryl and heteroaryl, and R^{19} is unsubstituted or substituted with one or two substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl and **=0.** In some embodiments, R^{19} is selected from phenyl and C_{6-10}heteroaryl, and R^{19} is substituted with one to three substituents selected from F, CF_2H, CF_3 and **=0.**

[00129] In some embodiments, R^{19} is:

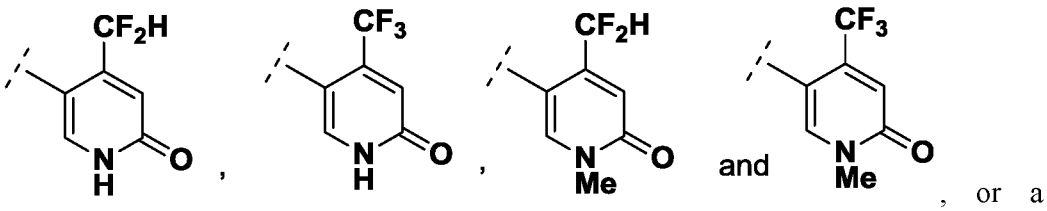


, or a tautomer thereof. The tautomer of this R^{19} group is

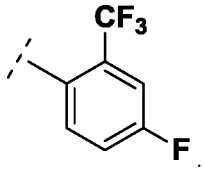


.

[00130] In some embodiments, R^{19} is selected from:



, or a tautomer thereof.

[00131] In some embodiments, R^{19} is  .

[00132] In some embodiments, R^{20} is selected from H, halo, CN, Ci-$_6$alkyl, Ci$_-$efluoroalkyl, OR^{27}, $NR^{28}R^{29}$, R^{30}, Ci$_{-6}$alkyleneR^{30}, OCi$_{-6}$alkyleneR^{30}, Ci.$_6$alkyleneNR^{28}R^{29}, Ci$_{-6}$alkyleneOR^{27}, OCi$_{-6}$alkyleneNR^{28}R^{29}, OCi$_{-6}$alkyleneOR^{27}, C(**0**)OR^{27} and C(**0**)NR^{28}R^{29}. In some embodiments, R^{20} is selected fromH, halo, CN, Ci-galkyl, Ci-$_6$fluoroalkyl, OR^{27}, $NR^{28}R^{29}$, R^{30}, Ci$_{-6}$alkyleneR^{30}, OCi$_{-6}$alkyleneR^{30}, Ci.$_6$alkyleneNR^{28}R^{29}, Ci$_{-6}$alkyleneOR^{27}, OCi$_{-6}$alkyleneNR^{28}R^{29} and OCi$_{-6}$alkyleneOR^{27}. In some embodiments, R^{20} is selected from H, CN, Ci$_{-6}$alkyl, OR^{27}, $NR^{28}R^{29}$, R^{30}, Ci$_-$$_6$alkyleneR^{30} and OCi$_{-6}$alkyleneR^{30}. In some embodiments, wherein R^{20} is selected from Ci-galkyl and R^{30}.

[00133] In some embodiments, R^{22} and R^{23} are independently selected from H, Ci-$_6$alkyl and heterocycloalkyl. In some embodiments, R^{22} and R^{23} are independently selected from H and Ci-$_6$alkyl.

[00134] In some embodiments, R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or two substituents selected from halo and Ci-$_6$alkyl. In some embodiments, R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

[00135] In some embodiments, R^{27} is selected from H, Ci-$_6$alkyl, Ci$_-$$_6$fluoroalkyl, C(**0**)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, **C 6**-ioaryl, heteroaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci$_-$$_6$alkyleneheterocycloalkyl. In some embodiments, R^{27} is selected from H, Ci$_{-6}$alkyl, Ci-$_6$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_3$-iocycloalkyl and Ci$_-$$_6$alkyleneheterocycloalkyl. In some embodiments, R^{27} is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl and Ci-$_6$alkyleneC $_3$-iocycloalkyl. In some embodiments, R^{27} is selected from Ci-$_6$alkyl, Ci-$_6$fluoroalkyl and heterocycloalkyl. In some embodiments, R^{27} is an unsubstituted or substituted monocyclic heterocycloalkyl selected from aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl,

thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomo rpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl.

[00136] In some embodiments, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ are each independently selected from H, **Ci**-ioalkyl, **Ci**-iofluoroalkyl, **C(0)Ci**-$_6$alkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, heteroaryl, $_{C\ 6}$-ioaryl, **Ci**-$_6$alkyleneC $_3$-iocycloalkyl, **Ci**-$_6$alkyleneC $_6$-ioaryl, **Ci**_$_6$alkyleneheteroaryl and **Ci**-$_6$alkyleneheterocycloalkyl. In some embodiments, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ are each independently selected from H, **Ci**-ioalkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, **Ci**_$_6$alkyleneC $_3$-iocycloalkyl and **Ci**-$_6$alkyleneheterocycloalkyl. In some embodiments, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ are each independently selected from H, **Ci**-ioalkyl and $_{C\ 3}$-iocycloalkyl.

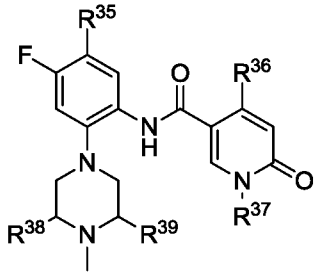
[00137] In some embodiments, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

[00138] In some embodiments, $\mathbf{R^{30}}$ is selected from **C(0)Ci**-$_6$alkyl, $_{C3-1}$ocycloalkyl, heterocycloalkyl, heteroaryl and $_{C\ 6}$-ioaryl. In some embodiments, $\mathbf{R^{30}}$ is selected from $_{C\ 3}$-iocycloalkyl and heterocycloalkyl. In some embodiments, $\mathbf{R^{30}}$ is heterocycloalkyl. In some embodiments $\mathbf{R^{30}}$ is an unsubstituted or substituted monocyclic heterocycloalkyl selected from aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl.

[00139] In some embodiments, $\mathbf{X^3}$ and $\mathbf{X^4}$ are each independently selected from $\mathbf{CR^{34}}$ and **N**, in which $\mathbf{R^{34}}$ is selected from H and **Ci**-$_6$alkyl. In some embodiments, $\mathbf{X^3}$ and

X^4 are CR^{34}, in which R^{34} is H. In some embodiments, X^1 and X^2 is CR^{34} and the other of X^1 and X^2 is N, in which R^{34} is H. In some embodiments, both of X^3 and X^4 are N.

[00140] The present application also include a compound of Formula (lb) or a pharmaceutically acceptable salt and/or solvate thereof:



(lb)

wherein:

R^{35} is selected from phenyl, Cs-eheteroaryl and Cs-eheterocycloalkyl, and R^{35} is substituted with one substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^{40}, SR^{40}, $S0_2R^{40}$, $NR^{41}R^{42}$, R^{43}, Ci$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkenyleneR^{43}, OCi$_{-6}$salkyleneR^{43}, SCi$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkyleneNR^{41}R^{42}, Ci$_{-6}$alkyleneOR^{40}, Ci$_{-6}$salkyleneSR^{40}, OCi$_{-6}$alkyleneNR^{41}R^{42}, SCi$_{-6}$alkyleneNR^{41}R^{42}, OCi$_{-6}$alkyleneOR^{40}, SCi$_{-6}$salkyleneOR^{40}, OCi$_{-6}$alkyleneSR^{40}, SCi$_{-6}$alkyleneSR^{40}, C(0)OR^{40}, C(S)OR^{40}, C(S)NR^{41}R^{42} and C(0)NR^{41}R^{42};

R^{36} is selected from CF_2H and CF_3;

R^{37} is selected from H and CH_3;

R^{38} and R^{39} are independently selected from H and CH_3

R^{40} is selected from H, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, heteroaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and is unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{44}, SR^{44}, $NR^{45}R^{46}$, Ci$_{-6}$alkyl, C(0)R^{44}, C(0)OR^{44}, C(0)NR^{45}R^{46}, S(0)Ci$_{-6}$alkyl, $S0_2$Ci-$_6$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-$_1$oaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$

$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{44}, Ci-$_6$alkyleneOR^{44}, Ci-$_6$alkyleneSR^{44} and Ci$_{-6}$alkyleneNR^{45}R^{46};

R^{41} and R^{42} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(O)C$_{6}$-i$_0$aryl, C(O)C$_{3}$-i$_0$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi$_{-6}$alkyl, C(0)OCi$_{-6}$fluoroalkyl, C(0)OC$_{6}$-ioaryl, C(0)OC$_{3}$-iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi$_{-6}$alkyl, C(0)NHCi$_{-6}$fluoroalkyl, C(O)NHC$_{6}$-i$_0$aryl, C(0)NHC$_{3}$-$_1$ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0$_2$Ci$_{-6}$alkyl, S0$_2$Ci.$_6$fluoroalkyl, S0$_2$C$_6$-ioaryl, S0$_2$C$_3$-iocycloalkyl, S0$_2$heteroaryl, S0$_2$heterocycloalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, heteroaryl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and each of R^{41} and R^{42} are independently unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{44}, SR^{44}, NR^{45}R^{46}, Ci$_{-6}$alkyl, C(0)R^{44}, C(0)OR^{44}, C(0)NR^{45}R^{46}, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C$_{6}$-i$_0$aryl, heteroaryl, C$_{3}$-$_1$ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{44}, Ci-$_6$alkyleneOR^{44}, Ci$_{-6}$alkyleneSR^{44} and Ci$_{-6}$alkyleneNR^{45}R^{46}, or

R^{41} and R^{42} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{44}, SR^{44}, NR^{45}R^{46}, Ci$_{-6}$alkyl, C(0)R^{44}, C(0)OR^{44}, C(0)NR^{45}R^{46}, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C$_{6}$-i$_0$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneR^{44}, Ci-$_6$alkyleneOR^{44}, Ci-$_6$alkyleneSR^{44} and Ci$_{-6}$alkyleneNR^{45}R^{46};

R^{43} is selected from C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(O)C$_{6}$-i$_0$aryl, C(0)C$_{3}$-$_1$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_{3}$-iocycloalkyl, heterocycloalkyl, heteroaryl and C$_6$-ioaryl, and R^{43} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{44}, SR^{44}, NR^{45}R^{46}, Ci-galkyl, C(0)R^{44}, C(0)OR^{44}, C(0)NR^{45}R^{46}, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C$_{6}$-i$_0$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci$_{-6}$alkyleneR^{44}, Ci$_{-6}$alkyleneOR^{44}, Ci$_{-6}$alkyleneSR^{44} and Ci$_{-6}$alkyleneNR^{45}R^{46};

R^{44} is selected from H, Ci_6alkyl, Ci.6fluoroalkyl, C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C3-iocycloalkyl, heterocycloalkyl, C6-ioaryl, Ci-6alkyleneC6-ioaryl, Ci-6alkyleneC3-locycloalkyl and Ci-6alkyleneheterocycloalkyl, and R^{44} is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-6alkyl, Ci-6fluoroalkyl, OH, SH, OCi-galkyl, OC^fluoroalkyl, SCi_6alkyl, SCi_6fluoroalkyl, NH_2, NHCi_6alkyl, N(Ci.6alkyl)(Ci_6alkyl), C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C(0)OH, C(0)OCi_salkyl, C(0)NH_2, C(0)NHCi_6alkyl, C(0)N(Ci_6alkyl)(Ci_6alkyl), S0$_2$Ci_6alkyl, S(0)Ci-6alkyl, C6-ioaryl, heteroaryl, C3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC6-loaryl, Ci-6alkyleneC3-iocycloalkyl, Ci-6alkyleneheteroaryl, Ci_6alkyleneheterocycloalkyl, Ci-6alkyleneOH, Ci-6alkyleneOCi-6alkyl, Ci-6alkyleneSH, C_{1-6}alkyleneSC_{1-6}alkyl, Ci_6alkyleneNH$_2$, C_{1-6}alkyleneNHC_{1-6}alkyl and Ci.salkyleneNiCi-galkyOiCi-galkyl);

R^{45} and R^{46} are each independently selected from H, Ci-6alkyl, Ci-6fluoroalkyl, C(0)Ci-6alkyl, C(0)Ci-6fluoroalkyl, C3-iocycloalkyl, heterocycloalkyl, C6-ioaryl, Ci_6alkyleneC6-ioaryl, Ci-6alkyleneC3-iocycloalkyl and Ci-6alkyleneheterocycloalkyl and each of R^{45} and R^{46} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, Ci-6alkyl, Ci-6fluoroalkyl, OH, SH, OCi-6alkyl, OCi-gfluoroalkyl, SCi_6alkyl, SCi_6fluoroalkyl, NH_2, NHCi_6alkyl, N(Ci.6alkyl)(Ci.salkyl), C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C(0)OH, C(0)OCi_6alkyl, C(0)NH_2, C(0)NHCi_6alkyl, C(0)N(Ci.6alkyl)(Ci_6alkyl), S0$_2$Ci_6alkyl, S(0)Ci_6alkyl, C6-i0aryl, heteroaryl, C3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC6-ioaryl, Ci-6alkyleneC3-locycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneOH, Ci-6alkyleneOCi-6alkyl, Ci-6alkyleneSH, Ci-6alkyleneSCi-6alkyl, Ci-6alkyleneNH$_2$, Ci_6alkyleneNHCi-6alkyl and Ci-6alkyleneN(Ci-6alkyl)(Ci-6alkyl), or

R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-6alkyl, Ci-6fiuoroalkyl, OH, SH, OCi-6alkyl, OCi-gfluoroalkyl, SCi_6alkyl, SCi_6fluoroalkyl, NH_2, NHCi_6alkyl, N(Ci.6alkyl)(Ci.salkyl), C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C(0)OH, C(0)OCi_6alkyl, C(0)NH_2, C(0)NHCi_6alkyl, C(0)N(Ci_6alkyl)(Ci_6alkyl), S0$_2$Ci_6alkyl, S(0)Ci_6alkyl, C6_i0aryl, heteroaryl, C3_iocycloalkyl, heterocycloalkyl, Ci_6alkyleneC6-ioaryl, Ci_6alkyleneC3.

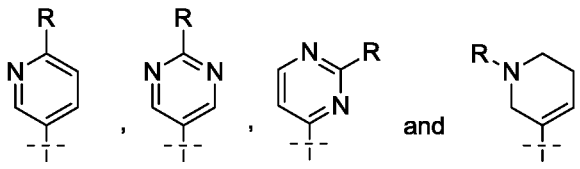
$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci$_-$ $_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl).

[00141] In some embodiments, R^{35} is selected from phenyl, pyrimidinyl, pyridinyl, dihydropyridine, pyrrolyl and dihydropyrrolyl, each of which is substituted with one substituent selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, =0, =S, OR^{40}, SR^{40}, S0$_2R^{40}$, $NR^{41}R^{42}$, R^{43}, Ci$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkenyleneR^{43}, OCi$_{-6}$alkyleneR^{43}, SCi. salkyleneR^{43}, Ci$_{-6}$alkyleneNR^{41}R^{42}, Ci$_{-6}$alkyleneOR^{40}, Ci$_{-6}$alkyleneSR^{40}, OCi. $_6$alkyleneNR^{41}R^{42}, SCi$_{-6}$alkyleneNR^{41}R^{42}, OCi$_{-6}$alkyleneOR^{40}, SCi$_{-6}$alkyleneOR^{40}, OCi. salkyleneSR^{40}, SCi$_{-6}$alkyleneSR^{40}, C(0)OR ^{40}, C(S)OR^{40}, C(S)NR^{41}R^{42} and C(0)NR ^{41}R^{42}.

[00142] In some embodiments, R^{35} is substituted with one substitutent selected from Ci-galkyl, Ci$_{-6}$fluoroalkyl, OR^{40}, $NR^{41}R^{42}$, R^{43}, Ci$_{-6}$alkyleneR^{43}, OCi$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkyleneNR^{41}R^{42}, Ci$_{-6}$alkyleneOR^{40}, OCi$_{-6}$alkyleneNR^{41}R^{42}, OCi$_{-6}$alkyleneOR^{40}, C(0)OR ^{40} and C(0)NR ^{41}R^{42}.

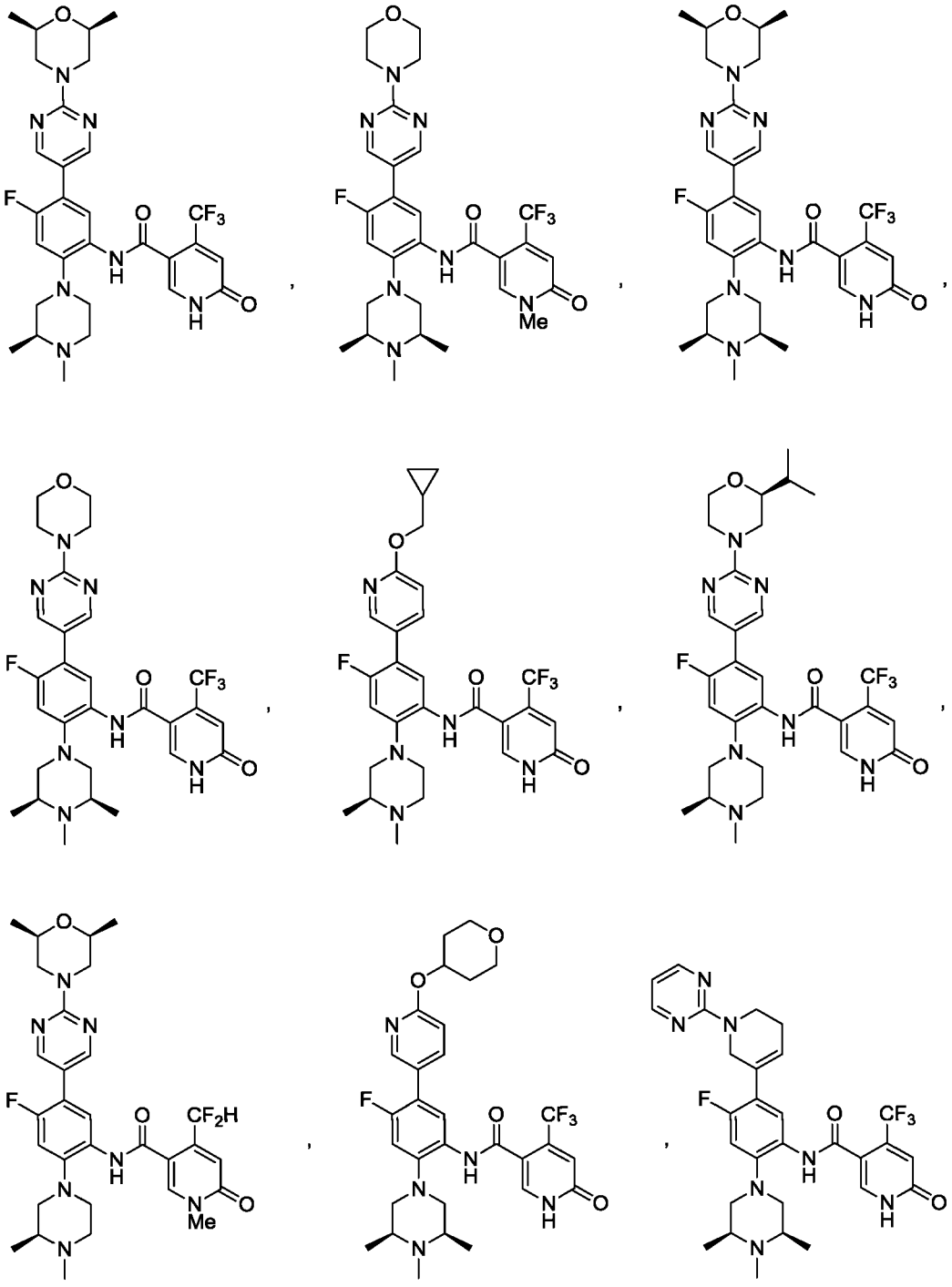
[00143] In some embodiments, R^{35} is substituted with R^{43} or Ci$_{-6}$alkyleneR^{43} wherein R^{43} is selected from C_{5-6}cycloalkyl, C_{5-6}heterocycloalkyl, C_{5-6}heteroaryl and phenyl, and R^{43} is unsubstituted or substituted with one to three substituents independently selected from halo and Ci-$_6$alkyl. In some embodiments, R^{43} is *Ce*-heterocycloalkyl. In some embodiments, R^{43} is selected from piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl. In some embodiments, R^{43} is morpholinyl, optionally substituted with one or two Me.

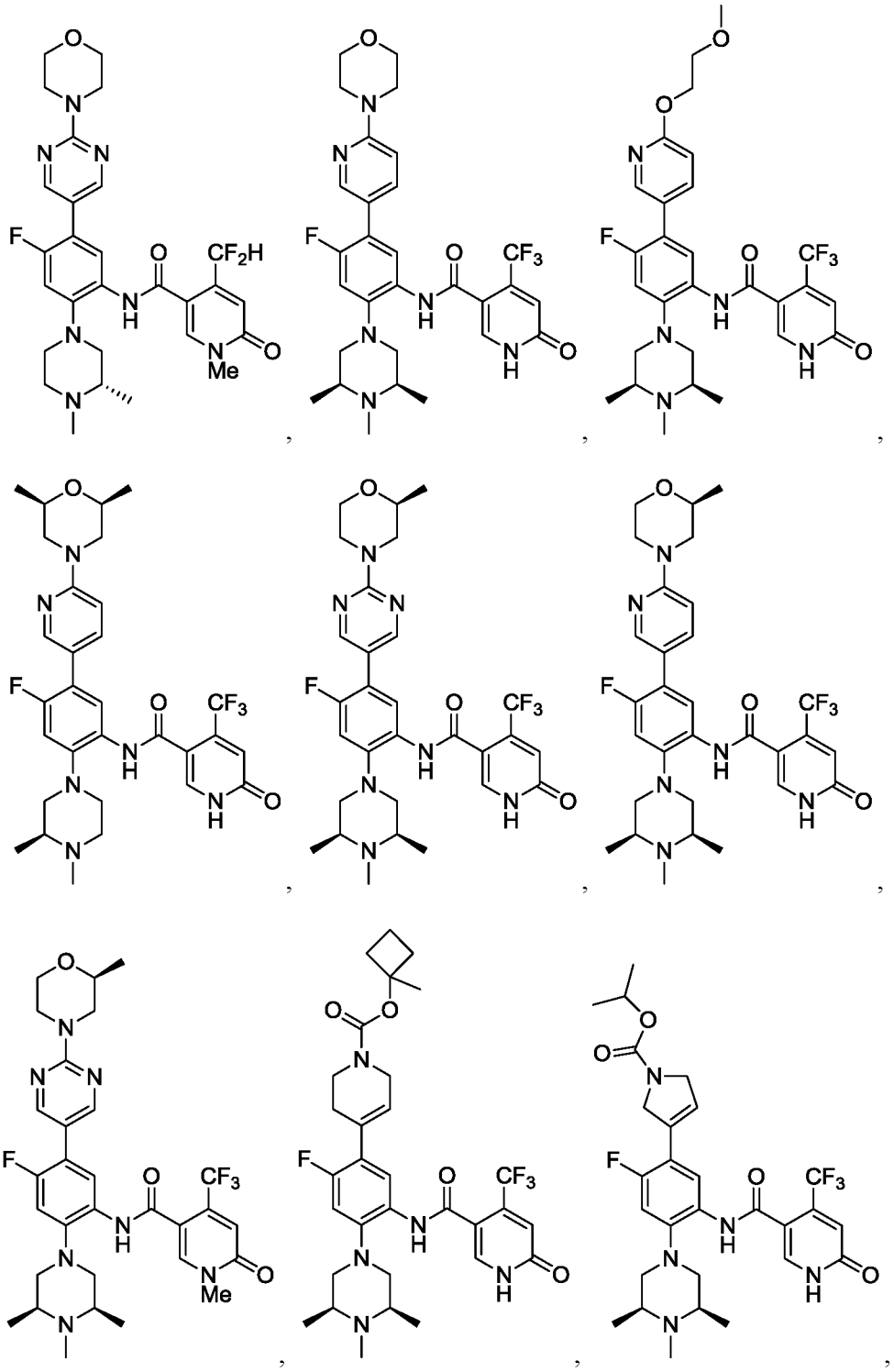
[00144] In some embodiments, R^{35} is selected from:

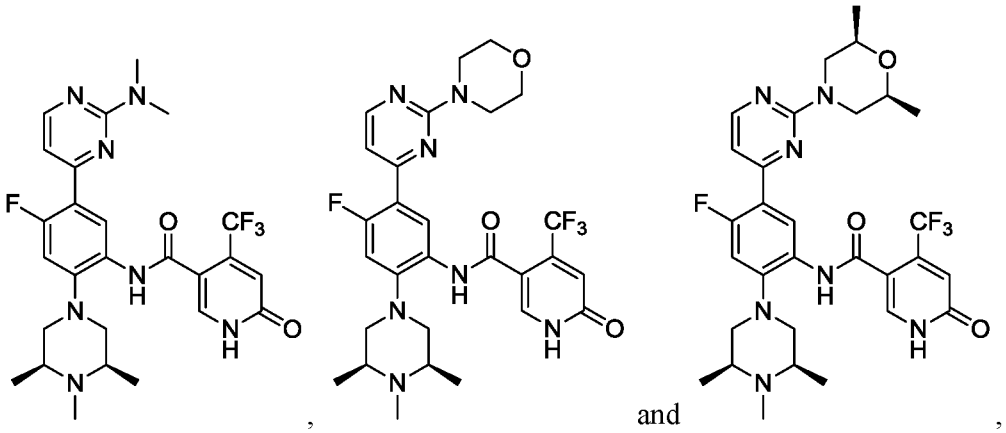


, wherein R is the subsituent.

[00145] In some embodiments, the compound of Formula Ib is selected from:

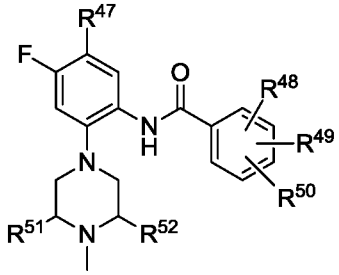






or a pharmaceutically acceptable salt and/or solvate thereof.

[00146] The present application also include a compound of Formula (Ic) or a pharmaceutically acceptable salt and/or solvate thereof:



(Ic)

wherein:

R^{47} is selected from phenyl, Cs-eheteroaryl and Cs-eheterocycloalkyl, and R^{47} is substituted with one substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^{53}, SR^{53}, $S0_2R^{53}$, $NR^{54}R^{55}$, R^{56}, Ci$_{-6}$alkyleneR^{56}, Ci$_{-6}$alkenyleneR^{56}, OCi. salkyleneR^{56}, SCi$_{-6}$alkyleneR^{56}, Ci$_{-6}$alkyleneNR^{54}R^{55}, Ci$_{-6}$alkyleneOR^{53}, Ci. salkyleneSR^{53}, OCi$_{-6}$alkyleneNR^{54}R^{55}, SCi$_{-6}$alkyleneNR^{54}R^{55}, OCi$_{-6}$alkyleneOR^{53}, SCi. salkyleneOR^{53}, OCi$_{-6}$alkyleneSR^{53}, SCi$_{-6}$alkyleneSR^{53}, C(0)OR ^{53}, C(S)OR^{53}, C(S)NR^{54}R^{55} and C(0)NR ^{54}R^{55};

R^{48}, R^{49} and R^{50} are independently selected from H, F, CF_3 and CF_2H, provided that at least one of R^{48}, R^{49} and R^{50} is not H;

R^{51} and R^{52} are independently selected from H and CH_3

R^{53} is selected from H, Ci_6alkyl, Ci.6fluoroalkyl, C(0)Ci _6alkyl, C(0)Ci _6fluoroalkyl, C 3-iocycloalkyl, heterocycloalkyl, C 6-ioaryl, heteroaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and is unsubstituted or substituted with one to three substituents selected from;

R^{54} and R^{55} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci _6alkyl, C(0)Ci _6fluoroalkyl, C(O)C6-i0aryl, C(0)C 3_iocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi _6alkyl, C(0)OCi _6fluoroalkyl, C(0)OC 6-ioaryl, C(0)OC 3_iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi _6alkyl, C(0)NHCi _6fluoroalkyl, C(O)NHC6-i0aryl, C(0)NHC 3-1ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0 2Ci_6alkyl, S0 2Ci. 6fluoroalkyl, S0 2C 6-ioaryl, S0 2C 3-iocycloalkyl, S0 2heteroaryl, S0 2heterocycloalkyl, C3_iocycloalkyl, heterocycloalkyl, heteroaryl, C6-ioaryl, Ci_6alkyleneC 3.iocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and each of R^{54} and R^{55} are independently unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci_6alkyl, C(0)R 57, C(0)OR 57, C(0)NR 58R59, S(0)Ci _6alkyl, S0 2Ci_6alkyl, C6-i0aryl, heteroaryl, C3-1ocycloalkyl, heterocycloalkyl, Ci_6alkyleneC 6-ioaryl, Ci.6alkyleneC 3.iocycloalkyl, Ci. 6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 57, Ci-6alkyleneOR 57, Ci-galkyleneSR57 and Ci_6alkyleneNR 58R59, or

R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci_6alkyl, C(0)R 57, C(0)OR 57, C(0)NR 58R59, S(0)Ci _6alkyl, S0 2Ci_6alkyl, C6-i0aryl, heteroaryl, C3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 57, Ci_ salkyleneOR 57, Ci_6alkyleneSR 57 and Ci_6alkyleneNR 58R59;

R^{56} is selected from C(0)Ci _6alkyl, C(0)Ci _6fluoroalkyl, C(O)C6-i0aryl, C(0)C 3-1ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C3-iocycloalkyl, heterocycloalkyl, heteroaryl and C 6-ioaryl, and R^{56} is unsubstituted or substituted with one to three substituents independently selected halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci_ 6alkyl, C(0)R 57, C(0)OR 57, C(0)NR 58R59, S(0)Ci _6alkyl, S0 2Ci_6alkyl, C6_i0aryl, heteroaryl, C3_iocycloalkyl, heterocycloalkyl, Ci_6alkyleneC 6-ioaryl, Ci_6alkyleneC 3.

$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{57}, Ci-galkyleneOR^{57}, Ci$_{-6}$alkyleneSR^{57} and Ci$_{-6}$alkyleneNR^{58}R^{59};

R^{57} is selected from H, Ci$_{-6}$alkyl, Ci.$_6$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl, and R^{57} is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-galkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi_salkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-$_1$oaryl, Ci$_{-6}$alkyleneC$_3$.iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci.$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci_salkyleneNiCi-galkyOiCi-galkyl);

R^{58} and R^{59} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C$_3$_iocycloalkyl, heterocycloalkyl, C$_6$_ioaryl, Ci.$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{58} and R^{59} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_{6-i0}$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, C$_{1-6}$alkyleneOC$_{1-6}$alkyl, Ci$_{-6}$alkyleneSH, Ci$_{-6}$alkyleneSCi$_{-6}$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci.$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{58} and R^{59} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci.$_6$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$,

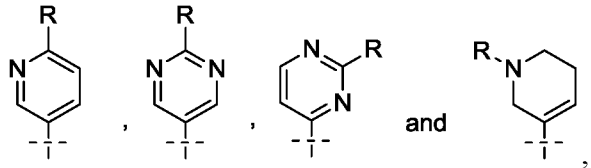
C(0)NHCi _6alkyl, C(0)N(Ci. 6alkyl)(C w alkyl), S0 2Ci_6alkyl, S(0)Ci _6alkyl, C6-i0aryl, heteroaryl, C 3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-1ocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneOH, Ci-6alkyleneOCi-6alkyl, Ci-6alkyleneSH, Ci-6alkyleneSCi-6alkyl, Ci-6alkyleneNH 2, Ci_6alkyleneNHCi-6alkyl and Ci-6alkyleneN(Ci-6alkyl)(Ci-6alkyl).

[00147] In some embodiments, R47 is selected from phenyl, pyrimidinyl, pyridinyl, dihydropyridine, pyrrolyl and dihydropyrrolyl, each of which is substituted with one substituent selected from halo, CN, Ci-6alkyl, Ci-6fiuoroalkyl, =0, =S, OR53, SR53, S0 2R53, NR54R55, R56, Ci_6alkyleneR56, Ci_6alkenyleneR56, OCi_6alkyleneR56, SCi. salkyleneR56, Ci_6alkyleneNR54R55, Ci_6alkyleneOR53, Ci_6alkyleneSR53, OCi. 6alkyleneNR54R55, SCi_6alkyleneNR54R55, OCi_6alkyleneOR53, SCi_6alkyleneOR53, OCi. salkyleneSR53, SCi_6alkyleneSR53, C(0)OR 53, C(S)OR53, C(S)NR54R55 and C(0)NR 54R55.

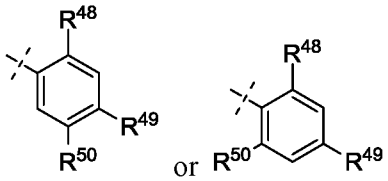
[00148] In some embodiments, R47 is substituted with one substituent selected from Ci-galkyl, Ci_6fluoroalkyl, OR53, NR54R55, R56, Ci_6alkyleneR56, OCi_6alkyleneR56, Ci_6alkyleneNR54R55, Ci_6alkyleneOR53, OCi_6alkyleneNR54R55, OCi_6alkyleneOR53, C(0)OR 53 and C(0)NR 54R55.

[00149] In some embodiments, R47 is substituted with R56 or Ci_6alkyleneR56 wherein R56 is selected from C 5-6cycloalkyl, Cs-eheterocycloalkyl, Cs-eheteroaryl and phenyl, and R56 is unsubstituted or substituted with one to three substituents independently selected from halo and Ci-6alkyl. In some embodiments, R56 is *Ce*-heterocycloalkyl. In some embodiments, R56 is selected from piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl. In some embodiments, R56 is morpholinyl, optionally substituted with one or two Me.

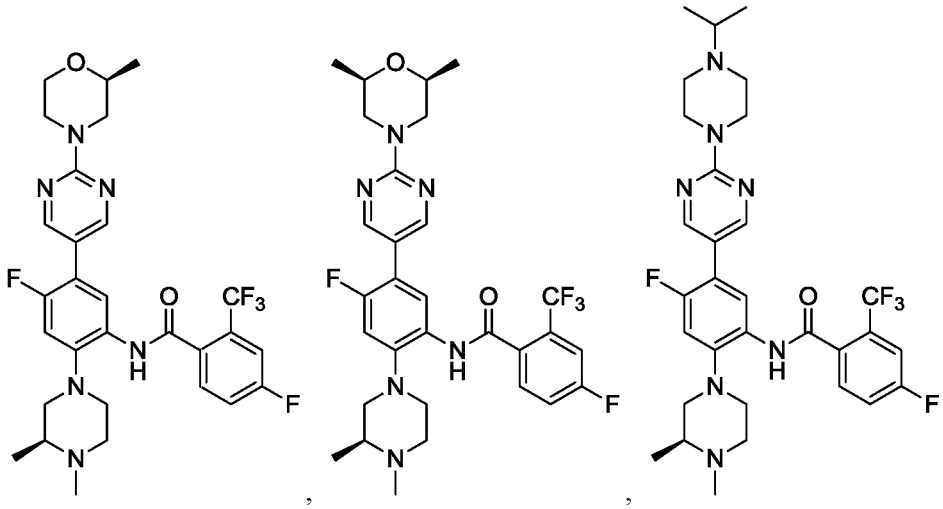
[00150] In some embodiments, R47 is selected from:

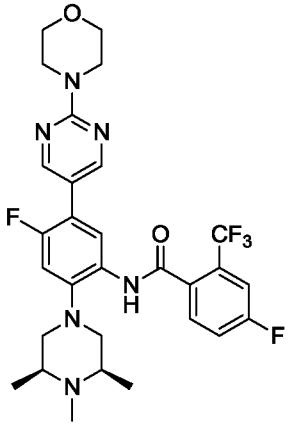

, wherein R is the subsituent.

[00151] In some embodiments, R^{48}, R^{49} and R^{50} are located on the phenyl ring as follows:


, wherein R^{48} is selected from CF_3 and CF_2H and R^{49} and R^{50} are independently selected from H and F. In some embodiments, both R^{49} and R^{50} are F. In some embodiments, R^{49} is F and R^{50} is H.

[00152] In some embodiments, the compound of Formula Ic is selected from:


and


, or a pharmaceutically acceptable salt and/or solvate thereof.

[00153] The compounds of the present application are suitably formulated in a conventional manner into compositions using one or more carriers. Accordingly, the present application also includes a composition comprising one or more compounds of the application and a carrier. The compounds of the application are suitably formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration *in vivo.* Accordingly, the present application further includes a pharmaceutical composition comprising one or more compounds of the application and a pharmaceutically acceptable carrier. In embodiments of the application the pharmaceutical compositions are used in the treatment of nay of the diseases, disorders or conditions described herein.

[00154] The compounds of the application are administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. For example, a compound of the application is administered by oral, inhalation, parenteral, buccal, sublingual, nasal, rectal, vaginal, patch, pump, topical or transdermal administration and the pharmaceutical compositions formulated accordingly. In some embodiments, administration is by means of a pump for periodic or continuous delivery. Conventional procedures and ingredients for the selection and preparation of suitable compositions are described, for example, in Remington's Pharmaceutical Sciences (2000 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999.

[00155] Parenteral administration includes systemic delivery routes other than the gastrointestinal (GI) tract, and includes, for example intravenous, intra-arterial, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary (for example, by use of an aerosol), intrathecal, rectal and topical (including the use of a patch or other transdermal delivery device) modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

[00156] In some embodiments, a compound of the application is orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it is enclosed in hard or soft shell gelatin capsules, or it is compressed into tablets, or it is incorporated directly with the food of the diet. In some embodiments, the compound is incorporated with excipient and used in the form of ingestible tablets,

buccal tablets, troches, capsules, caplets, pellets, granules, lozenges, chewing gum, powders, syrups, elixirs, wafers, aqueous solutions and suspensions, and the like. In the case of tablets, carriers that are used include lactose, corn starch, sodium citrate and salts of phosphoric acid. Pharmaceutically acceptable excipients include binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). In embodiments, the tablets are coated by methods well known in the art. In the case of tablets, capsules, caplets, pellets or granules for oral administration, pH sensitive enteric coatings, such as Eudragits™ designed to control the release of active ingredients are optionally used. Oral dosage forms also include modified release, for example immediate release and timed-release, formulations. Examples of modified-release formulations include, for example, sustained-release (SR), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), or continuous-release (CR or Contin), employed, for example, in the form of a coated tablet, an osmotic delivery device, a coated capsule, a microencapsulated microsphere, an agglomerated particle, e.g., as of molecular sieving type particles, or, a fine hollow permeable fiber bundle, or chopped hollow permeable fibers, agglomerated or held in a fibrous packet. Timed-release compositions are formulated, for example as liposomes or those wherein the active compound is protected with differentially degradable coatings, such as by microencapsulation, multiple coatings, etc. Liposome delivery systems include, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. In some embodiments, liposomes are formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. For oral administration in a capsule form, useful carriers or diluents include lactose and dried com starch.

[00157] In some embodiments, liquid preparations for oral administration take the form of, for example, solutions, syrups or suspensions, or they are suitably presented as a dry product for constitution with water or other suitable vehicle before use. When aqueous suspensions and/or emulsions are administered orally, the compound of the application is suitably suspended or dissolved in an oily phase that is

combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents are added. Such liquid preparations for oral administration are prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). Useful diluents include lactose and high molecular weight polyethylene glycols.

[00158] It is also possible to freeze-dry the compounds of the application and use the lyophilizates obtained, for example, for the preparation of products for injection.

[00159] In some embodiments, a compound of the application is administered parenterally. For example, solutions of a compound of the application are prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. In some embodiments, dispersions are prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. A person skilled in the art would know how to prepare suitable formulations. For parenteral administration, sterile solutions of the compounds of the application are usually prepared, and the pH's of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic. For ocular administration, ointments or droppable liquids are delivered, for example, by ocular delivery systems known to the art such as applicators or eye droppers. In some embodiment, such compositions include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or polyvinyl alcohol, preservatives such as sorbic acid, EDTA or benzyl chromium chloride, and the usual quantities of diluents or carriers. For pulmonary administration, diluents or carriers will be selected to be appropriate to allow the formation of an aerosol.

[00160] In some embodiments, a compound of the application is formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection are, for example, presented in unit

dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. In some embodiments, the compositions take such forms as sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and contain formulating agents such as suspending, stabilizing and/or dispersing agents. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. Alternatively, the compounds of the application are suitably in a sterile powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00161] In some embodiments, compositions for nasal administration are conveniently formulated as aerosols, drops, gels and powders. For intranasal administration or administration by inhalation, the compounds of the application are conveniently delivered in the form of a solution, dry powder formulation or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which, for example, take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container is a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which is, for example, a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. Suitable propellants include but are not limited to dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, heptafluoroalkanes, carbon dioxide or another suitable gas. In the case of a pressurized aerosol, the dosage unit is suitably determined by providing a valve to deliver a metered amount. In some embodiments, the pressurized container or nebulizer contains a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator are, for example, formulated containing a powder mix of a compound of the application and a suitable powder base such as lactose or starch. The aerosol dosage forms can also take the form of a pump-atomizer.

[00162] Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, wherein a compound of the application is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

[00163] Suppository forms of the compounds of the application are useful for vaginal, urethral and rectal administrations. Such suppositories will generally be constructed of a mixture of substances that is solid at room temperature but melts at body temperature. The substances commonly used to create such vehicles include but are not limited to theobroma oil (also known as cocoa butter), glycerinated gelatin, other glycerides, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol. See, for example: *Remington's Pharmaceutical Sciences,* 16th Ed., Mack Publishing, Easton, PA, **1980,** pp. 1530-1533 for further discussion of suppository dosage forms.

[00164] In some embodiments a compound of the application is coupled with soluble polymers as targetable drug carriers. Such polymers include, for example, polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, in some embodiments, a compound of the application is coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

[00165] A compound of the application including pharmaceutically acceptable salts and/or solvates thereof is suitably used on their own but will generally be administered in the form of a pharmaceutical composition in which the one or more compounds of the application (the active ingredient) is in association with a pharmaceutically acceptable carrier. Depending on the mode of administration, the pharmaceutical composition will comprise from about 0.05 wt% to about 99 wt% or about 0.10 wt% to about 70 wt%, of the active ingredient, and from about 1 wt% to

about 99.95 wt% or about 30 wt% to about 99.90 wt% of a pharmaceutically acceptable carrier, all percentages by weight being based on the total composition.

[00166] A compound of the application is either used alone or in combination with other known agents useful for treating diseases, disorders or conditions that are mediated or treatable by inhibition of binding between WDR5 protein and its binding partners, and those that are treatable with a WDR5 inhibitor, such as the compounds disclosed herein. When used in combination with other agents useful in treating diseases, disorders or conditions mediated or treatable by inhibition of binding between WDR5 protein and its binding partners, it is an embodiment that a compound of the application is administered contemporaneously with those agents. As used herein, "contemporaneous administration" of two substances to a subject means providing each of the two substances so that they are both active in the individual at the same time. The exact details of the administration will depend on the pharmacokinetics of the two substances in the presence of each other, and can include administering the two substances within a few hours of each other, or even administering one substance within 24 hours of administration of the other, if the pharmacokinetics are suitable. Design of suitable dosing regimens is routine for one skilled in the art. In particular embodiments, two substances will be administered substantially simultaneously, i.e., within minutes of each other, or in a single composition that contains both substances. It is a further embodiment of the present application that a combination of agents is administered to a subject in a non-contemporaneous fashion. In an embodiment, a compound of the present application is administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present application provides a single unit dosage form comprising one or more compounds of the application, an additional therapeutic agent, and a pharmaceutically acceptable carrier.

[00167] The dosage of a compound of the application varies depending on many factors such as the pharmacodynamic properties of the compound, the mode of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the frequency of the treatment and the type of concurrent treatment, if any, and the clearance rate of the compound in the subject to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. In some

embodiments, a compound of the application is administered initially in a suitable dosage that is adjusted as required, depending on the clinical response. Dosages will generally be selected to maintain a serum level of the compound of the application from about 0.01 μg/cc to about 1000 μg/cc, or about 0.1 μg/cc to about 100 μg/cc. As a representative example, oral dosages of one or more compounds of the application will range between about 1 mg per day to about 1000 mg per day for an adult, suitably about 1 mg per day to about 500 mg per day, more suitably about 1 mg per day to about 200 mg per day. For parenteral administration, a representative amount is from about 0.001 mg/kg to about 10 mg/kg, about 0.01 mg/kg to about 10 mg/kg, about 0.01 mg/kg to about 1 mg/kg or about 0.1 mg/kg to about 1 mg/kg will be administered. For oral administration, a representative amount is from about 0.001 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.01 mg/kg to about 1 mg/kg or about 0.1 mg/kg to about 1 mg/kg. For administration in suppository form, a representative amount is from about 0.1 mg/kg to about 10 mg/kg or about 0.1 mg/kg to about 1 mg/kg. In an embodiment of the application, compositions are formulated for oral administration and the one or more compounds are suitably in the form of tablets containing 0.25, 0.5, 0.75, 1.0, 5.0, 10.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 75.0, 80.0, 90.0, 100.0, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 mg of active ingredient per tablet. In embodiments of the application the one or more compounds of the application are administered in a single daily, weekly or monthly dose or the total daily dose is divided into two, three or four daily doses.

[00168] In the above, the term "a compound" also includes embodiments wherein one or more compounds are referenced.

III. Methods and Uses of the Application

Therapeutic Methods and Uses

[00169] The compounds of the application have been shown to be inhibitors of the binding of WDR5 to MLL1.

[00170] Accordingly, the present application includes a method for inhibition of binding of WDR5 to its binding partners in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds

of the application to the cell. The application also includes a use of one or more compounds of the application for inhibition of binding of WDR5 to its binding partners in a cell as well as a use of one or more compounds of the application for the preparation of a medicament for inhibition of binding of WDR5 to its binding partners in a cell. The application further includes one or more compounds of the application for use to inhibit binding of WDR5 to its binding partners in a cell.

[00171] It is an embodiment of the present application, in all aspects, that the binding partner for WDR5 is MLL1, or a portion thereof. In some embodiments, the binding partner for WDR5 is the WDR5 interacting (WIN) motif, consisting of amino acid residues 3762-3773 next to the SET domain in the MLL1 protein, *[J. Biol. Chem.,* **2008,** 283(47):32158-32161; *J. Biol. Chem.,* **2008**,283(50):35258-35264].

[00172] As the compounds of the application have been shown to be capable of inhibiting the binding of WDR5 to its binding partners, the compounds of the application are useful for treating diseases, disorders or conditions mediated or treatable by inhibition of binding between WDR5 protein and its binding partners. Therefore the compounds of the present application are useful as medicaments. Accordingly, the present application includes a compound of the application for use as a medicament.

[00173] The present application also includes a method of treating a disease, disorder or condition that is mediated or treatable by inhibition of binding between WDR5 protein and its binding partners comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

[00174] The present application also includes a use of one or more compounds of the application for treating a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners as well as a use of one or more compounds of the application for the preparation of a medicament for treating of a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners. The application further includes one or more compounds of the application for use in treating a disease,

disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners.

[00175] In an embodiment, the disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners is a neoplastic disorder. Accordingly, the present application also includes a method of treating a neoplastic disorder comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment of a neoplastic disorder as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of a neoplastic disorder. The application further includes one or more compounds of the application for use in treating a neoplastic disorder. In an embodiment, the treatment is in an amount effective to ameliorate at least one symptom of the neoplastic disorder, for example, reduced cell proliferation or reduced tumor mass, among others, in a subject in need of such treatment.

[00176] In another embodiment of the present application, the disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners is cancer. Accordingly, the present application also includes a method of treating cancer comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment of cancer as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of cancer. The application further includes one or more compounds of the application for use in treating cancer. In an embodiment, the compound is administered for the prevention of cancer in a subject such as a mammal having a predisposition for cancer.

[00177] In an embodiment, the cancer is selected from, but not limited to: Acute Lymphoblastic Leukemia, Adult; Acute Lymphoblastic Leukemia, Childhood; Acute Myeloid Leukemia, Adult; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer; Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer, Childhood; Bone

Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Cerebellar Astrocytoma, Childhood; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma, Childhood; Brain Tumor, Ependymoma, Childhood; Brain Tumor, Medulloblastoma, Childhood; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood; Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood; Brain Tumor, Childhood (Other); Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer, Childhood; Breast Cancer, Male; Bronchial Adenomas/Carcinoids, Childhood; Carcinoid Tumor, Childhood; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Carcinoma of Unknown Primary; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma, Childhood; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer, Childhood; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma, Childhood; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer, Childhood; Ewing's Family of Tumors; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer, Childhood; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma, Adult; Hodgkin's Lymphoma, Childhood; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma, Childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney Cancer; Laryngeal Cancer; Laryngeal Cancer, Childhood; Leukemia, Acute Lymphoblastic, Adult; Leukemia, Acute Lymphoblastic, Childhood; Leukemia, Acute Myeloid, Adult; Leukemia, Acute Myeloid, Childhood; Leukemia, Chronic Lymphocytic; Leukemia,

Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia, Adult Acute; Lymphoblastic Leukemia, Childhood Acute; Lymphocytic Leukemia, Chronic; Lymphoma, AIDS-Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin's, Adult; Lymphoma, Hodgkin's, Childhood; Lymphoma, Hodgkin's During Pregnancy; Lymphoma, Non-Hodgkin's, Adult; Lymphoma, Non-Hodgkin's, Childhood; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Male Breast Cancer; Malignant Mesothelioma, Adult; Malignant Mesothelioma, Childhood; Malignant Thymoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Nasopharyngeal Cancer, Childhood; Neuroblastoma; Non-Hodgkin's Lymphoma, Adult; Non-Hodgkin's Lymphoma, Childhood; Non-Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer, Childhood; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; Osteosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer, Childhood; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Childhood; Pancreatic Cancer, Islet Cell; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer, Adult; Primary Liver Cancer, Childhood; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell Cancer, Childhood; Renal Pelvis and Ureter,

Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Salivary Gland Cancer, Childhood; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Rhabdomyosarcoma, Childhood; Sarcoma, Soft Tissue, Adult; Sarcoma, Soft Tissue, Childhood; Sezary Syndrome; Skin Cancer; Skin Cancer, Childhood; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma, Adult; Soft Tissue Sarcoma, Childhood; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer, Childhood; Supratentorial Primitive Neuroectodermal Tumors, Childhood; T- Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Childhood; Thymoma, Malignant; Thyroid Cancer; Thyroid Cancer, Childhood; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Cancer of, Childhood; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma, Childhood; Vulvar Cancer; Waldenstrom's Macro globulinemia; and Wilms' Tumor. Metastases of the aforementioned cancers can also be treated in accordance with the methods described herein.

[00178] In an embodiment, the cancer is selected from solid cancer and leukemias. In another embodiment, the cancer is selected from leukaemia, lymphoma, non-Hodgkin's lymphoma, Burkitt lymphoma, MLL-fusion lymphoma, primary effusion leukemia and multiple myeloma. In a further embodiment of the present application, the cancer is selected from leukemia, melanoma, lung cancer, bladder cancer, colon cancer, brain cancer, ovarian cancer, breast cancer, prostate cancer, neuroblastoma and kidney cancer. In a further embodiment, the cancer is selected from leukemia, bladder cancer, prostate cancer, brain cancer and neuroblastoma. In a further embodiment, the cancer is selected from bladder cancer, acute myeloid leukemia (AML), gliomas, glioblastomas and MYCN-amplified neuroblastoma.

[00179] In an embodiment, the disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners is a disease, disorder or condition associated with an uncontrolled and/or abnormal cellular activity affected directly or indirectly by a binding of WDR5 to its binding

partners. In another embodiment, the uncontrolled and/or abnormal cellular activity that is affected directly or indirectly by binding of WDR5 to its binding partners is proliferative activity in a cell. Accordingly, the application also includes a method of inhibiting proliferative activity in a cell, comprising administering an effective amount of one or more compounds of the application to the cell. The present application also includes a use of one or more compounds of the application for inhibition of proliferative activity in a cell as well as a use of one or more compounds of the application for the preparation of a medicament for inhibition of proliferative activity in a cell. The application further includes one or more compounds of the application for use in inhibiting proliferative activity in a cell.

[00180] The present application also includes a method of inhibiting uncontrolled and/or abnormal cellular activities mediated directly or indirectly by binding of WDR5 to its binding partners in a cell, either in a biological sample or in a subject, comprising administering an effective amount of one or more compounds of the application to the cell. The application also includes a use of one or more compounds of the application for inhibition of uncontrolled and/or abnormal cellular activities mediated directly or indirectly by binding of WDR5 to its binding partners in a cell as well as a use of one or more compounds of the application for the preparation of a medicament for inhibition of uncontrolled and/or abnormal cellular activities mediated directly or indirectly binding of WDR5 to its binding partners in a cell. The application further includes one or more compounds of the application for use in inhibiting uncontrolled and/or abnormal cellular activities mediated directly or indirectly by binding of WDR5 to its binding partners in a cell.

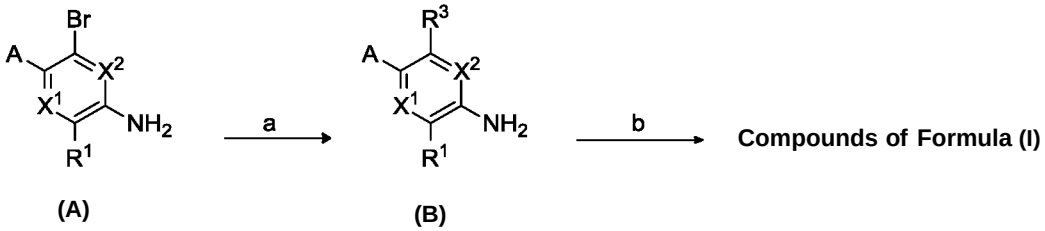
[00181] In further embodiments, the present application also includes a method of treating a disease, disorder or condition that is mediated or treatable by inhibition of binding between WDR5 protein and its binding partners comprising administering a therapeutically effective amount of one or more compounds of the application in combination with another known agent useful for treatment of a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners to a subject in need thereof. The present application also includes a use of one or more compounds of the application in combination with a known agent useful for treatment of a disease, disorder or condition mediated or treatable by

inhibition of binding between WDR5 protein and its binding partners, for treatment of a disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners.

[00182] In a further embodiment, the disease, disorder or condition mediated or treatable by inhibition of binding between WDR5 protein and its binding partners is cancer and the one or more compounds of the application are administered in combination with one or more additional cancer treatments. In another embodiment, the additional cancer treatment is selected from radiotherapy, chemotherapy, targeted therapies such as antibody therapies and small molecule therapies such as tyrosine-kinase inhibitors, immunotherapy, hormonal therapy and anti-angiogenic therapies.

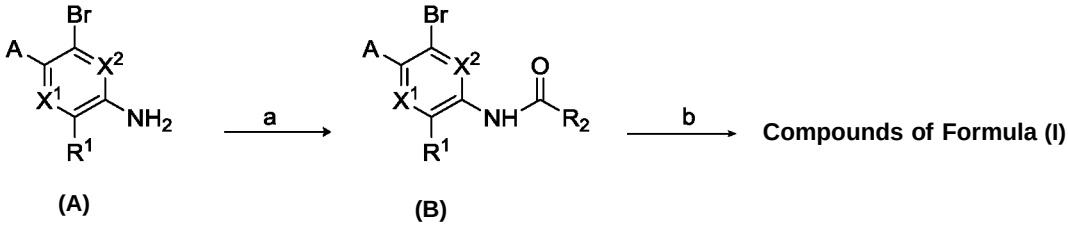
Methods of Preparing the Compounds of the Application

[00183] Scheme 1 illustrates one embodiment of a route to compounds of the application in which Suzuki or related coupling is performed on compounds **(A)** to afford intermediates **(B).** Subsequent coupling of **(B)** with a carboxylic acid or appropriate or acid halide provides compounds of the application.



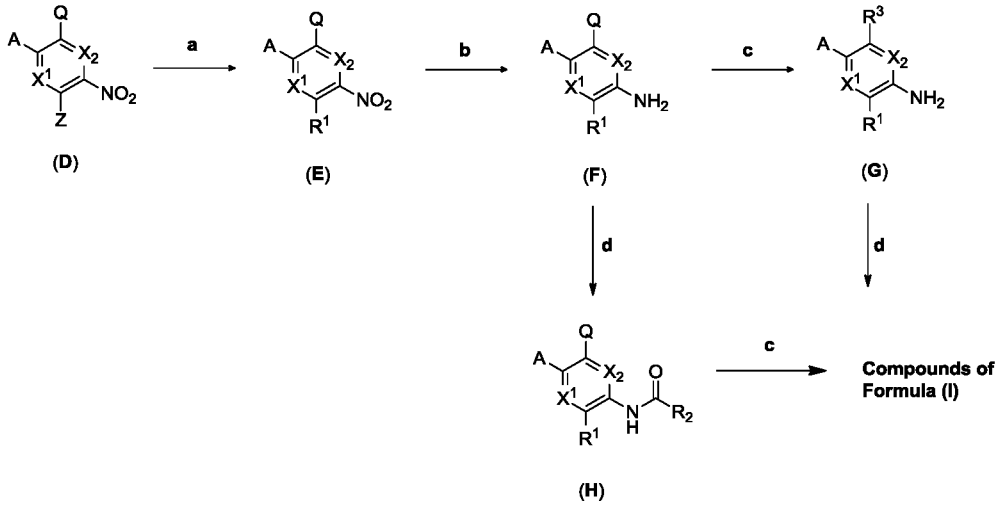
Scheme 1: a) $R^3B(OH)_2$ or boronate ester, $Pd(Amphos)Cl_2$, K_3PO4, dioxane/H_2**0 ,** μwave, 110°C; b) R^2C**(0**)OH, coupling agent or R^2C**(0**)X, wherein X is a halide, amine.

[00184] In an alternate embodiment, compounds of Formula (I) are prepared by first coupling the carboxylic acid or acyl halides with aniline **(A)** followed by Suzuki or related coupling (Scheme 2).



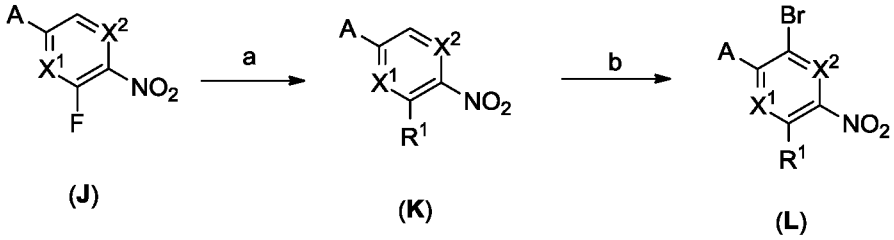
Scheme 2: a) $R^2C(O)OH$, coupling agent or $R^2C(O)X$, wherein X is a halide amine; b) $R^3B(OH)_2$ or boronate ester, $Pd(Amphos)Cl_2$, K_3PO_4, dioxane/H_2O, μwave, 110°C.

[00185] In some embodiments of the application, compounds of Formula (I) are prepared from the nitroaryl or nitroheteroaryl compounds **D** (Q = CI or Br; Z = F or Br). Nucleophilic aromatic substitution with, for example, various piperazines or amines provide intermediate **E**. In some embodiments, reduction of **E** under reductive conditions by various means, including catalytic hydrogenation and dissolving metal reductions both in their various forms [see House, H.O., *Modern Synthetic Reactions*, Second Edition, W.A. Benjamin, Inc., Menlo Park, California, publication (1972)] affords compounds **F**. Coupling of **F** with boronic acids or esters, for example under the Suzuki conditions *[Tetrahedron* **2002,** 58:9633-9695; *Organic Letters* **2006,** 8(9), 1787-1789] affords intermediate **G**. Related coupling reactions for the conversion of **F** to **G** or **H** to Formula **I** as described in Scheme 3 include the Heck (olefin) *[J. Am. Chem. Soc.* **1974** 96(4): 1133-1 136]; Stille (organostannane) *[Synthesis* **1992** 803-815]; Sonogashira (acetylene) *[Tetrahedron Lett* **1975** 16(50):4467-4470] and Negishi (organozinc) *[Aldrichimica Acta.*, **2005**,38(3):71-78] coupling reactions.



Scheme 3: a) piperazine or amine, base; b) Zn or Fe, alcohol solvent; c) $R^3B(OH)_2$ or boronate ester, $Pd(Amphos)Cl_2$, K_3P0_4, dioxane/H_20, μwave, 110°C; d) $R^2C(0)OH$, coupling agent or $R^2C(0)X$, where X is a halide, amine.

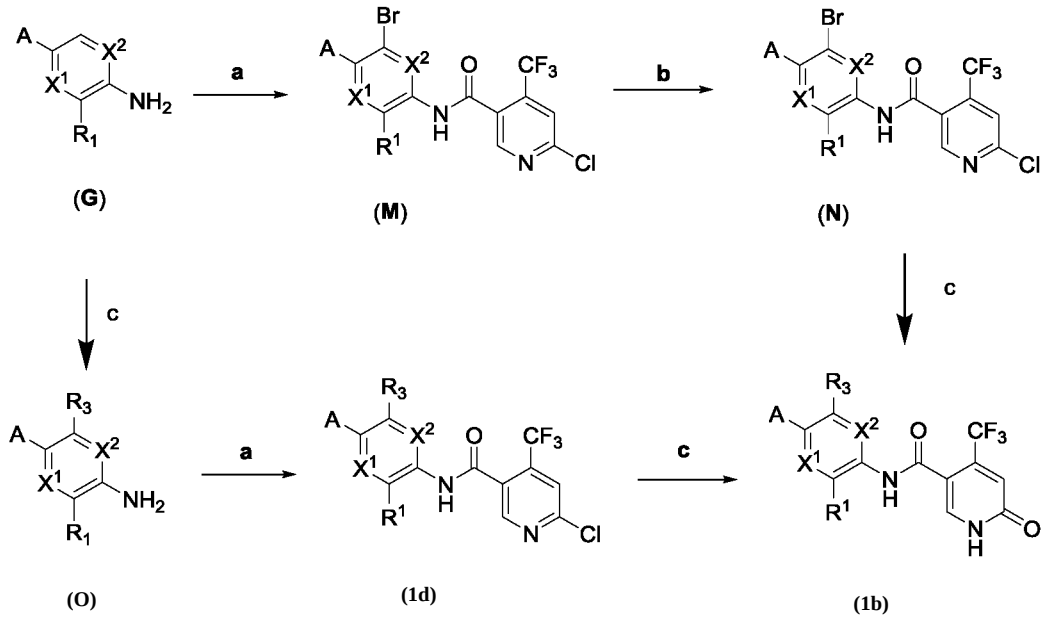
[00186] In some embodiments compounds of Formula (I) are prepared by treatment of compounds of Formula **F** with amines (e.g. piperazines) to afford the intermediate **K** (Scheme 4). In some embodiments, bromination of **K** with N-bromosuccinmide provides the versatile intermediate **L** which is transformed into Formula (I) according to Scheme 3.



(J) (K) (L)

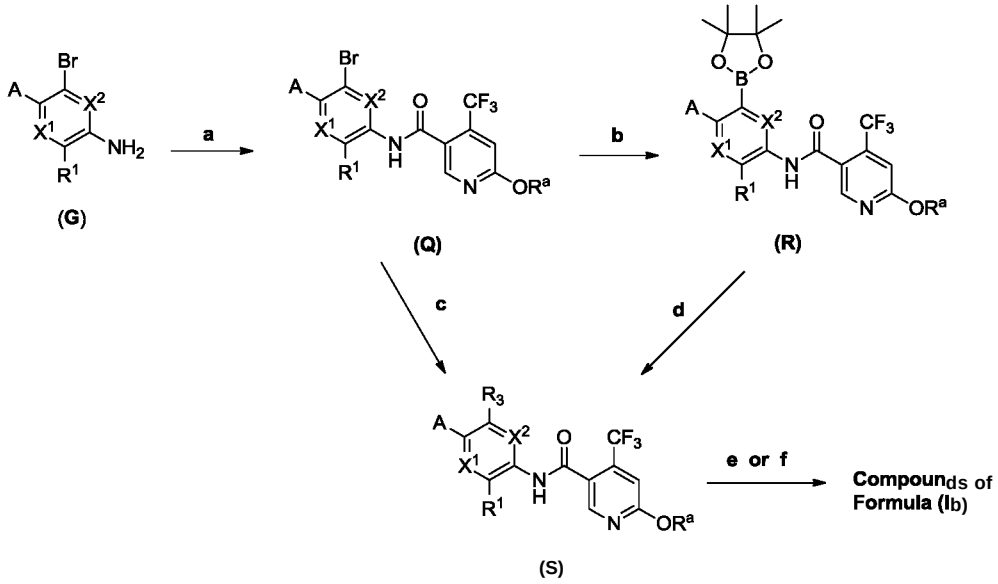
Scheme 4: a) piperazine or amines, base; b) N-bromosuccinimide.

[00187] In some embodiments of the application, compounds of Formula (I) wherein R^2 = 2-chloro-4-trifluoromethylpyridine or trifluoromethylpyrimidone are prepared as shown in Scheme 5. Therefore, in some embodiments, acylation of compounds **G** (prepared, for example, *via* Scheme 3) with the 6-chloro-4-(trifluoromethyl)nicotinic acid chloride (generated *in situ* from the corresponding acid and $SOCl_2$] gives amide **M.** Hydroylsis of **M** with sodium acetate in acetic acid under microwave conditions provides pyridone N. Coupling of N with boronic acids or esters, for example, under the Suzuki conditions deliver compounds of Formula (lb). Alternatively, in some embodiments, the Suzuki coupled intermediate **O** is acylated with the 6-chloro-4-(trifluoromethyl)nicotinic acid chloride to give **Id** which is subsequently hydrolysed to compounds **lb** (Scheme 5).

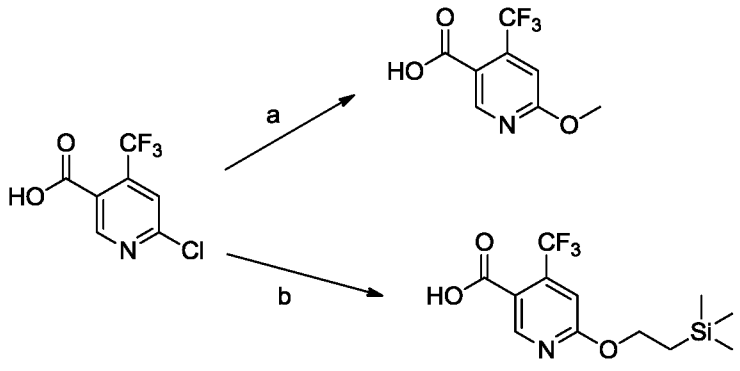


Scheme 5: a) $R^2C(0)OH$, coupling agent or $R^2C(0)X$, X is a halide, amine; b) NaOAc, AcOH, μwave, 160°C; c) $R^3B(OH)_2$ or boronate ester, $Pd(Amphos)Cl_2$, K_3PO4, dioxane/H_20, μwave, 110°C.

[00188] Scheme 6 illustrates another embodiment for the preparation of compounds of Formula (lb), wherein R^2 in the compounds of Formula I is trifluoromethyl pyrimidone. In some embodiments, acylation of aniline **G** with the 6-methoxy-4-(trifluoromethyl)nicotinic acid [R^a = Me] or 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid [R^a = $-CH_2CH_2TMS$] (generated from the corresponding acid and the alcohol, for example, as in Scheme 7) gives amide **Q.** In some embodiments, the amide **Q** is then transformed into the boronate ester **R.** In some embodiments, the Suzuki coupling of **R** to a variety halides affords intermediates **S.** In some embodiments, subsequent deprotection of **S** provides compounds of the present application (Formula **lb).** In some embodiments, compounds of Formula **lb** are prepared *via* Suzuki coupling to **Q** followed by deprotection (Scheme 6).



Scheme 6: a) $R^2C(0)OH$, coupling agent; b) bipinacolatodiboron, Pd $(dppf)_2Cl_2$, NaOAc, dioxane, 110°C; c) $R^3B(OH)_2$ or boronate ester, Pd(Amphos)Cl_2, K_3P0_4, dioxane/H_20, μwave, 110°C; d) R^3-halide or triflate, Pd(Amphos)Cl_2, K_3P0_4, dioxane/H_20, μwave, 110°C; e) HC1 or TFA; f) CsF or TBAF.



Scheme 7: a) NaOMe, MeOH; b) NaH, TMS-EtOH

[00189] Throughout the synthetic methods and processes described herein it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in *"Protective Groups in Organic Synthesis"*, T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, **(1999).** It is also to be understood that a

transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to one skilled in the art. Examples of transformations are given herein, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions of other suitable transformations are given in "Comprehensive Organic Transformations - A Guide to Functional Group Preparations" R.C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, *"Advanced Organic Chemistry"*, March, 4th ed. McGraw Hill (1992) or, *"Organic Synthesis"*, Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include, for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by one skilled in the art.

EXAMPLES

[00190] The following non-limiting examples are illustrative of the present application:

A. General Methods

[00191] Exemplary compounds of the application were synthesized using the methods described herein, or other methods, which are known in the art. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers (e.g. Aldrich, Enamine, Combiblock, Bepharm, and J&W PharmLab).

[00192] The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters ACQUITY UPLC system with a SQ (single quadrupole) MS and a photodiode array (PDA) detector (Milford, MA). The analytical columns were reversed phase Acqity UPLC BEH C18

(2.1 X 50 mm, 1.7 μm). A gradient elution was used (flow 0.4 mL/min), typically starting with mobile phase 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B). A gradient starting at 95% solvent A going to 5% in 1.8 min., holding for 0.5 min., going back to 95% in 0.5 min. and equilibrating the column for 0.5 min. Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

[00193] In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel IB2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well-known iodine vapor and other various staining techniques.

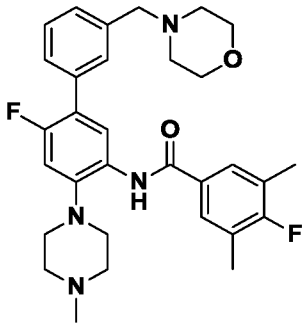
[00194] The compounds and/or intermediates were characterized by LCMS. General conditions were as follows. Low and High resolution Mass spectra were acquired on LC/MS systems using electrospray ionization methods from a range of instruments of the following configurations: Low resolution - Waters ACQUITY UPLC system with a SQ (single quadrupole) MS; Waters ACQUITY UPLC H-Class system with a 3100 (single quadrupole) MS. High resolution - Waters ACQUITY UPLC II system equipped with a Synapt Xevo QTof and Waters ACQUITY UPLC II system equipped with a Synapt G2S QTof mass spectrometer with an atmospheric pressure ionization source. *[M+HJ* refers to the protonated molecular ion of the chemical species.

[00195] Nuclear magnetic resonance (NMR) analysis was performed on a Bruker 500MHz NMR spectrometer using ICON-NMR, under TopSpin program control. Spectra were measured at 298K, unless indicated otherwise and were referenced relative to the solvent chemical shift.

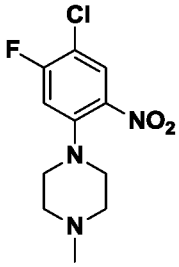
B. Synthesis of Compounds

[00196] The following compounds were prepared using one or more of the synthetic methods disclosed in Schemes 1 to 7:

Example 1: Synthesis of 4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide

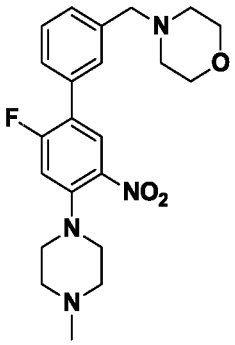


Step 1: Synthesis of 1-(4-chloro-5-fluoro-2-nitrophenyl)-4-methylpiperazine



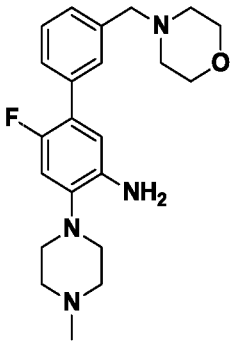
[00197] A microwave vial was charged with 1-bromo-4-chloro-5-fluoro-2-nitrobenzene (0.50 g, 1.965 mmol), palladium(II) acetate (0.044 g, 0.197 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 97% (0.114 g, 0.197 mmol) and cesium carbonate (0.960 g, 2.95 mmol). The vial was capped, evacuated and backfilled with nitrogen. Toluene (volume: 25 ml) and 1-methylpiperazine (0.196 ml, 1.769 mmol) were added *via* syringe and the reaction vial was evacuated and backfilled with nitrogen. The reaction was warmed to 40°C overnight. LCMS indicated about 75% conversion and ~3:1 for the desired product versus the nucleophilic aromatic substitution (SNAr) displacement of the ArF. The reaction was transferred to a round bottom flask with DCM and then concentrated onto celite. Purification by flash chromatography [0-10% MeOH/DCM + 1% NH_4OH; 100 g column] afforded an inseparable mixture of the two products 1-(4-chloro-5-fluoro-2-nitrophenyl)-4-methylpiperazine (0.428 g, 1.095 mmol, 55.7% yield) and 1-(5-bromo-2-chloro-4-nitrophenyl)-4-methylpiperazine. The mixture was used directly in the next step. LCMS $[M+H]^+$ 274 g/mol.

Step 2: Synthesis of 4-((2'-fluoro-4'-(4-methylpiperazin-1-yl)-5'-nitro-[1,1'-biphenyl]-3-yl)methyl)morpholine



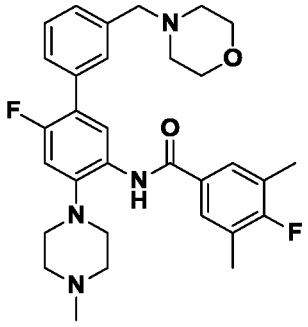
[00198] A vial was charged with the mixture obtained in l-(4-chloro-5-fluoro-2-nitrophenyl)-4-methylpiperazine,3-(4-morpholinomethyl)phenylboronic acid pinacol ester (0.498 g, 1.642 mmol), XPhos Pd G2 (0.017 g, 0.022 mmol), and XPhos (10.44 mg, 0.022 mmol). The vial was sealed with a cap and septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (volume: 10 ml) and a 2M aq. solution of sodium carbonate monohydrate (ACS) (2.74 ml, 5.47 mmol) were added *via* syringe and the vial was evacuated and backfilled with nitrogen an additional time. The reaction was heated at 90°C in an aluminum block overnight. LCMS indicated complete consumption of the starting material(s). The peak at 1.56 minutes ionized for the mass of the target product. The reaction was cooled to room temperature and concentrated onto celite. Purification by silica gel flash chromatography [1-10% MeOH/DCM + l% NH_4OH;] afforded the desired4-((2'-fluoro-4'-(4-methylpiperazin-l-yl)-5'-nitro-[l, 1'-biphenyl]-3-yl)methyl)mo rpholine (0.248 g, 0.598 mmol, 54.7% yield) as a yellow oil. LCMS $[M+H]^+$ 415 g/mol.

Step 3: Synthesis of 6-fluoro-4-(4-methylpiperazin-l-yl)-3'-(morpholinomethyl)-[l,l'-biphenylJ-3-amine



[00199] A solution of 4-((2'-fluoro-4'-(4-methylpiperazin-l-yl)-5'-nitro-[l ,l'-biphenyl]-3-yl)methyl)mo rpholine (0.248 g, 0.598 mmol) in MeOH) (volume: 10 ml) was hydrogenated in the presence of platinum(IV) oxide (0.014 g, 0.060 mmol) at 1 atm (balloon) of H_2 (g). After 18 h (overnight), LCMS indicated formation of two polar peaks, both indicating the desired product by MS. Celite was added to the reaction and the mixture was filtered eluting with MeOH. The filtrate was then concentrated onto celite and purified by silica gel flash chromatography [1-10% MeOH/DCM + 1% NH_4OH] to afford 6-fluoro-4-(4-methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-amine (0.130 g, 0.338 mmol, 56.5% yield) as a blue foam that was >90% the desired product by NMR and LCMS. LCMS $[M+H]^+$ 385 g/mol.

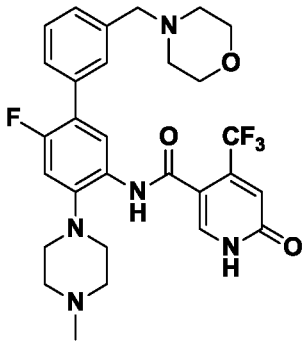
Step 4: Synthesis of 4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide



[00200] 4-Fluoro-3,5-dimethylbenzoic acid (0.016 g, 0.094 mmol) was activated with HATU (0.045 g, 0.117 mmol) and DIPEA (0.020 ml, 0.117 mmol) in N,N-dimethylformamide (DMF) (volume: 1 ml, ratio: 1.000) at room temperature. After 5 minutes, the solution was added to a solution of 6-fluoro-4-(4-methylpiperazin-l-yl)-3'-(moϕ holinomethyl)-[l, 1'-biphenyl]-3-amine (0.030 g, 0.078 mmol) in DMF (volume: 1 ml, ratio: 1.000) at room temperature. The reaction was warmed briefly (at 50°C for lh and then at 70°C for lh). The reaction was then stirred at room temperature overnight and then concentrated onto celite. The intermediate was purified by silica gel flash chromatography (reverse phase) on the Biotage [5-95% MeCN/Water; 30 g CI8 column] to afford 4-fluoro-N-(6-fluoro-4-(4-methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-yl)-3,5-dimethylbenzamide (0.009 g, 0.017 mmol, 21.57% yield) as a clear film that was pure by LCMS and NMR. ¾ NMR (500 MHz, DMSO-d_6) δ = 9.49 (s, 1H), 8.02 (d, J=8.6 Hz, 1H), 7.73 (d, J=6.8 Hz, 2H), 7.47 - 7.41 (m, 3H), 7.34 (d, J=6.8 Hz,

1H), 7.19 (d, J=12.2 Hz, 1H), 3.60 - 3.57 (m, 4H), 3.54 (s, 2H), 2.97 - 2.93 (m, 4H), 2.38 (br. s, 4H), 2.32 (s, 6H), 2.24 (s, 3H). LCMS $[M+H]^+$ 535 g/mol.

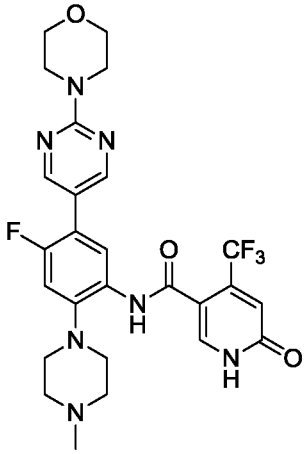
Example 2: Synthesis of 4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide



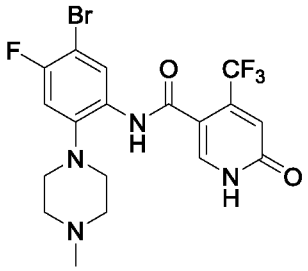
[00201] Diethyl chlorophosphate (0.045 ml, 0.312 mmol) was added to a solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (0.065 g, 0.312 mmol) in pyridine, anhydrous (0.945 ml, 11.70 mmol) at room temperature under nitrogen. After stirring for lh, this solution was added to a vial containing 6-fluoro-4-(4-methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-amine (step 3 from (a): 0.030 g, 0.078 mmol) under nitrogen and the reaction was heated to 70°C for 3 hours. The pyridine was removed under reduced pressure and LCMS of the residue (dissolved in DCM, MeCN and MeOH) indicated complete conversion to the desired product. The mixture was loaded onto celite purified by flash chromatography [0.5-10% DCM/MeOH + 1% NH_4OH] to methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (0.024 g, 0.042 mmol, 53.6% yield) as a clear film. ¾ NMR (500 MHz, DMSO-d_6) δ = 9.53 (s, 1H), 7.94 (s, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.40 - 7.38 (m, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.08 (d, J=12.5 Hz, 1H), 6.81 (s, 1H), 3.60 - 3.57 (m, 4H), 3.53 (s, 2H), 2.93 (br. s., 4H), 2.38 (br. s., 4H), 2.24 (s, 3H); LCMS $[M+H]^+$ 574 g/mol.

[00202] In a like manner, the following additional compounds of the application were prepared using schemes 1-7 and the yields disclosed are for the final synthetic step to afford the compounds of the present application:

Example 3: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

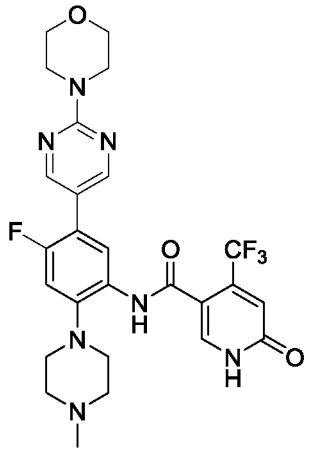


Step 1. N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)-!,6-dihydropyridine-3-carboxamide



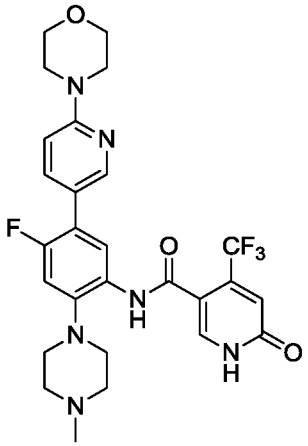
[00203] In a 10 ml microwave vial to a suspension of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (719 mg, 3.47 mmol) in anhydrous pyridine (4210 µï, 52.1 mmol) was slowly added diethyl chlorophosphate (514 µï, 3.56 mmol) at RT in an atmosphere of N_2. The reaction mixture was stirred at RT for 2 h. The suspension turned into a solution and then into a suspension again. To this mixture, 5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)aniline (250 mg, 0.868 mmol) was added and the reaction was heated at 70 °C for 3 h. After completion of the reaction, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous $Na_2SC>4$. The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the desired compound. LCMS C8 [M+l]+ = 459.4

Step 2: N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide



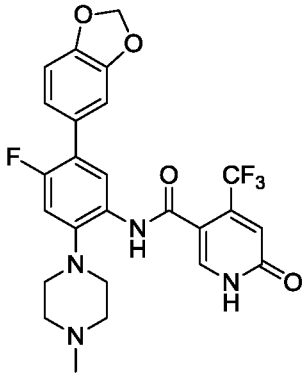
[00204] In a 5 mL microwave vial N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (29.67 mg, 0.062 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (54.3 mg, 0.187 mmol), sodium carbonate, anhydrous (65.9 mg, 0.622 mmol), XPhos (5.93 mg, 0.012 mmol) and XPhos Pd G2 (9.78 mg, 0.012 mmol) were dissolved in water (1166 μΐ) and 1,4-dioxane (1943 μΐ) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 120 °C. The solvent was evaporated and 15 ml of CH2CI2 were added. The suspension was sonicated and extracted from water. The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH2CI2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the desired compound in 61% yield. ^{1}H NMR (500 MHz, MeOD) δ 8.55 (s, 2H), 7.97 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 12.0 Hz, 1H), 6.92 (s, 1H), 3.86 - 3.82 (m, 4H), 3.78 - 3.74 (m, 4H), 3.01 (s, 4H), 2.66 (s, 4H), 2.37 (s, 3H); LCMS $[M+H]^+$ 562.7.

Example 4: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(6-morpholinopyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00205] The title compound was prepared in 78% yield similar to the sequence described above for the preparation of Example 3 except using 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-morpholine in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester to provide the title compound in 78% yield. 1H NMR (500 MHz, MeOD) δ 8.32 (s, 1H), 7.97 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 12.0 Hz, 1H), 6.92 (s, 1H), 6.91 (d, J = 9.1 Hz, 1H), 3.83 - 3.80 (m, 4H), 3.55 - 3.52 (m, 4H), 3.03 (s, 4H), 2.76 (s, 4H), 2.45 (s, 3H); LCMS $[M+H]^+$ 561.6.

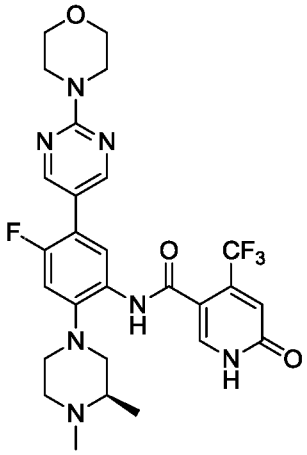
Example 5: N-(5-(benzo[d][l,3]dioxol-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00206] This example was prepared similar to the sequence described above for the preparation of Example 3 using 3,4-methylenedioxyphenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester to provide the title compound in 70% yield. ^{1}H NMR (500 MHz, MeOD) δ 7.96 (s, 1H), 7.88 (d, J = 8.3

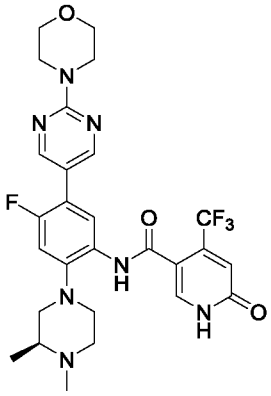
Hz, 1H), 7.06 (d, *J* = 12.0 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 2H), 6.92 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 5.99 (s, 2H), 3.02 (t, *J* = 4.9 Hz, 4H), 2.73 (s, 4H), 2.43 (s, *J* = 13.2 Hz, 3H); LCMS $[M+H]^+$ 519.5.

Example 6: (R)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholmopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



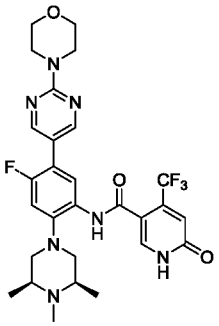
[00207] The title compound was prepared using (i?)-4-(4-chloro-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine and 2-(4-moϕ holino)pyrimidine-5-boronic acid pinacol ester to give the (i?)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-nitrophenyl)pyrimidin-2-yl)mo rpholine intermediate, which was reduced to the corresponding amine using standard methods. Diethyl chlorophosphate (4 equiv.) was added to a solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (4 equiv.) in pyridine at room temperature under N_2. After stirring for 1 h, the solution of activated acid was added to a vial containing (i?)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-aminophenyl)pyrirnidin-2-yl)mo rpholine (1 equiv.) under nitrogen and the reaction was heated to 70 °C for 3 h. The reaction mixture was concentrated onto celite and subjected to flash chromatography [0.5-10% DCM/MeOH + 1% NH40H] to afford the title compound in 19% yield. ¾ NMR (500MHz, DMSO-de) δ = 9.43 (br. s., 1H), 8.53 (s, 2H), 7.96 (s, 1H), 7.78 (d, *J*=8.4 Hz, 1H), 7.08 (d, *J*=12.2 Hz, 1H), 6.70 (s, 1H), 3.77 -3.73 (m, 4H), 3.70 - 3.66 (m, 4H), 3.08 - 2.95 (m, 2H), 2.88 - 2.72 (m, 2H), 2.41 (t, *J*=10.6 Hz, 1H), 2.35 - 2.30 (m, 1H), 2.25 - 2.18 (m, 4H), 0.97 (d, *J*=6.1 Hz, 3H); LCMS $[M+H]^+$ 576.

Example 7: (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholmopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

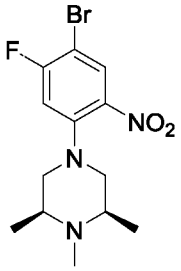


[00208] The title compound was prepared using (5)-4-(4-chloro-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine and 2-(4^ orpηo1iηo)pyriω ώηe-5-boroηic acid pinacol ester to give the (5)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-nitrophenyl)pyrimidin-2-yl)mo rpholine intermediate, which was reduced to the corresponding amine using standard methods. Diethyl chlorophosphate (4 equiv.) was added to a solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (4 equiv.) in pyridine at room temperature under N_2. After stirring for 1 h, the solution of activated acid was added to a vial containing (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-arninophenyl)pyrirnidin-2-yl)mo φ holine (1 equivalent) under nitrogen and the reaction was heated to 70 °C for 3 h. The reaction mixture was concentrated onto celite and subjected to flash chromatography [0.5-10% DCM/MeOH + 1% NH40H] to afford the title compound in 15% yield. ¾ NMR (500MHz, DMSO-de) δ = 9.45 (br. s., 1H), 8.53 (s, 2H), 7.95 (s, 1H), 7.78 (d, *J*=8.6 Hz, 1H), 7.08 (d, *J*=12.2 Hz, 1H), 6.72 (br. s., 1H), 3.77 - 3.74 (m, 4H), 3.69 - 3.66 (m, 4H), 3.00 (dd, *J*=11.0, 17.4 Hz, 2H), 2.87 - 2.72 (m, 2H), 2.44 - 2.30 (m, 3H), 2.21 (s, 4H), 0.97 (d, *J*=6.1 Hz, 3H); LCMS $[M+H]^+$ 576.4 .

Example 8: N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

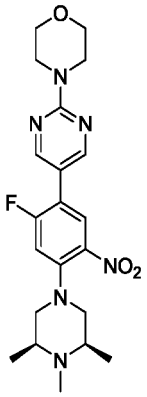


Step 1: (2S, 6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2, 6-trimethylpiperazine

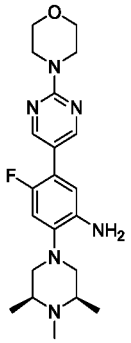


[00209] To a suspension of K_2CO_3 (0.456 g, 3.30 mmol) in toluene (10 mL) was added l-bromo-2,4-difluoro-5 -nitrobenzene (1.497 g, 6.29 mmol) and the reaction mixture was heated at 50 °C for 2 min before a solution of (2R,6S)- 1,2,6-trimethylpiperazine (0.806 g, 6.29 mmol) in toluene (3 mL) was slowly added over 3 min. The resulting mixture was stirred at 50 °C for 1 h. After adding water (20 mL), it was extracted with EtOAc (30 mL x 2) and the combined extracts were concentrated and dried under vacuum to give a dark orange red oil which solidified to a yellow solid (2.166 g, 100% yield). LCMS $[M + H]^+$= 348.3.

Step 2: 4-(5-(2-fluoro-5-nitro-4-((3S, 5R)-3, 4,5-trimethylpiperazin-l-yl)phenyl)pyrimidin-2-yl)morpholine

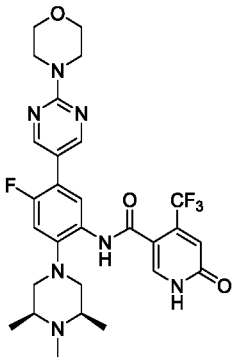


[00210] To a 20 mL microwave vial charged with (2S,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (1.04 g, 3 mmol), 2-(4^ orpηo1iηo)pyη'ηidiηe-5-boronic acid pinacol ester (1.22 g, 4.2 mmol), and Pd(dppf)Cl_2 (220 mg, 0.3 mmol, 10 mol%) was added dioxane (10 mL), followed by 1 M aq K_3PO_4 (5.0 mL, 5 mmol). The resulting mixture was irradiated in microwave at 110 oC for 2 h, diluted with **H_20** (10 mL) and extracted with EtOAc (30 mL x 2). The combined extracts were concentrated and purified by Biotage SNAP KP-Sil and 100 g column (EtOAc/hex 0-100% then MeOH/DCM 0-15%) to give the crude nitro. LCMS [M+H]+ = 431.3.



Step 3: 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline

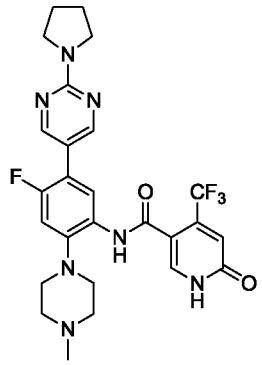
[00211] To a solution of 4-(5-(2-fluoro-5-nitro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)pyrimidin-2-yl)mo rpholine (1.081 g) in 1:1 MeOH/THF (30 mL) at ambient temperature was added a suspension of Raney-Nickel (129 mg, 0.5 mmol) in MeOH (2 mL), followed by hydrazine monohydrate (0.44 mL, 9 mmol) dropwise over 1 min. After addition, the reaction mixture was stirred at rt for 15 min. Additional MeOH (5 mL) and THF (5 mL) was added and the mixture was heated at 60 °C. Additional Raney-Nickel (129 mg, 0.5 mmol) in MeOH (2 mL) was added, followed by hydrazine monohydrate (0.44 mL, 9 mmol). The reaction mixture was heated at 60 °C for 30 min. The mixture was allowed to cool, passed through celite and rinsed with MeOH (30 mL x 2) and DCM (20 mL). The filtrate was concentrated to about 30 mL of volume. The resulting precipitate was collected by suction filtration to give the title compound as a grey solid. LC-MS [MH]+ 401.3.



Step 4: N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

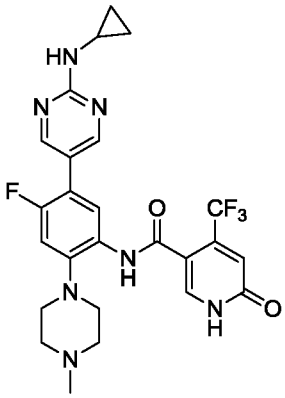
[00212] To a 25 mL round bottomed flask charged with 6-chloro-4-(trifluoromethyl)nicotinic acid (406 mg, 1.8 mmol) was added thionyl chloride (2.18 mL, 30 mmol). The resulting suspension was heated at 80 °C for 1 h. The mixture was evaporated to give a light yellow oil which was treated with DCM (10 mL), 4-fluoro-5-(2-morpholinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (601 mg, 1.5 mmol) and Et3N (0.63 mL, 4.5 mmol). The resulting mixture was stirred at ambient temperature for 1 h. After quenching with sat. aq NaHCCb (20 mL), the mixture was extracted with DCM (30 mL x 2) and the combined extracts were evaporated and dried to give the chloro intermediate as a light brown foam. The resulting chloropyridine intermediate was taken up in HOAc/H_2**0** (10 mL/3 mL) and NaOAc (246 mg, 3 mmol) was added in a 20 mL microwave vial. The mixture was irradiated in a microwave apparatus at 160 °C for 6 h. LCMS showed completion of the reaction. After removal of HOAc using a Rotovap at (bath heated to 60 °C), the residue was diluted with DCM (30 mL), basified with sat. NaHC0 $_3$ (20 mL) and extracted with DCM (50 mL x 2). The combined extracts were concentrated and purified by Biotage SNAP KP-Sil using a 50g column. Fractions showing clean product were combined concentrated and dried to give the title compound as an off-white solid (460 mg, 51% yield). ^{1}H NMR (500MHz, MeOD-d4) δ = 8.58 - 8.55 (m, 2H), 7.98 (s, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 7.10 (d, *J*=12.1 Hz, 1H), 6.93 (s, 1H), 3.89 - 3.82 (m, 4H), 3.81 - 3.75 (m, 4H), 3.08 (d, *J*=11.2 Hz, 2H), 2.67 - 2.52 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); ^{19}F NMR (471MHz, METHANOLS) δ = -63.80, -120.73; LCMS $[MH]^+$ 590.32.

[00213] *Example 9: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-(pyrrolidin-l-yl)pyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide*



[00214] The title compound was prepared similar to the sequence described above for the preparation of Example 3 using 2-(pyrrolidin-l-yl)pyrimidine-5-boronic acid pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester to give the title compound in 66% yield. ^{1}H NMR (500 MHz, MeOD) δ 8.51 (s, 2H), 7.97 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 12.0 Hz, 1H), 6.92 (s, 1H), 3.60 (t, *J* = 6.7 Hz, 4H), 3.02 (t, *J* = 5.0 Hz, 4H), 2.69 (s, *J* = 2.2 Hz, 4H), 2.40 (s, 3H), 2.05 - 2.03 (m, 4H); LCMS $[M+H]^{+}$ 546.38.

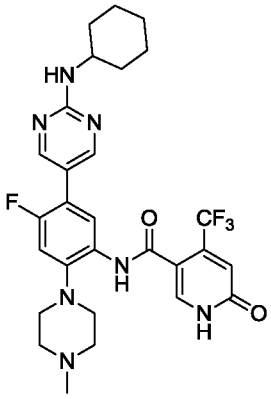
Example 10: N-(5-(2-(cyclopropylamino)pyrimidm-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00215] The title compound was prepared in 33% yield similar to the sequence described above for the preparation of Example 3 using 2-cyclopropylaminopyrimidine-5-boronic acid, pinacol ester in place of 2-(4^ orpηo1inο)pyrimidiηe-5-bθrοηic acid

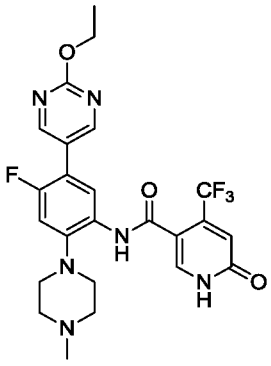
pinacol ester. ^{1}H NMR (500 MHz, MeOD-d $_4$) δ 8.47 (s, 2H), 8.03 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 11.7 Hz, 1H), 6.93 (s, 1H), 3.22 (s, 4H), 2.91 (s, 3H), 1.32 (dd, *J* = 9.0, 6.1 Hz, 4H); LCMS $[M+H]^+$ 532.5.

Example 11: N-(5-(2-(cyclohexylamino)pyrimidm-5-yl)-4-fluoro-2-(4-methylpiperazm-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



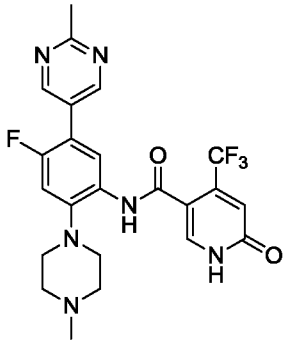
[00216] The title compound was prepared in 29% yield similar to the sequence described above for the preparation of Example 3 using 2-(cyclohexylamino)pyrimidine-5-boronic acid, pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.45 (s, 2H), 7.97 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 11.9 Hz, 1H), 6.92 (s, 1H), 3.86 - 3.75 (m, 1H), 3.01 (s, 4H), 2.69 (s, 4H), 2.39 (s, 3H), 2.02 (dd, *J* = 11.9, 2.2 Hz, 2H), 1.80 (dd, *J* = 10.5, 2.8 Hz, 2H), 1.68 (d, *J* = 12.9 Hz, 2H), 1.43 (d, *J* = 12.8 Hz, 2H), 1.31 (d, *J* = 13.4 Hz, 2H); LCMS $[M+H]^+$ 574.4.

Example 12: N-(5-(2-ethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



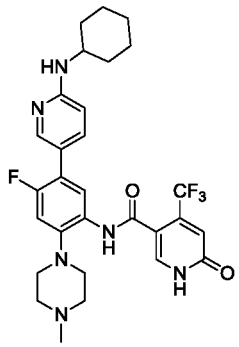
[00217] The title compound was prepared in 68% yield similar to the sequence described above for the preparation of Example 3 using 2-ethoxypyrimidine-5-boronic acid in place of 2-(4-morpholino)pyrimidine-5 -boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.74 (s, 2H), 7.98 (s, 1H), 7.95 (d, ***J*** = 8.2 Hz, 1H), 7.15 ***(d, J*** = 12.0 Hz, 1H), 6.92 (s, 1H), 4.50 (q, ***J*** = 7.1 Hz, 2H), 3.03 (s, 4H), 2.68 (s, 4H), 2.39 (s, 3H), 1.44 (t, ***J*** = 7.1 Hz, 3H); LCMS $[M+H]^+$ 520.9.

Example 13: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-methylpyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



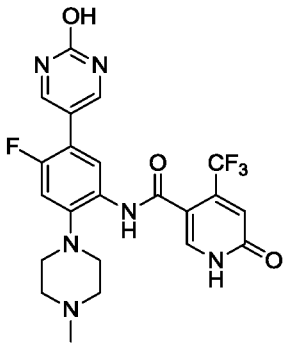
[00218] The title compound was prepared in 50% yield similar to the sequence described above for the preparation of Example 3 using 2-methylpyrimidin-5-ylboronic acid pinacol ester in place of 2-(4-morpholino)pyrimidine-5 -boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.89 (s, 2H), 7.98 (d, ***J*** = 7.9 Hz, 1H), 7.98 (s, 1H), 7.17 (d, ***J*** = 12.1 Hz, 1H), 6.93 (s, 1H), 3.06 (t, ***J*** = 4.2 Hz, 4H), 2.75 (s, 3H), 2.72 (s, 4H), 2.41 (s, 3H); LCMS $[M+H]^+$ 491.2.

Example 14: N-(5-(6-(cyclohexylamino)pyridin-3-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamide



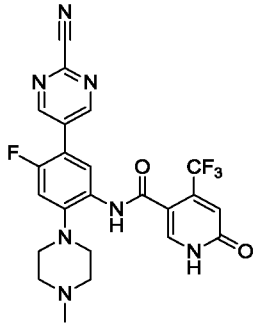
[00219] The title compound was prepared in 99% yield similar to the sequence described above for the preparation of Example 3 using 6-(cyclohexylamino)pyridine-3-boronic acid pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD-d$_4$) δ 8.11 (s, IH), 7.97 (s, IH), 7.88 (d, *J* = 8.2 Hz, IH), 7.62 (d, *J* = 8.9 Hz, IH), 7.08 (d, *J* = 12.0 Hz, IH), 6.92 (s, IH), 6.59 (d, *J* = 8.8 Hz, IH), 3.71 - 3.63 (m, IH), 3.03 (s, 4H), 2.77 (s, 4H), 2.46 (s, 3H), 2.03 (dd, *J* = 12.4, 2.7 Hz, 2H), 1.82 - 1.77 (m, 2H), 1.45 (td, *J* = 12.4, 3.3 Hz, 2H), 1.32 - 1.22 (m, 4H); LCMS [M+H]$^+$ 573.4 g/mol.

Example 15: N-(4-fluoro-5-(2-hydroxypyrimidin-5-yl)-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



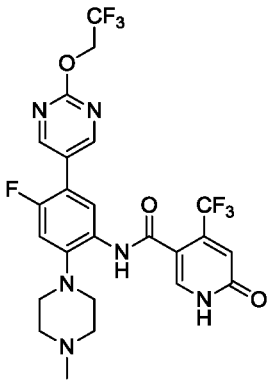
[00220] The title compound was isolated in 4% yield as a side product from the chromatographic purification of Example 12. ^{1}H NMR (500 MHz, MeOD-d$_4$) δ 8.53 (s, 2H), 7.99 (s, IH), 7.91 (d, *J* = 8.3 Hz, IH), 7.17 (d, *J* = 12.0 Hz, IH), 6.93 (s, IH), 3.11 (s, 4H), 3.03 (s, 4H), 2.66 (s, 3H); LCMS [M+H]$^+$ 493.3.

Example 16: N-(5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



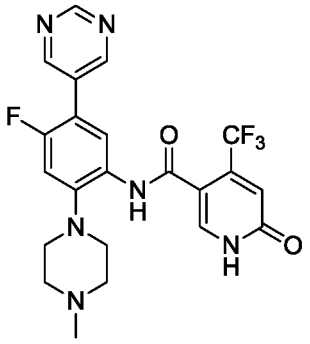
[00221] The title compound was prepared in 41% yield similar to the sequence described above for the preparation of Example 3 using 2-cyanopyrimidine-5-boronic acid pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD-d$_4$) δ 9.14 (s, 2H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.98 (s, 1H), 7.20 (d, *J* = 12.3 Hz, 1H), 6.93 (s, 1H), 3.11 - 3.07 (m, 4H), 2.74 (s, 4H), 2.43 (s, 3H); LCMS $[M+H]^+$ 501.8 g/mol.

Example 17: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-(2,2,2-Mfluoroethoxy)pyrimidin-5-yl)phenyl)-6<>xo-4-(Mfluoromethyl)-l,6-dihydropyridine-3-carboxamide



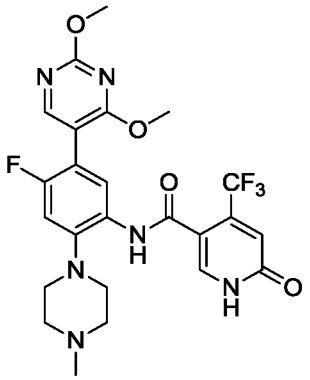
[00222] The title compound was prepared in 81% yield similar to the sequence described above for the preparation of Example 3 using 2-(2,2,2-trifluoroethoxy)pyrimidine-5-boronic acid, pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD-d4) δ 8.82 (s, 2H), 7.97 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 12.0 Hz, 1H), 6.92 (s, 1H), 5.01 (q, *J* = 8.6 Hz, 2H), 3.06 - 3.02 (m, 4H), 2.70 (s, 4H), 2.40 (s, 3H); LCMS $[M+H]^+$ 574.8.

Example 18: N-(4-fluoro-2-(4-methylpiperazin-l -yl)-5-(pyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



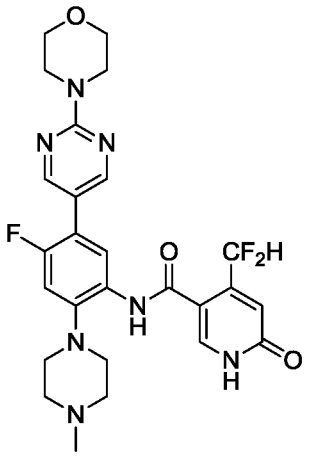
[00223] The title compound was prepared in 78% yield similar to the sequence described above for the preparation of Example 3 using 5-pyrimidine boronic acid pinacol ester in place of 2-(4-morpholino)pyrimidine-5 -boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD-d $_4$) δ 9.15 (s, 1H), 9.00 (s, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.98 (s, 1H), 7.18 (d, *J* = 12.1 Hz, 1H), 6.92 (s, 1H), 3.06 (t, *J* = 4.4 Hz, 4H), 2.69 (s, 4H), 2.40 (s, 3H); LCMS $[M+H]^+$ 476.9.

Example 19: N-(5-(2,4-dimethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



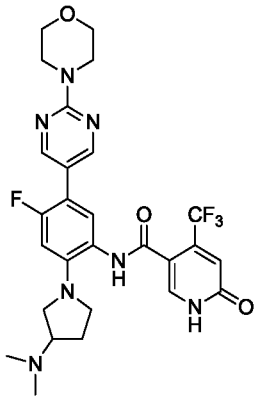
[00224] The title compound was prepared in 73% yield similar to the sequence described above for the preparation of Example 3 using 2,4-dimethoxypyrimidine-5-boronic acid, pinacol ester in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester. ¾ NMR (500 MHz, MeOD-d_4) δ 8.22 (s, 1H), 7.95 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 11.2 Hz, 1H), 6.92 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.03 (s, 4H), 2.71 (s, 4H), 2.41 (s, 3H); LCMS $[M+H]^+$ 537.3.

Example 20: 4-(difluoromethyl)-N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide

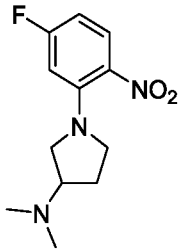


[00225] In a 5 ml microwave vessel to a suspension of 4-(difluoromethyl)-6-hydroxynicotinic acid (60.9 mg, 0.322 mmol) in anhydrous pyridine (391 µï, 4.83 mmol) was added slowly diethyl chlorophosphate (47.7 µï, 0.330 mmol) at RT in an atmosphere of nitrogen. The reaction mixture was stirred for 2 h. The suspension turned homogeneous and then a precipitate formed. To this mixture, 4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-mo rpholinopyrirnidin-5-yl)aniline (30 mg, 0.081 mmol) was added and the reaction was heated at 70 °C for 3 h. After completion, the pyridine was removed in vacuo and the residue partitioned between EtOAc (3 mL) and saturated aqueous $NaHC0_3$ (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous Na_2S0_4. The solvent was evaporated in vacuo yielding the crude product. The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% DCM, 10% MeOH, 1% NH_4Ac/DCM) to afford the desired compound in 72% yield. ¾ NMR (500 MHz, MeOD-d_4) δ 8.55 (d, J = 1.1 Hz, 2H), 8.03 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.30 (t, J = 55.0 Hz, 1H), 7.10 (d, J = 12.1 Hz, 1H), 6.81 (s, 1H), 3.85 - 3.82 (m, 4H), 3.77 - 3.75 (m, 4H), 3.02 (s, 4H), 2.67 (s, 4H), 2.38 (s, 3H); LCMS $[M+H]^+$ 544.4.

Example 21: N-[2-[3-(dimethylamino)pyrrolidin-l-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

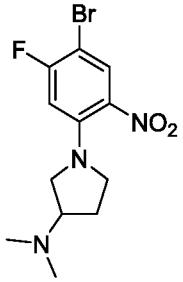


Step 1: l-(5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



[00226] A suspension of 3-(dimethylamino)pyrrolidine (0.40 mL, 3.1 mmol) and K_2C0_3 (0.22 g, 1.6 mmol) in toluene (4 mL) was warmed to 45 °C. After 10 minutes 2,4-difluoro-1-nitrobenzene (0.35 mL, 3.1 mmol) was added dropwise. The reaction was maintained at 45 °C for 1 h. The reaction was concentrated onto celite and flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] afforded l-(5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.33 g, 41 %). LCMS [M+H]+: 254.0.

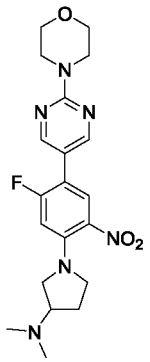
Step 2: l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



[00227] A solution of l-(5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.325 g, 1.3 mmol) and NBS (0.22 g, 1.3 mmol) in acetic acid (10 mL) was heated at 105 °C for 2 h. The reaction was cooled to room temperature and poured into water. The mixture was carefully neutralised with Na_2C03 (2M Aq.) and the resultant was extracted exhaustively with DCM. The combined extracts were dried over magnesium sulfate,

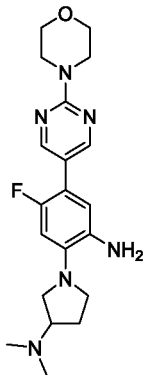
filtered and concentrated to dryness. Flash chromatography [1-10% DCM/MeOH + 1% NH40H] afforded the title compound (0.184 g, 43 %). LCMS [M+H]+: 332.2.

Step 3: l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



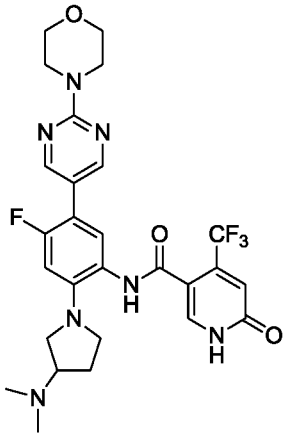
[00228] A 30 mL vial was charged with a mixture of l-(4-bromo-5-fiuoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.092 g, 0.277 mmol), 2-(4-Morpholino)pyrimidine-5-boronic acid pinacol ester (0.113 g, 0.388 mmol), XPhos Pd G2 (4.36 mg, 5.54 μηιοϊ) and XPhos (2.64 mg, 5.54 μηιοϊ). The vial was sealed with a cap/septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (4 ml) and 2M Aq sodium carbonate (0.692 ml, 1.385 mmol) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated in an aluminum block overnight at 95 °C. LCMS [BJW-5015-0054-01; more polar method] indicated clean conversion to the desired product. The reaction mixture was loaded onto celite and purified by flash [0.5-10% MeOH/DCM + 1% NH_4OH] to afford l-(5-fluoro-4-(2-moφ holinopyrilnidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyl ·rolidin-3-amine (0.271 mmol, 98 % yield) as a yellow film that was >95% pure by LCMS. LCMS [M+H]+: 417.3.

Step 4. l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine



[00229] A mixture of l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.113 g, 0.271 mmol), iron (0.076 g, 1.357 mmol) and acetic acid (3 ml) was heated to 85 °C for 1 h. The reaction mixture was cooled, diluted with DCM, and decanted by pipette to a round bottom flask. LCMS indicated complete consumption of the starting nitro compound. Concentration onto celite followed by flash [0.1-10% MeOH/DCM + 1% NH_4OH] afforded l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine (0.204 mmol, 75 % yield) [BJW-501 5-0056-02] as a yellow foam that was -92% pure by LCMS. LCMS [M+H]+ = 387.3

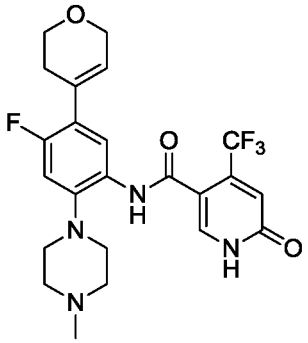
Step 5: N-[2-[3-(dimethylamino)pyrrolidin-l-ylJ-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



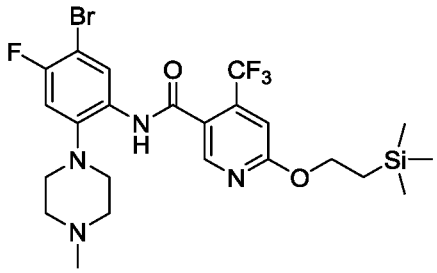
[00230] Diethyl chlorophosphate (0. 118 ml, 0.81 8 mmol) was added to a stirring solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (0.169 g, 0.818 mmol) in pyridine (Py) (2 ml) at room temperature. After stirring for 45 minutes the solution of activated acid was added to a stirring solution of l-(2-amino-5-fiuoro-4-(2-

morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine (0.079 g, 0.204 mmol) also in pyridine (2 ml) at room temperature. The reaction was heated to 75 °C for ~5 h. LCMS indicated complete conversion to the desired product along with the excess nicotinic acid. The reaction was concentrated onto celite and purified by flash RP on the biotage [5-95% MeCN/water - no modifier] to afford N-(2-(3-(dimetiiylainino)pyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (0.064 mmol, 32 % yield) as a tan solid. 1H-NMR (500 MHz, DMSO-d6) δ = 12.56 (br. s., 1H), 9.82 (s, 1H), 8.51 (s, 2H), 7.96 (br. s., 1H), 7.32 (d, *J*=7.5 Hz, 1H), 6.81 (s, 1H), 6.67 (d, *J*=13.3 Hz, 1H), 3.76 - 3.67 (m, 8H), 3.41 - 3.38 (m, 2H), 3.26 - 3.22 (m, *J*=8.6, 8.6 Hz, 1H), 2.64 (br. s., 2H), 2.19 - 2.13 (m, 6H), 2.07 (br. s., 1H),1.74 - 1.67 (m, 1H); LCMS [M+H]+ 576.5.

Example 22: N-[5-(3, 6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



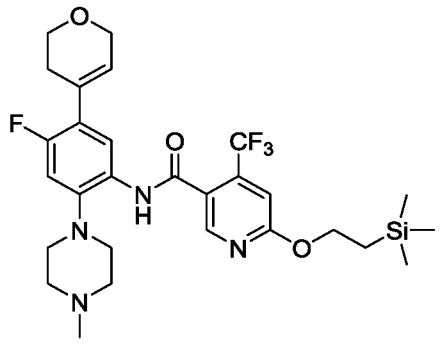
Step 1: N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l -yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00231] To a solution of 4-(1iifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (800 mg, 2.60 mmol) in pyridine (6.0 mL) was added slowly diethyl chlorophosphate (0.384 ml, 2.65 mmol) at rt in an atmosphere of argon, and the reaction

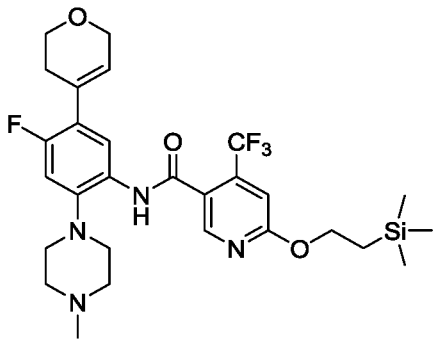
mixture was stirred at rt for about 1 h. The clear solution became cloudy/suspension. To this was then added 5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)aniline (150 mg, 0.521 mmol) in one lot, and the reaction mixture was heated to 90°C under argon atmosphere. The reaction was complete in 2 h. A mixture of the desired product along with the excess 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid was observed. The reaction mixture was concentrated to dryness and the residue was co-evaporated twice with toluene to remove the residual pyridine. The residue was taken up in DCM and adsorbed onto celite and purified on Isco column (24 g), to afford the title compound as a beige solid (237 mg). LCMS [M + H]+ = 577.6

Step 2. N-(5-(3, 6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



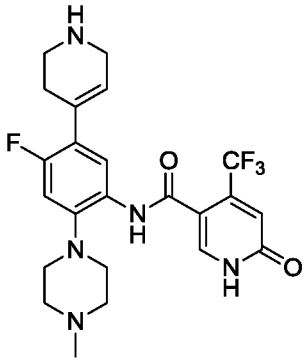
[00232] N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l -yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (35 mg, 0.061 mmol) and 3,6-dihydro-2H-pyran-4-boronic acid, pinacol ester (17.83 mg, 0.085 mmol) were mixed in 1,4-dioxane (2 ml). Potassium phosphate tribasic reagent grade, >=98% (25.7 mg, 0.121 mmol) was added as a solution in 0.5 ml water and the vial was flushed with nitrogen. Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (4.29 mg, 6.06 μmoï) was added, the vial was sealed, and the mixture heated in a microwave reactor to 110°C for 30 minutes. The crude mixture was concentrated onto celite and purified on Isco (4G) column, eluting with DCM containing 0-2 % methanol. The product containing fractions were combined and concentrated to afford the title compound as a pale yellow glassy solid (34 mg). LCMS [M+H]+ = 581.4.

Step 3: N-(5-(3, 6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide

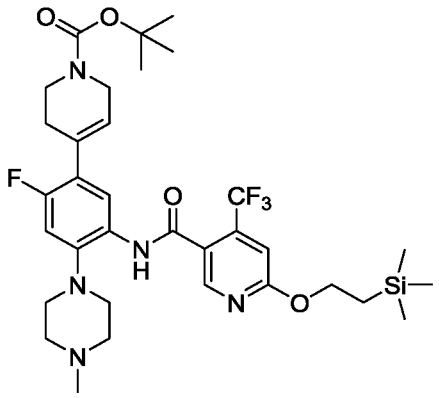


[00233] TFA (1 ml) was added to a solution of the N-(5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-2-(trifluoromethyl)-4-(2-(trimethylsilyl)ethoxy)benzamide in DCM (2 ml) at RT and the reaction mixture was stirred at RT. LCMS showed completion of the reaction after 0.5 h. The mixture was concentrated to dryness, and the residue was triturated with diethylether. The solid was filtered and dried under high vacuum to obtain the desired product as a beige solid (22 mg). ^{1}H NMR (500MHz, MeOD-d$_4$) δ = 8.02 (s, 1H), 7.84 - 7.74 (m, 1H), 7.06 (d, *J*=12.2 Hz, 1H), 6.98 - 6.93 (m, 1H), 6.11 (br. s., 1H), 4.31 (q, *J*=2.7 Hz, 2H), 3.92 (t, *J*=5.4 Hz, 2H), 3.61 (d, *J*=11.4 Hz, 2H), 3.29 - 3.21 (m, 2H), 2.97 (s, 3H), 2.72 - 2.64 (m, 4H), 2.72 - 2.64 (m, 4H), 2.51 (br. s., 2H). LCMS [M+H]+ 481

Example 23: N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

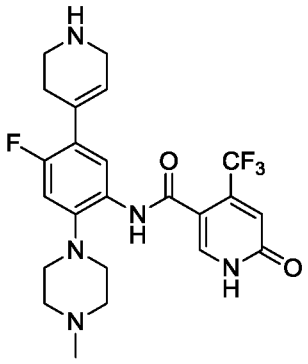


Step 1: tert-butyl 4-(2-fluoro-4-(4-methylpiperazin-l-yl)-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate



[00234] *N*-(5-Bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (35 mg, 0.061 mmol) and tert-butyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-l,2,3,6-tetrahydropyridine-1-carboxylate (26.2 mg, 0.085 mmol) were mixed in 1,4-dioxane (1.5 ml). Potassium phosphate tribasic reagent grade, >=98% (25.7 mg, 0.121 mmol) was added as a solution in 0.5 ml water and the vial was flushed with nitrogen. Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (4.29 mg, 6.06 μηοϊ) was added, the vial was sealed, and the mixture heated in a microwave reactor to 110°C for 30 minutes. The crude mixture was concentrated onto celite and purified on silica gel chromatography, eluting with hexanes containing 0-50 % ethylacetate. The product containing fractions were combined and concentrated to afford the title compound as a white foam (27 mg). LCMS [M+H]+ = 681.2.

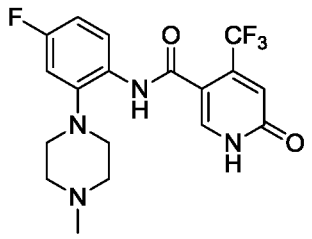
Step 2: N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



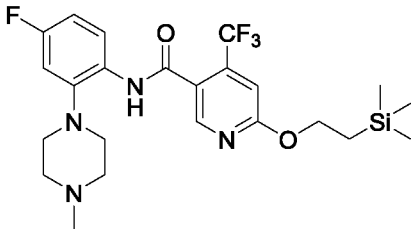
[00235] TFA (1 ml) was added to a solution of the starting material in DCM (2 ml) at RT and the reaction mixture was stirred at RT. LCMS showed completion of

the reaction after 0.5 h. The reaction mixture was concentrated to dryness, and the residue was triturated with diethylether. The solid was filtered and dried under high vacuum to obtain the desired product as a pale yellow solid (29 mg, 93% yield). 1H-NMR (500MHz, METHANOL-d4) δ = 8.01 (s, 1H), 7.87 (d, *J*=7.9 Hz, 1H), 7.11 (d, *J*=12.1 Hz, 1H), 6.95 (s, 1H), 6.09 (br. s., 1H), 3.89 (d, *J*=2.4 Hz, 2H), 3.62 (d, *J*=11.4 Hz, 2H), 3.48 (t, *J*=6.1 Hz, 2H), 3.40 - 3.34 (m, 2H), 3.31 - 3.22 (m, 2H), 3.17 - 3.07 (m, 2H), 2.97 (s, 3H), 2.80 (br. s., 2H). LCMS [M+H]+ = 480

Example 24: N-[4-fluoro-2-(4-methylpiperazin-l -yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide (Comparative Example)



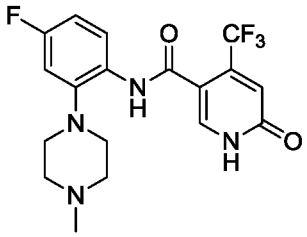
Step 1: N-(4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00236] *N*-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (35 mg, 0.061 mmol) and l-methyl-l,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (18.93 mg, 0.085 mmol) were mixed in 1,4-dioxane (1.5 ml). Potassium phosphate tribasic reagent grade, >=98% (25.7 mg, 0.121 mmol) was added as a solution in 0.5 ml water and the vial was flushed with nitrogen. Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (4.29 mg, 6.06 μmoï) was added, the vial was sealed, and the mixture heated in a microwave reactor to 110°C for 30 minutes. The crude mixture was concentrated onto celite and purified on Isco (4G) column, eluting with hexanes containing 0-60 % EA. The product containing

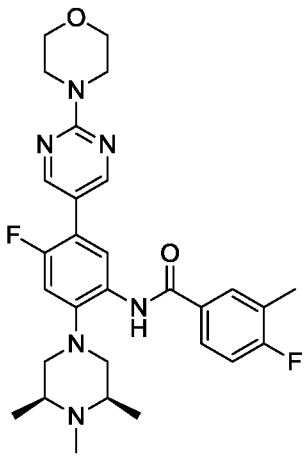
fractions were combined and concentrated to afford the title compound as a pale yellow foam (13.5 mg, 44.7% yield). LCMS [M+H]+ = 499.6.

Step 2: N-[4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00237] TFA (1 mL) was added to a solution of the starting material in DCM (2 ml) at RT and the reaction mixture was stirred at RT. LCMS showed completion of the reaction after 1.5 h. The reaction mixture was concentrated to dryness, and the residue was triturated with diethyl ether. The solid was filtered and dried under high vacuum to obtain the desired product as a pale yellow solid.(10 mg, 65% yield). ^-NMR (500MHz, METHANOL-d4) δ = 7.89 (s, 1H), 7.70 (dd, *J*=6.0, 8.8 Hz, 1H), 6.97 (dd, *J* = 2.8, 10.0 Hz, 1H), 6.88 (dt, *J*=2.8, 8.4 Hz, 1H), 6.83 (s, 1H), 3.50 (d, *J*=ll.l Hz, 2H), 3.21 - 3.18 (m, 2H), 3.17 - 3.09 (m, 2H), 3.02 - 2.93 (m, 2H), 2.86 (s, 3H); LCMS [M+H]+ 399.

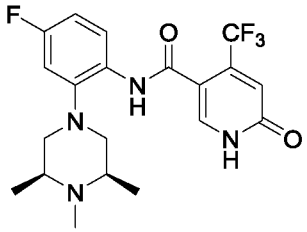
Example 25: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yljphenyl]'-3-methylbenzamide



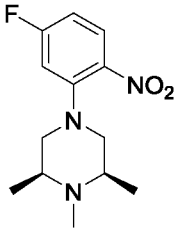
[00238] To a 25 mL RBF charged with 4-fluoro-3-methylbenzoic acid (46 mg, 0.3 mmol) was added thionyl chloride (0.364 mL, 5 mmol). The resulting suspension was heated at 80 °C for 1 h. It was evaporated to give a light yellow oil which was

treated with DCM (3 mL), 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol, obtained from Step 3, Example 8 above) followed by EtsN (0.042 mL, 0.3 mmol). The resulting dark red mixture was stirred at rt 1 h, quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with DCM (20 mL x 2). The combined extracts were concentrated and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-5%) to give the title compound as a beige solid (43.1 mg, 80%). ^{1}H-NMR (500MHz, CHLOROFORM-d) δ 9.18 (s, 1H), 8.65 (d, *J*=8.2 Hz, 1H), 8.59 (s, 2H), 7.82 (dd, *J*=1.8, 7.1 Hz, 1H), 7.78 - 7.69 (m, 1H), 7.17 (t, *J*=8.8 Hz, 1H), 7.02 (d, *J*=11.2 Hz, 1H), 3.92 - 3.85 (m, 4H), 3.85 - 3.78 (m, 4H), 2.92 (d, *J*=11.0 Hz, 2H), 2.70 (t, *J*=10.9 Hz, 2H), 2.46 - 2.37 (m, 8H), 1.18 (d, *J*=1.0 Hz, 6H); LC-MS $[M + H]^+$ 537.43.

Example 26: N-[4-fluoro-2-[(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide (Comparative Example)



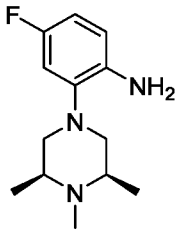
Step 1: cis-4-(5-fluoro-2-nitrophenyl)-1,2,6-trimethylpiperazine



[00239] A suspension of cis-l,2,6-trimethylpiperazine (0.40 g, 3.1 mmol) and potassium carbonate (0.26 g, 1.9 mmol) in toluene (4 mL) was warmed to 45 °C. After 10 minutes 2,4-difiuoro-l -nitrobenzene (0.35 mL, 3.1 mmol) was added dropwise. The reaction was stirred at 45 °C for 1 h and then cooled to room temperature. The reaction mixture was partitioned between DCM and water and the layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated onto celite and purified by flash

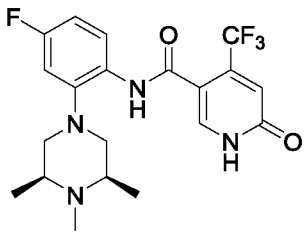
chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] to afford cis-4-(5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.71 g, 85 %). LCMS [M+H]+: 268.2.

Step 2: cis-4-fluoro-2-(3,4,5-trimethylpiperazin-l-yl)aniline



[00240] A solution of cis-4-(5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.155 g, 0.58 mmol) in methanol (5 mL) was hydrogenated in the presence of platinum **(rV)** oxide (0.013 g, 0.058 mmol) at 1 atm of H_2 (g). After 6 h the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] to afford cis-4-fluoro-2-(3,4,5-trimethylpiperazin-l-yl)aniline (0.11 g, 82 %). LCMS [M+H]+: 238.1.

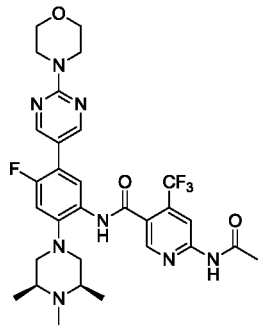
Step 3: cis-N-(4-fluoro-2-(3,4,5-trimethylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)-!,6-dihydropyridine-3-carboxamide



[00241] A suspension of 6-chloro-4-(trifluoromethyl)nicotinic acid (0.057 g, 0.25 mmol) and thionyl chloride (0.8 mL, 10 mmol) was heated at 80 °C for 1 h. The reaction mixture was concentrated to dryness to afford the acid chloride which was suspended in anhydrous dichloromethane (5 mL) and treated with cis-4-fiuoro-2-(3,4,5-trimethylpiperazin-l-yl)aniline (0.050 g, 0.2 mmol) and triethylamine (0.09 mL, 0.6 mmol) at room temperature. After 1 h the reaction was quenched with sat. aq NaHCCb (10 mL) and extracted into DCM. The combined extracts were concentrated and the residue was dried under reduced pressure to afford cis-6-chloro-N-(4-fiuoro-2-(3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)nicotinamide. The resulting chloropyridine intermediate was taken up in HOAc/H_20 (7 mL/2mL) and sodium acetate (0.035 g, 0.42 mmol) was added. The mixture was irradiated in a microwave apparatus at

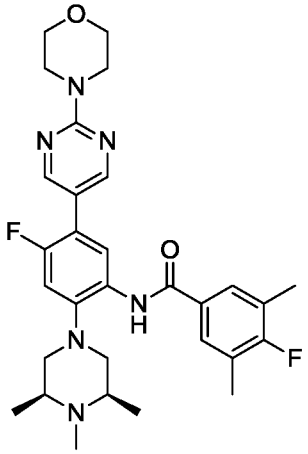
160 °C for 4 h. The reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] to afford the title compound cis-N-(4-fluoro-2-(3,4,5-trimethylpiperazin-1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide (0.063 g, 67 %). ¾-NMR (500MHz, DMSO-d6) δ = 12.44 (br. s., 1H), 9.41 (s, 1H), 7.88 (s, 1H), 7.64 (dd, *J*=6.6, 8.4 Hz, 1H), 6.99 - 6.86 (m, 2H), 6.81 (s, 1H), 2.97 (d, *J*=11.0 Hz, 2H), 2.43 (t, *J*=10.9 Hz, 2H), 2.37 - 2.30 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 427.1

Example 27: 6^cetamido-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-4-(trifluoromethyl)pyridim-3-carboxamide



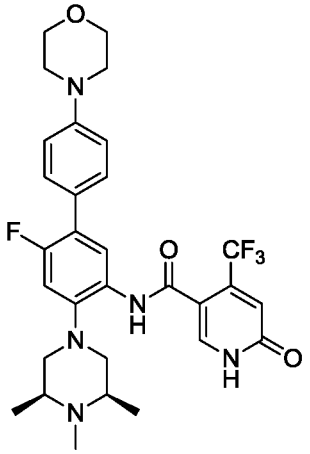
[00242] To a 5 mL microwave vial charged with 6-chloro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)nicotinamide (60.7 mg, 0.1 mmol, prepared using the procedure described in the synthesis of Example 8), acetamide (30 mg, 0.5 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 10 mol%), xantphos (12 mg, 0.02 mmol, 20 mol%) and K_2C0_3 (41 mg, 0.3 mmol) was added dioxane (3 mL). The resulting mixture was irradiated in microwave at 140 °C for 2 h. After passing through microfilter, the filtrate was concentrated, purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-5%), reversed phase C18 column (gradient: CH_3CN (0.1% TFA)/H_20 5-90%), porapak column and triturated with MeOH (2 mL) to give the title compound as a white solid (24.6 mg, 38% yield). ^{1}H-NMR (500MHz, $CDC1_3$) δ 8.74 (s, 1H), 8.68 - 8.56 (m, 5H), 8.15 (s, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 3.93 - 3.86 (m, 4H), 3.84 - 3.79 (m, 4H), 3.52 (d, *J*=4.6 Hz, 1H), 2.84 (d, *J*=11.0 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.35 - 2.25 (m, 8H), 1.13 (d, *J*=6.2 Hz, 6H); LC-MS $[M + H]^+$ 631.3.

Example 28: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3, 5-dimethylbenzamide

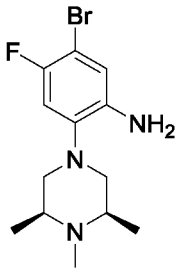


[00243] To a 25 mL RBF charged with 4-fluoro-3,5-dimethylbenzoic acid (50 mg, 0.3 mmol) was added thionyl chloride (0.364 mL, 5 mmol). The resulting suspension was heated at 80 °C for 1 h. It was evaporated to give a light yellow oil which was treated with DCM (3 mL), 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol, obtained from the procedure used to produce Example 8 above) followed by EtsN (0.042 mL, 0.3 mmol). The resulting dark red mixture was stirred at rt for 1 h. After quenching with sat. $NaHC0_3$ (10 mL), it was extracted with DCM (20 mL x 2). The combined extracts were concentrated, loaded onto celite, dried and purified using Biotage SNAP KP-Sil 50 g (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-8%). Fractions showing pure product were combined, concentrated, triturated with MeOH (3 mL), suction filtered and rinsed with MeOH (0.5 mL) to give a white solid. The filter cake was dried under vacuum to give a pale beige solid (4.6028-4.5767g=26.1mg, yield 47% based on 99.70% purity). ^{1}H NMR (500MHz, $CDC1_3$) δ = 9.19 (s, 1H), 8.65 (d, *J*=8.3 Hz, 1H), 8.60 (s, 2H), 7.62 (d, *J*=6.7 Hz, 2H), 7.02 (d, *J*=11.2 Hz, 1H), 3.93 - 3.86 (m, 4H), 3.85 - 3.79 (m, 4H), 2.94 (d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=10.9 Hz, 2H), 2.51 - 2.41 (m, 2H), 2.41 - 2.35 (m, 9H), 1.19 (d, *J*=6.2 Hz, 6H); LC-MS $[M + H]^+$ 551.3.

Example 29: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(rifluoromethyl)-lH-pyridine-3-carboxamide

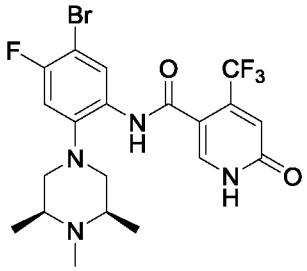


Step 1: 5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)aniline



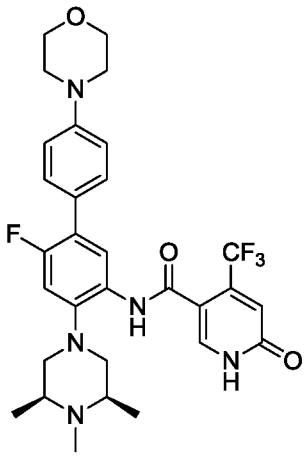
[00244] The (2S,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine obtained from Example 8, Step 1 (2.16 g) was dissolved in MeOH (30 mL) and to it was added a suspension of Raney-Nickel, 2800 (269 mg, 3.14 mmol) in MeOH (5 mL), followed by hydrazine monohydrate (0.912 mL, 18.86 mmol). The reaction was exothermic. After completion of the addition, the resulting mixture was stirred at rt for 30 min. It was then heated to 50 °C and treated with additional hydrazine monohydrate (0.61 mL, 12.57 mmol), followed by Raney-Nickel, 2800 (0.162 g, 1.886 mmol). The resulting mixture was heated at 50 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated and purified by Biotage SNAP KP-Sil 50 g (gradient: MeOH/DCM 0-15%) to give, after concentration of fractions showing product, 975 mg of the aniline product as alight brown solid. LCMS $[M+H]^+$ 318.3.

Step 2: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



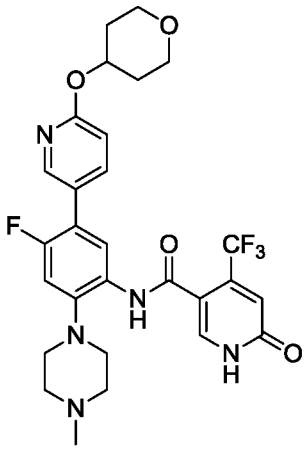
[00245] To a 25 mL RBF charged with 6-chloro-4-(trifluoromethyl)nicotinic acid (271 mg, 1.2 mmol) was added thionyl chloride (3.64 mL, 50 mmol). The resulting suspension was heated at 80 °C for 1 h, then cooled and evaporated with a rotary evaporator to give a light yellow oil which was treated with DCM (10 mL), 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (316 mg, 1 mmol) and EtsN (0.42 mL, 3 mmol). The resulting mixture was stirred for 16 h at ambient temperature. The mixture was quenched with sat. aq NaHCCb (10 mL), extracted with DCM (30 mL x 2) and the combined extracts were evaporated and dried to give a light brown solid. A mixture of this solid, NaOAc (164 mg, 2 mmol) in HOAc/H_2**0** (7 mL/2mL) in a 20 mL microwave vial was heated at 160 °C for 4 h. Solvents were removed using a rotary evaporator at 60 °C and the residue was treated with sat. $NaHC0_3$ (20 mL) and extracted with DCM (60 mL + 30 mL). The extracts were concentrated and purified by Biotage SNAP KP-Sil 50 g (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-20%). Fractions containing product were concentrated and dried under vacuum to give a light beige solid (304 mg). LCMS $[M + H]^+$ = 505.38.

Step 4: N-(6-fluoro-4'-morpholino-4-(⁽3S,5R)-3,4,5-trimethylpiperazin-l -yl)-[l, 1'-biphenylJ-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00246] To a 5 mL microwave vial charged with N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol), 4-(morpholino)phenylboronic acid (41.4 mg, 0.2 mmol), and $Pd(dppf)Cl_2$ (14.6 mg, 0.02 mmol, 20 mol%) was added dioxane (3 mL), followed by 1 M aq K_3PO4 (0.5 mL, 0.5 mmol). The resulting mixture was irradiated in microwave at 110 °C for 2 h. LCMS showed completion of the reaction. The crude reaction mixture was loaded onto celite, dried and purified using Biotage SNAP KP-Sil 25g (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-30%). Fractions showing impure product were concentrated, loaded onto celite, and repurified by Biotage SNAP C18 30g (gradient: CH_3CN (0.1% TFA)/H_2**0** 5-30%). Fractions showing product were combined, passed through porapak 6cc, concentrated and dried to give the title compound as an off white solid (24.6 mg, 40% yield). ^-NMR (500 MHz, MeOD-d_4) δ 7.96 (s, 1H), 7.92 (d, *J*=7.9 Hz, 1H), 7.47 (d, *J*=8.4 Hz, 2H), 7.07 - 7.00 (m, 3H), 6.92 (s, 1H), 3.91 - 3.81 (m, 4H), 3.25 - 3.17 (m, 4H), 3.05 (d, *J*=ll.l Hz, 2H), 2.67 - 2.52 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.0 Hz, 6H); LC-MS $[M+H]^+$ 588.36.

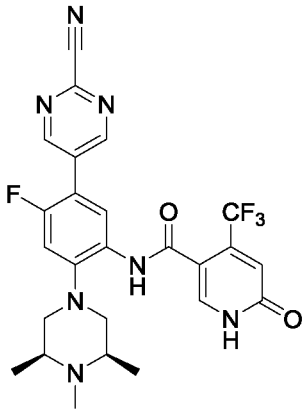
Example 30: N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(oxan-4-yloxy)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



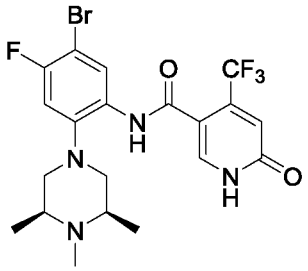
[00247] To a 5 mL microwave vial charged with N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.08 mg, 0.063 mmol), 2-(tetrahydropyran-4-yloxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (57.7 mg, 0.189 mmol), sodium carbonate, anhydrous (66.8 mg, 0.630 mmol) and XPhos (6.01 mg, 0.013 mmol), XPhos Pd G2

(9.92 mg, 0.013 mmol) was added water (1970 µï) / 1,4-dioxane (1182 µï) to give a white suspension. The resultant mixture was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 120 °C. The solvent (dioxane) was evaporated and 15 ml of DCM were added. The suspension was sonicated and the organic phase was removed and concentrated (3X). The resulting crude black oil was purified using a Biotage column, (100-0%, CH2C12: 10% MeOH in DCM + NH_4Ac; in 10 min and isocratic for 5min [new isolera 2.3] using KP-SIL lOg column. Collected at 0% of the DCM) to yield the final product. The product was freeze dried for 2 days to yield 26.0 mg (68% yield) of the desired target compound. ¾-NMR NMR (500 MHz, MeOD) δ 8.29 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 11.9 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 5.26 (tt, *J* = 8.4, 4.0 Hz, 1H), 3.98 (dt, *J* = 9.4, 4.5 Hz, 2H), 3.63 (ddd, *J* = 11.8, 9.1, 2.9 Hz, 2H), 3.05 (s, 4H), 2.80 (s, 4H), 2.48 (s, 3H), 2.13 - 2.06 (m, 2H), 1.82 - 1.74 (m, 2H); LCMS [M+H]+ = 576.3.

Example 31: N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

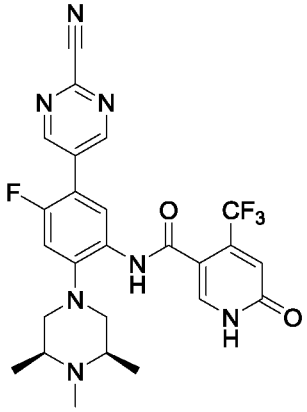


Step 1: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00248] In a 10 mL microwave vial to a suspension of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (1048 mg, 5.06 mmol) in pyridine, anhydrous (6139 µl, 76 mmol) was added slowly diethyl chlorophosphate (749 µl, 5.19 mmol) at RT in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. The suspension turned into a solution and then into a suspension again. To this, 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (400 mg, 1.265 mmol) was added and the reaction was heated at 70 °C for 3 h. After completion, pyridine was removed in vacuo and the residue partitioned between dichloromethane (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo yielding the crude product which was purified by flash column chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the title compound (192 mg, 30%). ^1H NMR (500 MHz, MeOD) δ 8.10 (d, *J* = 7.4 Hz, 1H), 7.92 (s, 1H), 7.09 (d, *J* = 10.1 Hz, 1H), 6.90 (s, 1H), 3.00 (d, *J* = 11.0 Hz, 2H), 2.57 (t, *J* = 11.0 Hz, 2H), 2.54 - 2.49 (m, 2H), 2.35 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 6H); LCMS $[M+l]^+$ = 505.00.

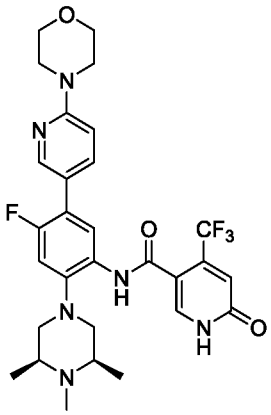
Step 2: N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3S, 5RJ-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00249] To a 5 mL microwave vial charged with N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (29.85 mg, 0.059 mmol), prepared according to the method described in Example 29), 2-cyanopyrimidine-5-boronic acid pinacol ester (40.9 mg, 0.177 mmol), sodium carbonate, anhydrous (62.6 mg, 0.591 mmol) and XPhos (5.63 mg, 0.012 mmol),

XPhos Pd G2 (9.30 mg, 0.012 mmol) was added in water (1846 µï) / 1,4-dioxane (1108 µï) to give a white suspension that was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 120 °C. The solvent was evaporated and 15 ml of DCM was added. The suspension was sonicated and the organic phase was removed and concentrated (3X). The crude black oil was purified using a Biotage column, (100-0%, $CH_2C\,l_2$: 10% MeOH in $CH_2C\,l_2$ + NH_4Ac; in 10 min and isocratic for 5min using KP-SIL lOg column. Collected at 0% of the $CH_2C\,l_2$) to yield an impure product. The product was freeze dried for 2 days to yield the crude product that was purified via preparatory HPLC. The fractions were evaporated and the concentrate was slowly passed through a ionic exchange column Rxn CX 6cc with MeOH and NH_4OH. The product was lyophilized to yield 8.1 mg (26% yield) of the title compound. ¾-NMR (500 MHz, MeOD) δ 9.14 (s, 2H), 8.04 (d, J = 8.2 Hz, 1H), 7.96 (s, 1H), 7.16 (d, J = 12.4 Hz, 1H), 6.92 (s, 1H), 3.15 (d, J = 11.6 Hz, 2H), 2.65 (t, J = 11.2 Hz, 2H), 2.61 - 2.54 (m, 2H), 2.39 (s, 3H), 2.03 (s, 1H), 1.17 (d, J = 6.1 Hz, 6H); LCMS [M+H]+ 530.

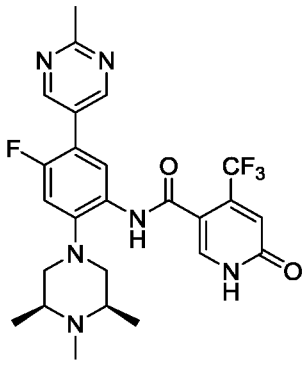
Example 32: N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3S,5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridin^ -3-carboxamide



[00250] A procedure was used similar to that used for Example 31 above using N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-aihydropyridine-3-carboxamide (28.89 mg, 0.057 mmol), 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo rpholine (49.8 mg, 0.172 mmol), sodium carbonate, anhydrous (60.6 mg, 0.572 mmol) and XPhos (5.45 mg, 0.011 mmol), XPhos Pd G2 (9.00 mg, 0.011 mmol) to give 33.7 mg (82% yield) of the title compound. ¾-NMR (500 MHz, MeOD-d_4) δ 8.32 (s, 1H), 7.96 (s, 1H), 7.90 (d, J = 8.3

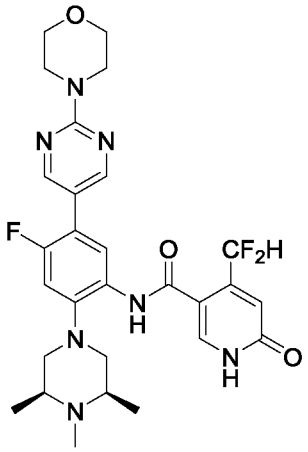
Hz, 1H), 7.78 (d, J = 9.8 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.92 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 3.83 - 3.80 (m, 4H), 3.56 - 3.53 (m, 4H), 3.13 (d, J = 11.6 Hz, 2H), 2.80 (s, 2H), 2.70 (t, J = 11.3 Hz, 2H), 2.53 (s, 3H), 1.23 (d, J = 6.2 Hz, 6H); LCMS [M+H]+ 589.

Example 33: N-[4-fluoro-5-(2-methylpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(rifluoromethyl)-lH-pyridine-3-carboxamide

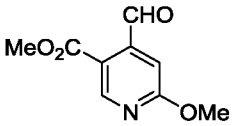


[00251] A procedure was used similar to that used for Example 31 above with N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (28.40 mg, 0.056 mmol), 2-methylpyrimidin-5-ylboronic acid pinacol ester (37.1 mg, 0.169 mmol), sodium carbonate, anhydrous (59.6 mg, 0.562 mmol) and XPhos (5.36 mg, 0.011 mmol), XPhos Pd G2 (8.84 mg, 0.011 mmol) gave 17.3 mg (59% yield) of the title compound. ^-NMR (500 MHz, MeOD) δ 8.89 (s, 2H), 7.97 (d, J = 9.3 Hz, 1H), 7.96 (s, 1H), 7.14 (d, J = 12.1 Hz, 1H), 6.92 (s, 1H), 3.11 (d, J = 11.1 Hz, 2H), 2.74 (s, 3H), 2.67 - 2.56 (m, 4H), 2.40 (s, 3H), 1.17 (d, J = 6.0 Hz, 6H); LCMS [M+H]+ 519.

Example 34: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3S, 5R)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide

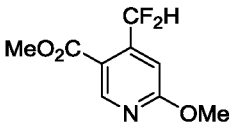


Step 1: methyl 4-formyl-6-methoxynicotinate



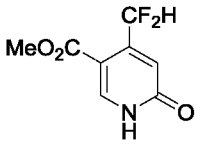
[00252] To a solution of the commercially available 5-bromo-2-methoxyisonicotinaldehyde (5.0 g, 23.2 mmol, leq) in MeOH was added triethylamine (12eq), Pd (dppfjC^ (O.leq) at 70°C under 50 psi of CO gas in a steel bomb for 16h. Subsequent reaction work-up and flash column chromatography on silca-gel afforded 1.8 g (39% yield) of the desired compound, methyl 4-formyl-6-methoxynicotinate; LCMS $[M + H]^+$ 196.

Step 2: methyl 4-(difluoromethyl)-6-methoxynicotinate



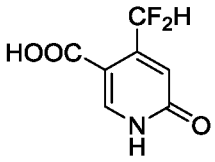
[00253] To a solution of the methyl 4-formyl-6-methoxynicotinate (1.8 g, 9.2 mmol, leq) in DCM was added DAST fluoride (4eq) at -78°C and the mixture was maintained at RT for 16h. TLC analysis indicated formation of less polar spot. Subsequent reaction work-up and flash column chromatography on silca-gel afforded 1.3 g (65% yield) of the desired intermediate, methyl 4-(difiuoromethyl)-6-methoxynicotinate; LCMS $[M + H]^+$ 218.

Step 3: methyl 4-(difluoromethyl)-6-oxo-l, 6-dihydropyridine-3-carboxylate



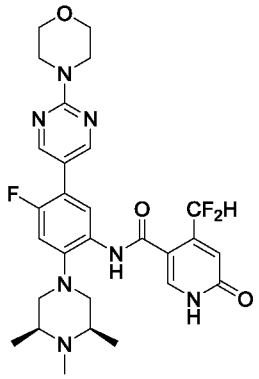
[00254] A solution of the methyl 4-(difluoromethyl)-6-methoxynicotinate (2.5 g, 11.5 mmol, leq) and Nal (3eq) in acetonitrile was treated with TMS-chloride (3eq) at RT. The resulting mixture was heated to 90°C for 3h. TLC analysis indicated formation of polar spot. Reaction work-up and trituration with ether gave 1.7g (73% yield) of the intermediate, methyl 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylate; LCMS $[M + H]^+$ 204.

Step 4: 4-(difluoromethyl)-6-oxo-l ,6-dihydropyridine-3-carboxylic acid



[00255] A solution of the methyl 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylate (1.7 g, 8.3 mmol, leq) in MeOH : THF : Water (3:2:1) was treated with $LiOH.H_20$ (4.5eq) at RT and heated to 75°C for 16h. TLC analysis indicated consumption of the starting material. Removal of the organic solvent under vacuum followed by neutralization to acidic pH gave 1.15g (73% yield) of the desired acid, 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylic acid as a white solid; LCMS $[M + H]^+$ 190.

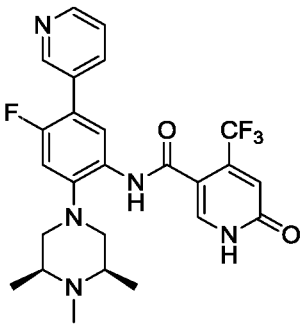
Step 5: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



[00256] In a 10 ml microwave vial to a suspension of 4-(difiuoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylic acid (37.2 mg, 0.197 mmol) in anhydrous pyridine (239 µï, 2.95 mmol) was added slowly diethyl chlorophosphate (29.1 µï,

0.202 mmol) at ambient temperature in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. To this mixture then was added 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (obtained from Example 8, Step 3) and the reaction was heated at 70 °C for 3 h. After completion, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous Na_2S0_4. The solvent was evaporated *in vacuo* yielding the crude product. Purification was performed via Biotage column, (100-0%, DCM: 10% MeOH in DCM + NH4Ac; in 10 min and isocratic for 5min [new isolera 2.3] using KP-SIL lOg column) to yield the product that was lyophilized for 1 day to obtain after further purification using prep HPLC 15.7 mg (55% yield) of the title compound. ^{1}H-NMR (500 MHz, MeOD) δ 8.54 (d, J = 1.1 Hz, 2H), 8.01 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 55.1 Hz, 3H)7.06 (d, J = 12.1 Hz, 1H), 6.81 (s, 1H), 3.86 - 3.81 (m, 4H), 3.78 - 3.74 (m, 4H), 3.07 (d, J = 11.2 Hz, 2H), 2.60 (t, J = 11.1 Hz, 2H), 2.54 (d, J = 6.2 Hz, 2H), 2.37 (s, 3H), 1.15 (d, J = 6.1 Hz, 6H); LCMS [M+H]+ 572.

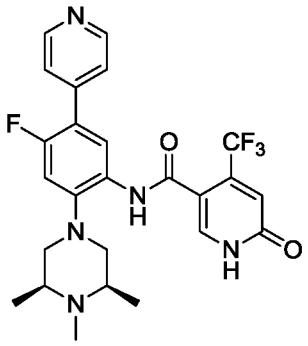
Example 35: N-[4-fluoro-5-pyridin-3-yl-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00257] The title compound (23.2 mg, 56%) was prepared according to a procedure similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (40.4 mg, 0.08 mmol) and 3-pyridinylboronic acid (20 mg, 0.16 mmol). ^{1}H-NMR (500MHz, METHANOL-d4) δ 8.75 (s, 1H), 8.55 (d, J=5.2 Hz, 1H), 8.06 (d, J=7.9 Hz, 1H), 7.98 (s, 1H), 7.98 (d, J=7.2 Hz, 2H), 7.56 (dd, J=5.0, 8.0 Hz, 1H), 7.13

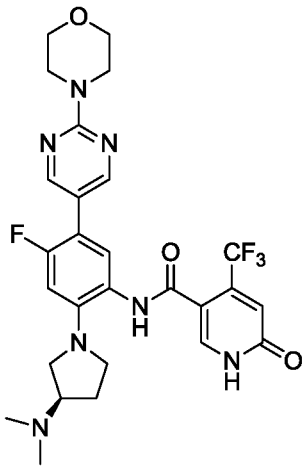
(d, J=12.1 Hz, IH), 6.93 (s, IH), 3.12 (d, J=11.4 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.61 - 2.52 (m, 2H), 2.40 (s, 3H), 1.19 (d, J=6.1 Hz, 6H); LC-MS [M + H]+ 504.25.

Example 36: *N-[4-fluoro-5-pyridin-4-yl-2-[(3R, 5SJ-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide*



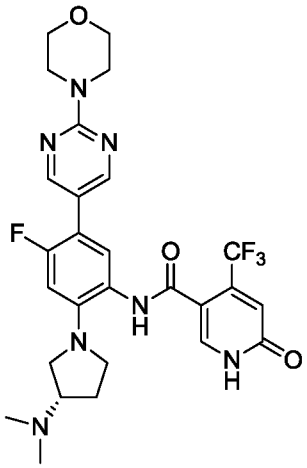
[00258] The title compound (24.0 mg, 58% yield) was prepared according to a procedure similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (40.4 mg, 0.08 mmol) and 4-pyridylboronic acid (20 mg, 0.16 mmol). ^-NMR (500 MHz, METHANOL-d4) δ 8.62 (d, J=5.3 Hz, 2H), 8.04 (d, J=8.2 Hz, IH), 7.98 (s, IH), 7.67 (d, J=4.9 Hz, 2H), 7.12 (d, J=12.5 Hz, IH), 6.93 (s, IH), 3.14 (d, J=11.4 Hz, 2H), 2.69 - 2.61 (m, 2H), 2.61 - 2.52 (m, 2H), 2.39 (s, 3H), 1.19 (d, J=6.1 Hz, 6H); LC-MS [M + H]+ 504.25.

Example 37: *N-[2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide*



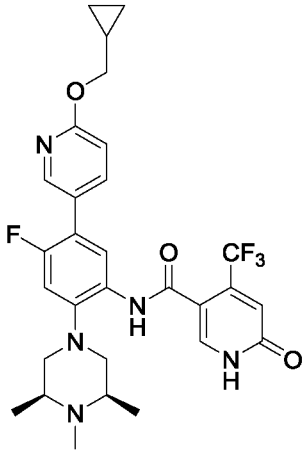
[00259] The title compound was prepared similar to the sequence described above for the preparation of Example 21 above using (R)-(+)-3-(dimethylamino)pyrrolidine in place of racemic 3-(dimethylamino)pyrrolidine in Step 1 to give the title compound (31 mg, 22% yield for the last step). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.56 (br. s., 1H), 9.82 (s, 1H), 8.51 (s, 2H), 7.96 (br. s., 1H), 7.32 (d, J=7.5 Hz, 1H), 6.81 (s, 1H), 6.67 (d, J=13.3 Hz, 1H), 3.76 - 3.67 (m, 8H), 3.41 - 3.38 (m, 2H), 3.26 - 3.22 (m, J=8.6, 8.6 Hz, 1H), 2.64 (br. s., 2H), 2.19 - 2.13 (m, 6H), 2.07 (br. s., 1H), 1.74 - 1.67 (m, 1H); LCMS [M+H]+ 576.3.

Example 38: N-[2-[(3S)-3-(dimethylamino)pyrrolidin-l-ylJ-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

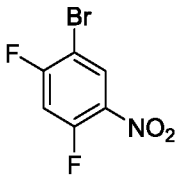


[00260] The title compound was prepared similar to the sequence described above for the preparation of Example 21 using (S)-(-)-3-(dimethylamino)pyrrolidine in place of racemic 3-(dimethylamino)pyrrolidine in Step 1 to give 28 mg (23% yield) of the title compound for the last step/H-NMR (500MHz, DMSO-d6) δ = 12.56 (br. s., 1H), 9.82 (s, 1H), 8.51 (s, 2H), 7.96 (br. s., 1H), 7.32 (d, J=7.5 Hz, 1H), 6.81 (s, 1H), 6.67 (d, J=13.3 Hz, 1H), 3.76 - 3.67 (m, 8H), 3.41 - 3.38 (m, 2H), 3.26 - 3.22 (m, J=8.6, 8.6 Hz, 1H), 2.64 (br. s., 2H), 2.19 - 2.13 (m, 6H), 2.07 (br. s., 1H), 1.74 - 1.67 (m, 1H); LCMS [M+H]+ 576.1.

Example 39: *N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3S,5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide*

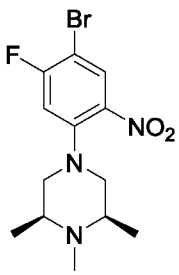


Step 1: l-bromo-2,4-difluoro-5-nitrobenzene



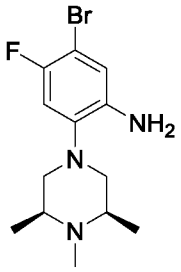
[00261] To a suspension of l-bromo-2,4-difluorobenzene (lOg, 52.1mmol, l.Oeq) in cold H2SO4 (37.9mL) was added Conc.HN0 $_3$ (33.3mL) in a dropwise manner keeping the internal temp 20°C, stirred for 10 min at 0°C then, the reaction mixture was poured into a mixture of diethyl ether (250mL) and ice water (250mL) with vigorous stirring. The organic layer was separated and the aqueous layer was again extracted with Et_20 (250mL). The combined organic layer was washed with Satd. sodium bicarbonate (2 X 200 mL) followed by satd. brine (2 X 200 mL) solution. The separated organic layer was dried over Na_2S0_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO¾ 100-200 mesh) using 15% EtOAc in pet ether as an eluent to give l-bromo-2,4-difluoro-5 -nitrobenzene (52g, 72% yield) as a yellow color liquid. LCMS: M+H]+ 272.23.

Step 2: (2S, 6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine



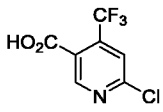
[00262] To a solution of l-bromo-2,4-difluoro-5-nitrobenzene (2.71g, 21.1mmol, leq) in ethanol (lOOmL) was added TEA (3.49mL, 25.2mmol, 1.19eq) under argon for 20 mins then followed by addition of (2S,6R)- 1,2,6-trimethylpiperazine (5.0 g, 21.1 mmol, 1.7 eq) at RT under argon atmosphere and heated to 85°C for 16 h. TLC analysis indicated formation of polar spot. Then, the reaction mixture was cooled to RT, solvent was evaporated under reduced pressure, the crude product was poured on ice-water (300mL), and extracted with EtOAc (2X lOOmL). The combined organic layers were dried over Na_2S0_4 and concentrated under reduced pressure to give crude product which was purified by combiflash column chromatography using 3% methanol in DCM as an eluent to afford l-bromo-2,4-difiuoro-5 -nitrobenzene (5.2 g, 70%) as a pale yellow color liquid. LCMS: [M+H]+ 348.15.

Step 3: 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline



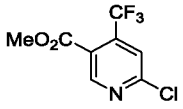
[00263] To a solution of l-bromo-2,4-difluoro-5-nitrobenzene (2.5 g, 7.2 mmol, leq) in ethanol: water (30mL:10mL) was added NH_4C1 (0.95g, 57.97mmol, 4+4eq) followed by iron powder (3.24 g, 57.9 mmol, 4+4eq) at RT under argon atmosphere and heated to 80°C for 16h. TLC analysis indicated formation of polar spot. Then, the reaction mixture was cooled to RT, filtered through a celite bed washed with methanol, and the filtrate was concentrated under reduced pressure to give crude product which was purified by neutral alumina column chromatography using 100% DCM as an eluent to afford 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (1.3 g, 59.1%) as an off white solid. LCMS: $[M + H]^+$ 316.13.

Step 4: 6-chloro-4-(trifluoromethyl)nicotinic acid



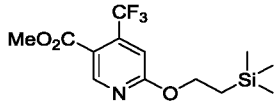
[00264] To a solution of butyl magnesium chloride (27.8mL, 47.2mmol, 0.7eq, 1.7 M in THF) in THF was added butyl lithium (30.0mL, 74.3mmol, l.leq, 2.5M in hexane) at 0°C and the reaction mixture was stirred for 10 min, then diluted with THF (80mL) and cooled to -78°C. Then, 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (17.5g, 67.5mmol, leqm procedure described in Example 93) in THF (30mL) was added and the reaction mixture was stirred for 1h at same temperature, before being poured onto crushed dry ice then slowly allowed to warm to RT for 16h. TLC indicated polar spot and the reaction mixture was concentrated and acidified with 2N HC1 (80mL) and extracted with EtOAc (2X 500mL). The organic layer was separated, dried with sodium sulfate and concentrated under reduced pressure to give crude residue. The crude compound was recrystallized from n-pentane (30mL) and dried using high vacuum to give 6-chloro-4-(trifluoromethyl)nicotinic acid (lOg, 66.6%) as an off white solid compound. LCMS: [M+H]+ 224.05.

Step 5: methyl 6-chloro-4-(trifluoromethyl)nicotinate



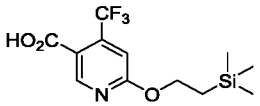
[00265] To a solution of 6-chloro-4-(trifluoromethyl)nicotinic acid (16.6g, 75.1mmol, leq) in acetone (160mL), potassium carbonate (15.55 g, 112.6mmol, 1.5eq) and dimethylsulphate (8.21mL,97.6 mmol,1.3eq) was added at 0°C and the reaction mixture was allowed to come to RT and stirred for 2h.TLC analysis indicated formation of a non-polar spot. The reaction mixture was concentrated under reduced pressure and gave crude residue. The crude compound was dissolved in EtOAc (500mL) and washed with brine (2 X 200mL) and water (2X200mL). The separated organic layer was dried over Na_2S0_4 and concentrated under reduced pressure to result in crude product; which was purified by column chromatography (silica gell00-200mesh) using as an eluent 0-2% EtOAc in petroleum ether to give methyl 6-chloro-4-(trifluoromethyl)nicotinate (13g, 72.22%) as a liquid compound. LCMS: [M+H]+ 240.08.

Step 6: methyl 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinate



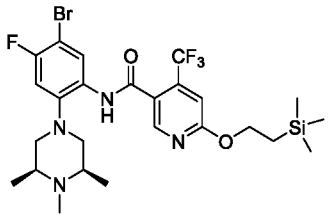
[00266] To a suspension of methyl 6-chloro-4-(trifluoromethyl)nicotinate (12.7g, 53.1mmol, leq) in toluene (120mL), TMS-ethanol (4.71 mL,53.1 mmol,l eq), cesium carbonate (51.8g, 159.4mmol, 3eq) and BINAP (3.571g, 5.3mmol, O.leq) were degassed with for 15 min and $Pd(OAc)_2$ (0.95g, 4.2mmol, 0.08eq) was added then the reaction mixture was heated to 120°C for 2h. TLC analysis indicated formation of a non-polar spot. The reaction mixture was diluted with EtOAc (500mL), filtered with a celite pad and concentrated under reduced pressure to result in crude product which was purified by column chromatography (silica gell00-200mesh) using 5% EtOAc in petroleum ether as an eluent to afford the desired compound (9.0g, 65%) as a pale yellow color liquid. LCMS: $[M + H]^+$: 294.15.

Step 7: 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid



[00267] To a solution of methyl 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinate (20g, 62.3mmol, leq) in THF: MeOH: $\mathbf{H_20}$ (60mL: 40mL: 20mL), lithium hydroxide monohydrate (10 g, 249.2 mmol, 4 eq) was added and the reaction mixture was stirred at RT for 16h.TLC analysis indicated polar spot. The reaction was concentrated under reduced pressure and gave crude compound. The crude compound was acidified with 2N HC1 (20mL), then the obtained precipitate was filtered off and washed with diethyl ether (50mL) and dried under high vacuum to give the desired compound 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (9.2g, 48.40%) as an off white solid . LCMS: $[M + H]^+$ 306.20.

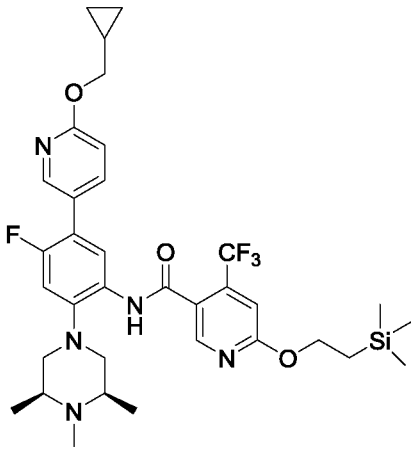
Step 8: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00268] To a solution of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (6.0g, 19.5mmol, l.Oeq) in dry DMF (70mL), HATU (11.13g, 29.3mmol, 1.5 eq) and DIPEA (6.6mL, 39.0mmol, 2.0eq) were added at RT and the reaction mixture was stirred

for 10 min. Then 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (5.8g, 19.5 mmol, l.Oeq) was added and the reaction mixture was stirred for 48 h. TLC analysis indicated formation of a non-polar spot. The reaction mixture was diluted with EtOAc (2 X500mL) and washed with cold water (2X500mL) & Brine (2X200mL), The separated organic layers were combined, dried over Na_2S04 and concentrated under reduced pressure to give crude product which was purified by column chromatography (Neutral $AI2O_3$) using as an eluent 10%- 20% EtOAc in petroleum ether to give the title compound (5.2 g, 45%) as an off white solid. LCMS: $[M + H]^+$: 604.8.

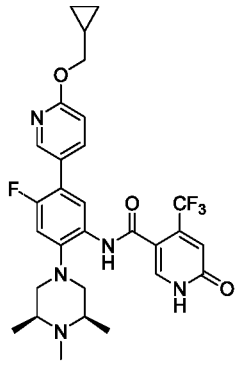
Step 9: N-(5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00269] To a 20 mL microwave vial charged with N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.532 g, 0.879 mmol), 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (0.363 g, 1.318 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.062 g, 0.088 mmol) and potassium phosphate tribasic reagent grade, >98% (0.373 g, 1.757 mmol) was added water (1.464 ml) /1,4-dioxane (13.18 ml) to give a white suspension that was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 110 °C. The reaction was monitored by LCMS, which indicated that the reaction was complete. The solvent (dioxane) was evaporated and 15 ml of DCM were added. The suspension was sonicated and the organic phase was removed and concentrated (3X).

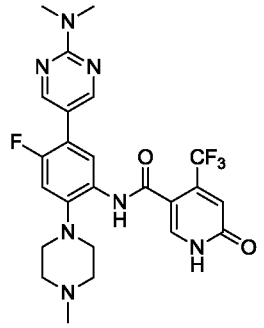
The crude brown oil was purified using a Biotage column, (100-0%, CH2CI2: 10% MeOH in CH_2Cl_2 + NH_4Ac; in 10 min and isocratic for 5 min using KP-SIL 50g column. Collected at 10% of the CH_2Cl_2) to yield the intermediate product. The fractions were evaporated and the resulting product was lyophilized to give 295 mg (49.4% yield) of the target silylated intermediate. LCMS [M-H]- = 672.1.

Step 10: N-(5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



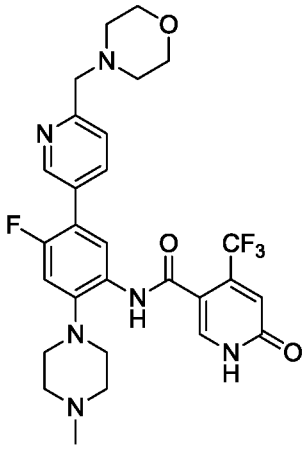
[00270] To a solution of N-(5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (135.26 mg, 0.201 mmol) in dry DMF (401 μL) was added CsF (91 mg, 0.602 mmol) and heated at 60 °C for 1 h. The reaction was monitored by LCMS which indicated that the reaction was complete. The mixture was diluted with water and extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water, brine solution, concentrated under reduce pressure and freeze dried for 2 days to yield the title compound (0.182 mmol, 91 % yield). ^-NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 7.95 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.86 (dd, J = 8.6, 0.9 Hz, 1H), 7.09 (d, J = 12.0 Hz, 1H), 6.92 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.15 (d, J = 7.1 Hz, 2H), 3.11 (d, J = 9.5 Hz, 2H), 2.75 - 2.62 (m, 4H), 2.46 (s, 3H), 1.35 - 1.25 (m, 1H), 1.20 (d, J = 5.6 Hz, 6H), 0.64 - 0.58 (m, 2H), 0.39 - 0.34 (m, 2H); LCMS [M+H]+ 574.

Example 40: N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00271] A procedure similar to that employed in Example 3, Step 2 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.53 mg, 0.064 mmol), N,N-dimethyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (47.8 mg, 0.192 mmol), anhydrous sodium carbonate (67.8 mg, 0.640 mmol), XPhos (6.10 mg, 0.013 mmol), and XPhos Pd G2 (10.07 mg, 0.013 mmol) gave 27.4 mg (78% yield) of the title compound as a white powder. ^{1}HNMR (500 MHz, MeOD) δ 8.41 (d, J = 1.1 Hz, 2H), 7.87 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 12.0 Hz, 1H), 6.82 (s, 1H), 3.12 (s, 6H), 2.92 (s, 4H), 2.62 (s, 4H), 2.32 (s, 3H); LCMS [M+H]+ 520.

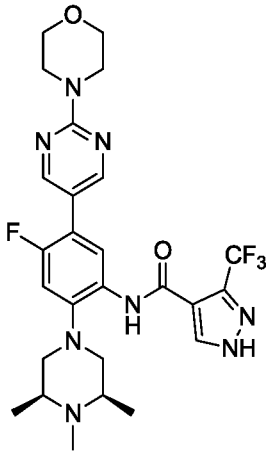
Example 41: N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(morpholin-4-ylmethyl)pyridin-3-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide



[00272] A procedure similar to that of Example 3 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.77 mg, 0.064 mmol) and 6-(morpholinomethyl)pyridin-3-ylboronic acid (42.9 mg, 0.193 mmol) afforded 22.5 mg (55.9 % yield) of the title compound. ^{1}H-

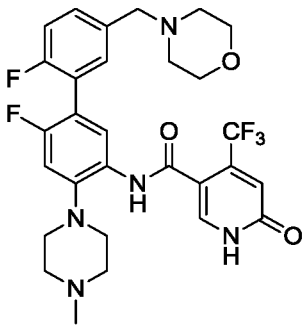
NMR (500 MHz, MeOD) δ 8.73 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 11.8 Hz, 1H), 6.94 (s, 1H), 3.93 (s, 2H), 3.78 (s, 4H), 3.21 (s, 4H), 2.84 (s, 3H), 2.76 (s, 4H); LCMS [M+H]+ 575.

Example 42: *N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenyl]-3-(trifluoromethyl)-lH-pyrazole-4-carboxamide*



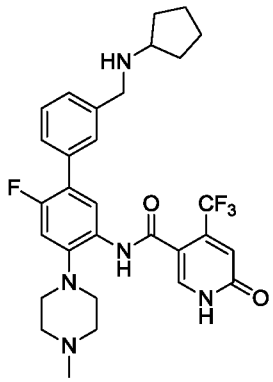
[00273] The title compound was prepared according to a method similar to that used in Example 34 above using 3-(trifluoromethyl)pyrazole-4-carboxylic acid (27 mg, 0.15 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (20 mg, 0.05 mmol) to give 18.1 mg (62% yield) of the product as a white solid. ^{1}H NMR (500MHz, METHANOL-d4) δ 8.58 (s, 2H), 8.39 (br. s., 1H), 7.98 (d, J=8.2 Hz, 1H), 7.11 (d, J=12.0 Hz, 1H), 3.89 - 3.83 (m, 4H), 3.80 - 3.75 (m, 4H), 3.04 (d, J=11.4 Hz, 2H), 2.63 (t, J=11.2 Hz, 2H), 2.55 - 2.46 (m, 2H), 2.37 (s, 3H), 1.15 (d, J=6.2 Hz, 6H); LC-MS [M + H]+ = 569.39.

Example 43: N-(2',6-difluoro-4-(4-methylpiperazin-l-yl)-5'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



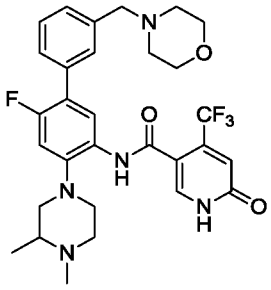
[00274] A procedure similar to that of Example 3 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (29.41 mg, 0.062 mmol), 4-(4-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzyl)mo rpholine (59.4 mg, 0.185 mmol), sodium carbonate, anhydrous (65.3 mg, 0.616 mmol), XPhos (5.88 mg, 0.012 mmol), and XPhos Pd G2 (9.70 mg, 0.012 mmol) afforded 30.6 mg (81% yield) of the title compound as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 7.95 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 9.2, 6.1 Hz, 2H), 7.18 - 7.14 (m, 1H), 7.09 (d, *J* = 11.2 Hz, 1H), 6.92 (s, 1H), 3.74 - 3.66 (m, 4H), 3.57 (s, 2H), 3.04 (s, 4H), 2.68 (s, 4H), 2.49 (s, 4H), 2.39 (s, 3H)); LCMS $[M+H]^+$ 592 g/mol.

Example 44: N-(3'-((cyclopentylamino)methyl)-6-fluoro-4-(4-methylpiperazin-l-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide

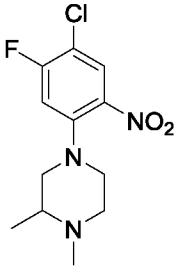


[00275] A procedure was employed similar that to described in Example 3 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.51 mg, 0.064 mmol), 3-(N-cyclopentylaminomethyl)phenylboronic acid, pinacol ester, HC1 (64.8 mg, 0.192 mmol), anhydrous sodium carbonate, (67.8 mg, 0.639 mmol), XPhos (6.10 mg, 0.013 mmol), and XPhos Pd G2 (10.06 mg, 0.013 mmol) to give 0.68 mg (1.7% yield) of the title compound. ^{1}H NMR (500 MHz, MeOD) δ 8.08 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 12.0 Hz, 1H), 6.79 (d, *J* = 6.4 Hz, 1H), 4.05 (s, 2H), 3.38 (p, *J* = 7.3 Hz, 1H), 3.04 - 2.99 (m, 4H), 2.65 (s, 4H), 2.36 (s, 3H), 2.06 (dt, *J* = 12.5, 7.0 Hz, 2H), 1.81 - 1.75 (m, 2H), 1.65 - 1.54 (m, 4H); LCMS $[M+H]^+$ = 562.7.

Example 45: N-(4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenylJ-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

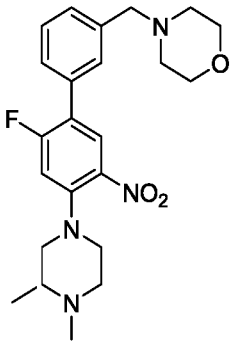


Step 1: 4-(4-chloro-5-fluoro-2-nitrophenyl)-1,2-dimethylpiperazine



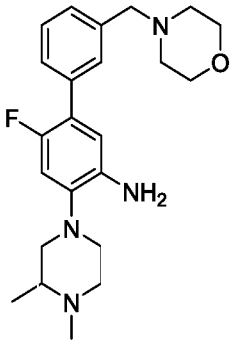
[00276] A microwave vial was charged with l-bromo-4-chloro-5-fluoro-2-nitrobenzene (0.50 g, 2.0 mmol), 1,2-dimethyl-piperazine (0.39 g, 2.1 mmol), palladium acetate (0.044 g, 0.20 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.11 g, 0.20 mmol) and cesium carbonate (2.1 g, 6.4 mmol). The vial was capped, evacuated and backfilled with nitrogen. Toluene (25 mL) was added via syringe and the reaction vial was evacuated and backfilled with nitrogen an additional time. The reaction was warmed to 50 °C overnight. The reaction mixture was concentrated onto celite and purified by flash chromatography [0-10% MeOH/DCM + 1% NH_4OH] to afford an inseparable mixture of the desired Buchwald product [4-(4-chloro-5-fluoro-2-nitrophenyl)-l, 2-dimethylpiperazine] along with undesired by-product [4-(5-bromo-2-chloro-4-nitrophenyl)-l, 2-dimethylpiperazine]. This mixture was carried forward to the next step where the corresponding products were separable by flash chromatography. LCMS $[M+H]^+$ = 288.3.

Step 2: 4-((4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-nitro-[l,1'-biphenylJ-3-yl)methyl)morpholine



[00277] A vial was charged with the mixture obtained in Step 1 (0.22 g), 3-(4-morpholinomethyl)phenylboronic acid pinacol ester (0.16 g, 0.52 mmol), XPhos Pd G2 (0.006 g, 0.007 mmol) and XPhos (0.004 g, 0.007 mmol). The vial was sealed with a septum cap and evacuated and backfilled with nitrogen. 1,4-Dioxane (4 mL) and a 2M aq. solution of sodium carbonate (0.90 mL, 1.7 mmol) were added *via* syringe. The vial was evacuated and backfilled an additional time before being heated at 100 °C in an aluminum block overnight. The reaction was cooled to room temperature and concentrated directly onto celite. Flash chromatography [0.5-5% MeOH/DCM + 1% NH_4OH] afforded the desired 4-((4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-nitro-[1,1'-biphenyl]-3-yl)methyl)morpholine (0.18 g, 62%). LCMS $[M+H]^+$: 429.7.

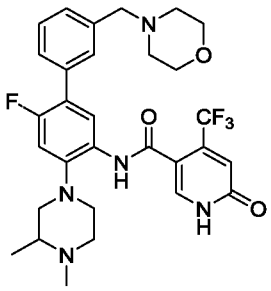
Step 3: 4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenylJ-3-amine



[00278] A mixture of 4-((4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-nitro-[l ,1'-biphenyl]-3-yl)methyl)morpholine (0.18 g, 0.43 mmol), iron (0.12 g, 2.2 mmol) and acetic acid (4 mL) was heated to 80 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with DCM and the liquids were decanted by pipette. Concentration onto celite followed by flash chromatography [0.5-10% MeOH/DCM +

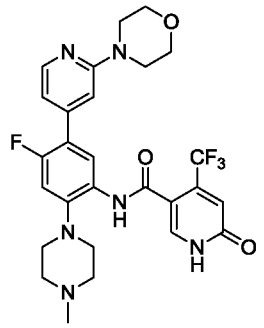
1% NH_4OH] afforded 4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l,r-biphenyl]-3-amine (0.32 mmol, 75 %). LCMS $[M+H]^+$: 399.7.

Step 4: N-(4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenylJ-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



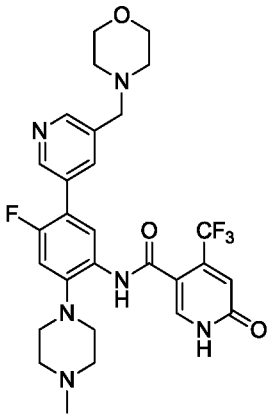
[00279] Diethyl chlorophosphate (0.186 ml, 1.285 mmol) was added to a stirring solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (0.266 g, 1.285 mmol) in pyridine (3 ml) at room temperature. After stirring for 1h the solution of activated acid was added to a stirring solution of 4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenyl]-3-amine (0.128 g, 0.321 mmol) also in pyridine (3 ml) at room temperature. The reaction was heated to 75 °C overnight. LCMS indicated the presence of the desired product along with the excess nicotinic acid. The reaction was concentrated onto celite and purified by RP flash on the Biotage [5-95% MeCN/water] to afford 135 mg of crude product that was not of sufficient purity by NMR and LCMS. The mixture was loaded onto celite and purified by silica gel chromatography [1-25% MeOH/DCM + 1% NH40H] to afford the title compound (106 mg, 53.4 % yield) as a colorless solid after lyophilization. ^1H NMR (500 MHz, DMSO-d6) δ 9.52 (s, 1H), 7.94 (s, 1H), 7.75 (d, *J*=8.44 Hz, 1H), 7.29-7.47 (m, 4H), 7.06 (d, *J*=12.47 Hz, 1H), 6.81 (s, 1H), 3.58 (t, *J*=4.40 Hz, 4H), 3.53 (s, 2H), 2.99-3.09 (m, 2H), 2.80-2.87 (m, 1H), 2.74-2.80 (m, 1H), 2.32-2.46 (m, 6H), 2.23-2.27 (m, 1H), 0.99 (d, *J*=6.24 Hz, 3H); LCMS $[M+H]^+$ 574 g/mol.

Example 46: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholinopyridin-4-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00280] A procedure employed similar to that of Example 3 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (29.10 mg, 0.061 mmol), 2-morpholinopyridine-4-boronic acid, pinacol ester (53.1 mg, 0.183 mmol) gave 17.4 mg (50.7% yield) of the target compound as a white powder. ^{1}H NMR (500 MHz, MeOD) δ 8.16 (d, J = 5.4 Hz, 1H), 7.97 (s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 12.2 Hz, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.91 (d, J = 5.1 Hz, 1H), 3.84 - 3.80 (m, 4H), 3.54 - 3.50 (m, 4H), 3.03 (t, J = 4.9 Hz, 4H), 2.68 (s, J = 2.0 Hz, 4H), 2.39 (s, 3H); LCMS $[M+H]^+$ 561 g/mol.

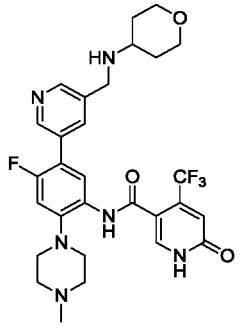
Example 47: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(morpholinomethyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00281] A procedure employed similar to that of Example 29 above using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (19.4 mg, 0.041 mmol) and 4-((5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-3-yl)methyl)morpholine (37.1 mg, 0.122 mmol) gave 15.5 mg (64.4% yield) of the title compound as pale yellow powder. ^{1}H NMR (500 MHz, CD3CN-D20) δ 8.74 (s, 1H), 8.57 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H),

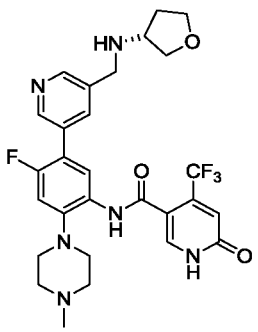
8.04 (s, 1H), 7.89 (s, 1H), 7.21 (d, J = 11.8 Hz, 1H), 6.91 (s, 1H), 3.99 (s, 2H), 3.74 (s, 4H), 3.40 (s, 4H), 3.17 (s, 4H), 2.84 (s, 3H), 2.83 (s, 4H). LCMS $[M+H]^+$ 575 g/mol.

Example 48: N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(((tetrahydro-2H-pyran-4-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



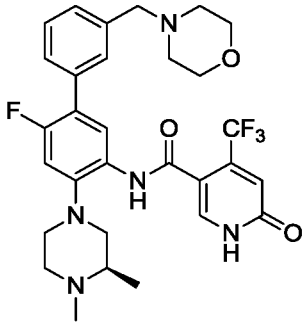
[00282] A procedure was employed similar to that of Example 3 using N-(5-bromo-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.52mg, 0.066 mmol) and 4-((6-fiuoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-3-yl)methyl)mo rpholine (64.2 mg, 0.199 mmol) to give 11.9 mg (30.1% yield) of the title compound. 'HNMR (500 MHz, MeOD) δ 8.67 (t, J = 2.1 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.07 (t, J = 2.6 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.98 (s, 1H), 7.15 (d, J = 12.0 Hz, 1H), 6.92 (s, 1H), 3.99 (s, 2H), 3.98 - 3.95 (m, 2H), 3.42 (td, J = 12.0, 2.2 Hz, 2H), 3.06 - 3.02 (m, 4H), 2.85 (ddd, J = 15.2, 9.4, 4.2 Hz, 1H), 2.67 (s, J = *2.1* Hz, 4H), 2.38 (s, 3H), 1.95 (ddd, J = 6.6, 4.2, 2.0 Hz, 2H), 1.50 (ddd, J = 24.2, 12.2, 4.6 Hz, 2H); LCMS $[M+H]^+$ 589 g/mol.

Example 49: (R)-N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(((tetrahydrofuran-3-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

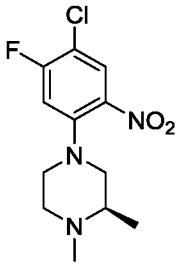


[00283] A procedure was employed similar to that of Example 3 using N-(5-bromo-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (20.46 mg, 0.043 mmol) and (R)-N-((5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-3-yl)methyl)tetrahydrofuran-3-amine (39. 1 mg, 0.129 mmol) to give the title compound (16.0 mg) in 60.5% yield. ^{1}H NMR (500 MHz, MeOD) δ 8.85 (s, 1H), 8.72 (d, *J* = 2.0 Hz, 1H), 8.23 (t, *J* = 2.3 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 8.05 (s, 1H), 7.26 (d, *J* = 11.8 Hz, 1H), 6.94 (s, 1H), 4.39 (d, *J* = 2.4 Hz, 2H), 4.11 - 4.06 (m, 2H), 4.02 (ddd, *J* = 11.0, 6.9, 2.5 Hz, 1H), 3.87 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.76 (dt, *J* = 15.5, 8.4 Hz, 1H), 2.94 (s, 3H), 2.45 (dtd, *J* = 13.4, 8.1, 5.0 Hz, 1H), 2.13 (dtd, *J* = 11.3, 7.6, 3.3 Hz, 1H); LCMS $[M+H]^+$ 575 g/mol.

Example 50: (R)-N-(4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



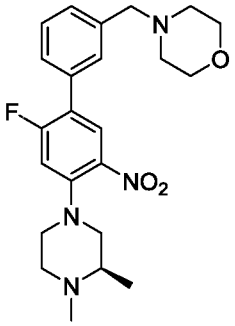
Step 1: (R)-4-(4-chloro-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine



[00284] A vial was charged with l-bromo-4-chloro-5-fluoro-2 -nitrobenzene (1.0 g, 3.93 mmol), (R)-l,2-dimethyl-piperazine dihydrochloride (0.772 g, 4.13 mmol), palladium(II) acetate (0.088 g, 0.393 mmol), Xantphos (0.227 g, 0.393 mmol) and cesium carbonate (5.12 g, 15.72 mmol). The vial was sealed with a septum and evacuated and back-filled with nitrogen. Toluene (15 ml) was added and the vial was evacuated and back-filled again. The reaction was warmed to 50 °C. After 7.5 h total

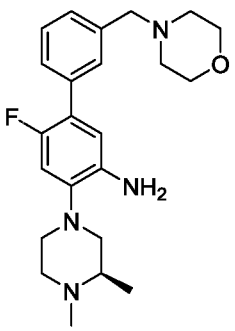
reaction time, LCMS indicated the complete consumption of the starting material. The reaction mixture was transferred to a round bottom flask with DCM and then concentrated onto celite. Flash [0.5-10% MeOH/DCM + 1% NH_4OH] afforded 490 mg (41.2% yield) of the title compound. LCMS [M+H]+ = 288.3

Step 2: (R)-4-((4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-nitro-[1,l'-biphenyl]-3-yl)methyl)morpholine



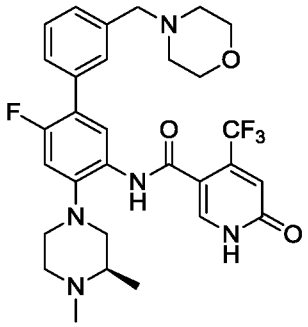
[00285] A 30 mL vial was charged with a mixture of (R)-4-(4-chloro-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine (0.050 g, 0.174 mmol), 3-(4-moφholinomethyl)phenylboronic acid pinacol ester (0.074 g, 0.243 mmol), XPhos Pd G2 (2.73 mg, 3.48 μηιοΐ) and XPhos (1.657 mg, 3.48 μηιοΐ). The vial was sealed with a cap/septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (2 ml) and 2M Aq sodium carbonate (0.434 ml, 0.869 mmol) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated in an aluminum block overnight at 100 °C. LCMS indicated very clean conversion to the desired product. The reaction mixture was loaded onto celite and purified by flash chromatography [0.1-5% MeOH/DCM + 1% NH_4OH] to afford the product (0.152 mmol, 87 % yield) as a yellow film.

Step 3: (R)-4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenylJ-3-amine



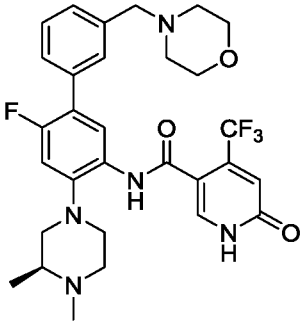
[00286] A mixture of (R)-4-((4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-nitro-[1,1'-biphenyl]-3-yl)methyl)morpholine (0.065 g, 0.152 mmol), iron (0.042 g, 0.758 mmol) and acetic acid (2 ml) was heated to 80 °C for 1 h. The heating block was tumed off and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with DCM and decanted by pipette to a round bottom flask. LCMS indicated complete conversion to the desired product. Concentration onto celite followed by flash [0.1-10% MeOH/DCM + 1% NH_4OH] afforded the product (0.123 mmol, 81 % yield) as a brown film that was pure by LCMS. LCMS [M + H]+ = 399.5.

Step 4: (R)-N-(4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



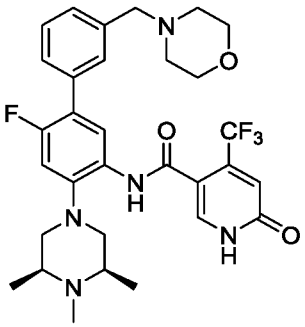
[00287] Diethyl chlorophosphate (0.071 ml, 0.492 mmol) was added to a stirring solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (0.102 g, 0.492 mmol) in pyridine (1.5 ml) at room temperature. After stirring for 30 minutes the solution of activated acid was added to a stirring solution of (R)-4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[l, 1'-biphenyl]-3-amine (0.049 g, 0.123 mmol) also in pyridine (1.5 ml) at room temperature. The reaction was heated to 75 °C for ~3 h. The reaction was concentrated onto celite and purified by flash [1-25% MeOH/DCM + 1% NH_4OH] to afford crude product that was ~92% pure [254 nm]. This material was loaded onto celite and repurified on the biotage [5-95% MeCN/water - no modifier] to afford the title compound (0.022 mmol, 17.99 % yield) as a tan solid that was pure by LCMS. ^1H NMR (500MHz, DMSO-de) δ = 9.41 (br. s., 1H), 7.97 (s, 1H), 7.80 (d, *J*=8.7 Hz, 1H), 7.47 - 7.29 (m, 5H), 7.06 (d, *J*=12.5 Hz, 1H), 6.69 (br. s., 1H), 3.57 (t, *J*=4.3 Hz, 4H), 3.52 (s, 2H), 3.07 - 2.97 (m, 2H), 2.86 - 2.74 (m, 2H), 2.45 - 2.40 (m, 2H), 2.39 - 2.34 (m, 5H), 2.21 (s, 3H), 0.98 (d, *J*=6.2 Hz, 3H); LCMS $[M+H]^+$ 574 g/mol.

Example 51: (S)-N-(4-(3, 4-dimethylpiperazin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[1, 1'-biphenyl] -3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



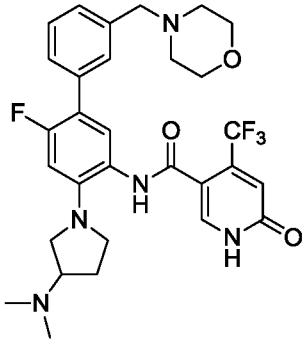
[00288] The title compound was prepared similar to the sequence described above for the preparation of Example 50 above using (S)- 1,2-dimethyl-piperazine hydrochloride in place of racemic 1,2-dimethyl-piperazine in Step 1, to give 19.0 mg (28% yield) of the title compound in the last step. ¾I NMR (500MHz, DMSO-de) δ = 9.44 (s, 1H), 7.96 (s, 1H), 7.78 (d, *J*=8.6 Hz, 1H), 7.47 - 7.28 (m, 4H), 7.06 (d, *J*=12.5 Hz, 1H), 6.73 (s, 1H), 3.57 (t, *J*=4.3 Hz, 4H), 3.52 (s, 2H), 3.07 - 2.98 (m, 2H), 2.86 - 2.74 (m, 2H), 2.45 - 2.33 (m, 6H), 2.26 - 2.19 (m, 4H), 0.98 (d, *J*=6.1 Hz, 3H); LCMS [M+H]+: 588.4.

Example 52: N-(5-fluoro-3'-(morpholinomethyl)-4-(⁽3R,5SJ-3,4,5-trimethylpiperazin-l-yl)-[1, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide

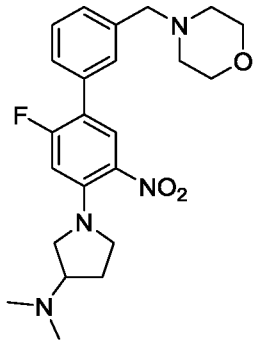


[00289] The sequence described above for the preparation of Example 50 using cis-1,2,6-trimethyl-piperazine in place of racemic 1,2-dimethyl-piperazine was used to give 7 mg (21% yield) of the title compound in the final step. ¾ NMR (500MHz, DMSO-de) δ = 9.30 (br. s., 1H), 8.01 (s, 1H), 7.84 (d, *J*=8.6 Hz, 1H), 7.48 - 7.28 (m, 4H), 7.04 (d, *J*=12.3 Hz, 1H), 6.55 (br. s., 1H), 3.57 (t, *J*=4*3* Hz, 4H), 3.52 (s, 2H), 3.01 (d, *J*=10.9 Hz, 2H), 2.40 - 2.31 (m, 7H), 2.20 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ = 602.4.

Example 53: N-(4-(3-(dimethylamino)pyrrolidin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[1, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

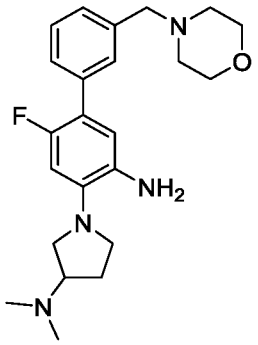


Step 1: 1-(2-fluoro-3'-(morpholinomethyl)-5-nitro-[1,1'-biphenyl]-4-yl)-N,N-dimethylpyrrolidin-3-amine



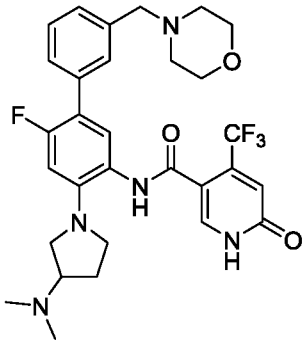
[00290] A vial was charged with a mixture of l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.092 g, 0.28 mmol, prepared as described in Example 21 above), 3-(4-morpholinomethyl)phenylboronic acid pinacol ester (0.12 g, 0.39 mmol), XPhos Pd G2 (0.0044 g, 0.005 mmol) and XPhos (0.0026 g, 0.005 mmol). The vial was sealed with a septum cap and evacuated and backfilled with nitrogen. 1,4-Dioxane (4 mL) and 2M Aq sodium carbonate (0.70 mL, 1.4 mmol) were added via syringe. The vial was evacuated and backfilled an additional time before being heated at 95 °C overnight. The reaction was cooled to room temperature and concentrated directly onto celite. Flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] afforded 1-(2-fluoro-3'-(morpholinomethyl)-5 -nitro-[1,1'-biphenyl] -4-yl)-N,N-dimethylpyrrolidin-3-amine (0.110 g, 86 %). LCMS [M+H]+: 429.5.

Step 2: l-(5-amino-2-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]'-4-yl)-N,N-dimethylpyrrolidin-3-amine



[00291] A mixture of l-(2-fluoro-3'-(mo rpholinomethyl)-5-nitro-[l, 1'-biphenyl]-4-yl)-N,N-dimethylpyrrolidin-3-amine (0.11 g, 0.26 mmol), iron (0.070 g, 1.3 mmol) and acetic acid (3 mL) was heated to 85 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with DCM and the liquids were decanted by pipette. Concentration onto celite followed by flash chromatography [0.1-10% MeOH/DCM + 1% NH40H] afforded l-(5-amino-2-fluoro-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-4-yl)-N,N-dimethylpyrrolidin-3-amine (0.061 g, 60 %). LCMS $[M+H]^+$: 399.5.

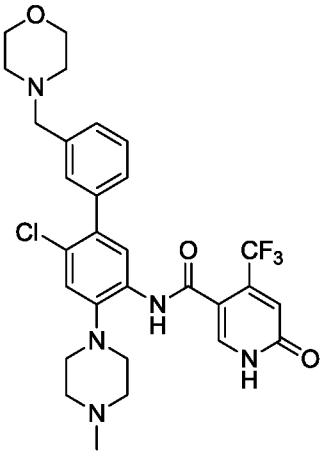
Step 3: N-(4-(3-(dimethylamino)pyrrolidin-l-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



[00292] Diethyl chlorophosphate (0.090 mL, 0.61 mmol) was added to a stirring solution of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (0.130 g, 0.61 mmol) in pyridine (2 mL) at room temperature. After stirring for 45 minutes the solution of activated acid was added to a stirring solution of l-(5-amino-2-fluoro-3'-(morpholinomethyl)-[l ,1'-biphenyl]-4-yl)-N,N-dimethylpyrrolidin-3-amine (0.061 g, 0.15 mmol) also in pyridine (2 mL) at room temperature. The reaction was heated to 75 °C for 5 h. The reaction mixture was concentrated onto celite and reverse phase chromatography [5-95% MeCN/water; CI8 column] afforded the title compound (28.0 mg, 30 % yield). ^{1}H-NMR (500 MHz, DMSO-d6) δ 12.57 (br. s., 1H), 9.82 (d,

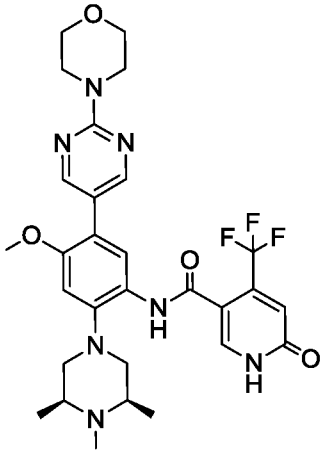
J=5.14 Hz, 1H), 7.97 (br. s., 1H), 7.34-7.43 (m, 3H), 7.22-7.33 (m, 2H), 6.80 (d, J=5.38 Hz, 1H), 6.66 (dd, J=5.99, 14.31 Hz, 1H), 3.58 (br. s., 4H), 3.51 (d, J=5.87 Hz, 2H), 3.40-3.42 (m, 2H), 3.26 (m, 1H), 2.64 (br. s., 1H), 2.38 (br. s., 4H), 2.12-2.22 (m, 7H), 2.09 (d, J=3.79 Hz, 1H), 1.71 (d, J=7.70 Hz, 1H); LCMS [M+H]+ = 588.5.

Example 54: N-(6-chloro-4-(4-methylpiperazin-l-yl)-3'-(morpholinomethyl)-[l, 1'-biphenylJ-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (Comparative Example)

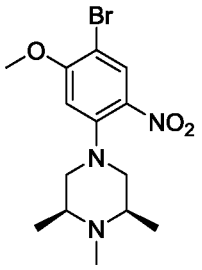


[00293] To a 2 ml microwave vial containing a suspension of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (103 mg, 0.499 mmol) in pyridine, anhydrous (603 µï, 7.48 mmol) was added slowly diethyl chlorophosphate (72.1 µï, 0.499 mmol) at rt in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 1 h. To this mixture was added 6-chloro-4-(4-methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-amine (50 mg, 0.125 mmol, prepared in a similar manner to examples hereinabove) and the reaction was heated at 70 °C for 2 h. After completion, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous Na_2S0_4. The solvent was evaporated in vacuo yielding the crude product. Purification was performed via preparative HPLC to yield the title compound (10.4 mg, 12% yield). ¾ NMR (500 MHz, MeOD) δ 8.47 (s, 1H), 7.96 (s, 1H), 7.95 (s, 1H), 7.45 (s, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 5.6 Hz, 2H), 7.36 (s, 1H), 6.92 (s, 1H), 3.72 - 3.70 (m, 4H), 3.64 (s, 2H), 3.05 (t, J = 4.4 Hz, 4H), 2.80 (s, 4H), 2.54 (s, 4H), 2.48 (s, 3H); LCMS $[M+H]^+$ 591 g/mol.

Example 55: N-[4-methoxy-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridme-3-carboxamide (Comparative Example)

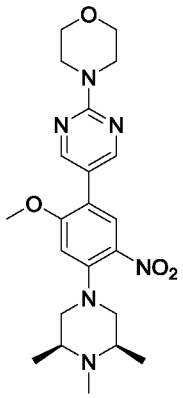


Step 1: cis-4-(4-bromo-5-methoxy-2-nitrophenyl)-l,2, 6-trimethylpiperazine



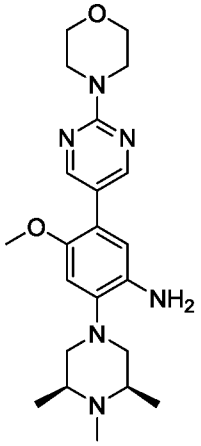
[00294] A solution of l-bromo-4-fluoro-2-methoxy-5-nitrobenzene (0.250 g, 1.0 mmol) in PhMe (1 mL) was slowly added to a rapidly stirring mixture of cis-1,2,6-trimethylpiperazine (0.13 g, 1.0 mmol) and K_2CO_3 (0.070 g, 0.50 mmol) in PhMe (2 mL) at 45 °C. After 2 h the heat was turned off and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded cis-4-(4-bromo-5-methoxy-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.33 g, 92 %). LCMS [M+H]+: 358.3.

Step 2: 4-(5-(2-methoxy-5-nitro-4-(cis-3, 4,5-trimethylpiperazin-l -yl)phenyl)pyrimidin-2-yl)morpholine



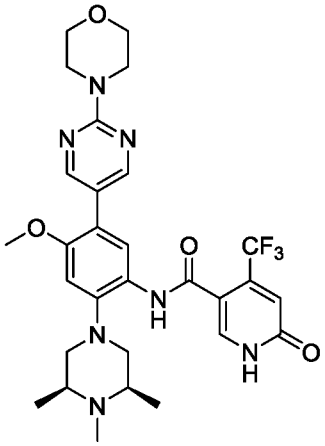
[00295] A reaction vial was charged with a mixture of cis-4-(4-bromo-5-methoxy-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.11 g, 0.31 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (0.098 g, 0.34 mmol), XPhos Pd G2 (5 mg, 6 μηιοΐ) and XPhos (3 mg, 6 μηιοΐ). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and 2 M aqueous sodium carbonate (0.5 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 90 °C in an aluminum block for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford 4-(5-(2-methoxy-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)pyrimidin-2-yl)moipholine (0.14 g, 100 %). LCMS [M+H]+: 443.3.

Step 3: 4-methoxy-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline



[00296] A mixture of 4-(5-(2-methoxy-5-nitro-4-(cis-3,4,5-trimethylpiperazin-1-yl)phenyl)pyrimidin-2-yl)morpholine (0.14 g, 0.31 mmol), $SnCl_2$ (0.24 g, 1.2 mmol) and EtOH (5 mL) was heated to 75 °C for 1 h. The heat was turned off and the reaction was allowed to stir at room temperature overnight. The reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] to afford 4-methoxy-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.11 g, 83 %). LCMS [M+H]+: 413.6.

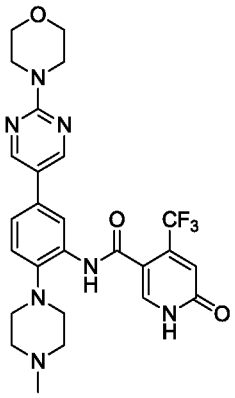
Step 4: N-(4-methoxy-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00297] 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.056 g, 0.18 mmol) was activated with HATU (0.069 g, 0.18 mmol) and N,N-diisopropylethylamine (0.03 mL, 0.18 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of 4-methoxy-5-(2-moϕ holinopyrirnidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.050 g, 0.12 mmol) in DMF (1 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-7.5% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with TFA (1 mL) at room temperature. After stirring for 2 h the volatiles were removed under a stream of air and the title compound was isolated by a catch and release protocol using a SCX2 silica cartridge to afford the title compound (0.067 g, 92 %). ¾I NMR (500MHz, DMSO-d6) δ = 9.37 (s, 1H), 8.47 (s, 2H), 7.90 (s, 1H), 7.57 (s, 1H), 6.85 - 6.74 (m, 2H), 3.81 (s, 3H), 3.75 - 3.72 (m, 4H), 3.70

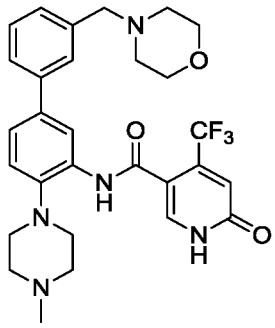
- 3.66 (m, 4H), 3.00 (br d, *J*=10.9 Hz, 3H), 2.47 - 2.43 (m, IH), 2.38 - 2.30 (m, 2H), 2.21 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 602.5.

Example 56: N-(2-(4-methylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide (Comparative Example)



[00298] The procedure followed was similar to that used for Example 3 above using N-(5-bromo-2-(4-methylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (51.9 mg, 0.108 mmol) and 2-(4^ orpηo1iηo)pyrimidiηe-5-boronic acid pinacol ester (95 mg, 0.325 mmol) to afford the title compound (39.5 mg, 55% yield) as a white solid. IH NMR (500 MHz, DMSO) δ 9.45 (s, IH), 8.63 (s, 2H), 8.01 (d, J = 2.0 Hz, IH), 7.98 (s, IH), 7.42 (dd, J = 8.3, 2.2 Hz, IH), 7.25 (d, J = 8.3 Hz, IH), 6.80 (s, IH), 3.74 (q, J = 4.5 Hz, 4H), 3.68 (q, J = 4.5 Hz, 4H), 2.87 (t, J = 4.4 Hz, 4H), 2.47 (s, 4H), 2.22 (s, 3H); LCMS [M+H]+ 544.

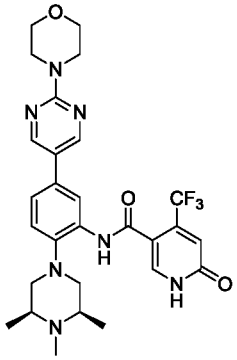
Example 57: N-[2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide (Comparative Example)



[00299] 6-Hydroxy-4-(trifluoromethyl)nicotinic acid (69.2 mg, 0.327 mmol) was dissolved/suspended in $SOCl_2$ (1 mL) and stirred at 70 °C for 2 h. The $SOCl_2$ was

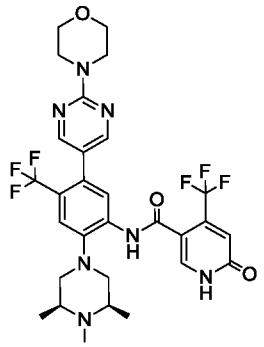
removed under reduced pressure (h/v lh). The residue was dissolved in DCM and 4-(4-methylpiperazin-l-yl)-3'-(mo rpholinomethyl)-[l, 1'-biphenyl]-3-amine (100 mg, 0.273 mmol, prepared using methods similar to those described for Example 29) was added in one portion before pyridine (28.7 µï, 0.355 mmol) was added. The reaction mixture was stirred for 3d, diluted with sat. aq. sodium bicarbonate solution and extracted with DCM (3 x 5 mL). The combined organic phases were loaded on silica gel and subjected to purification via Biotage (25 g column, MeOH/DCM 0-30 %, 30 CV) to give the title compound (15 mg, 8.91 % yield). ^{1}H-NMR (500 MHz, MeOD) δ 8.77 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.08 (dd, J = 8.1, 2.3 Hz, 1H), 8.02 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.55 (dd, J = 8.3, 2.1 Hz, 1H), 7.42 (t, J = 4.2 Hz, 1H), 6.94 (s, 1H), 3.79 (s, 2H), 3.75 - 3.73 (m, 4H), 3.15 (s, 4H), 2.72 (s, 4H), 2.63 (s, 3H); LCMS [M+H]+ 557.

Example 58: N-(5-(2-morpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamide (Comparative Example)

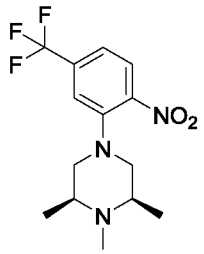


[00300] N-(5-bromo-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-&hydropyridine-3-carboxamide (39 mg, 0.08 mmol) and 2-(4-moϕ holino)pyrimidine-5-boronic acid pinacol ester (35 mg, 0.12 mmol) were employed in a procedure similar to Step 3, Example 31 to give the title compound as a beige solid (13.0 mg, 28% yield). ^{1}H-NMR (500MHz, METHANOL-d4) δ 8.64 (s, 2H), 8.17 (s, 1H), 8.00 (s, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.33 (d, J=8.2 Hz, 1H), 6.92 (s, 1H), 3.87 - 3.81 (m, 4H), 3.81 - 3.75 (m, 4H), 3.00 (d, J=11.4 Hz, 2H), 2.67 (t, J=ll.l Hz, 2H), 2.59 - 2.47 (m, 2H), 2.39 (s, 3H), 1.18 (d, J=6.2 Hz, 6H); LC-MS [M + H]+ 572.26.

Example 59: N-[5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5SJ-3,4,5-trimethylpiperazin-l-yl]-4-(trifluoromethyl)phenyl]-6<>xo-4-(trifluo romethyl)-1H-pyridine-3-carboxamide

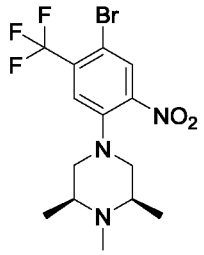


Step 1: (2S, 6R)-1,2, 6-trimethyl-4-(2-nitro-5-(trifluoromethyl)phenyl)piperazine



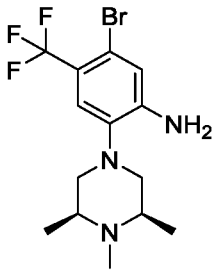
[00301] To a solution of 3-fluoro-4-nitrobenzotrifiuoride (1 g, 4.78 mmol) in DMSO (2 ml) was added (2R,6S)-l,2,6-trimethylpiperazine (0.644 g, 5.02 mmol) and diisopropylethylamine (0.9 ml, 5.25 mmol). Slight exothermicity was observed. The resulting dark red solution was stirred at RT for lh. Only traces of the starting material were observed. The reaction mixture was diluted with water (30 ml) and extracted with EtOAc (3 x 25 ml). The combined organic phase was washed with water, and brine, dried over Na_2S0_4 and concentrated to obtain an orange oil as the desired product. (1.481 g, 98 %). After standing overnight,, the oil became an orange solid. This was taken to the next step without any purification. LCMS [M+H]+ 318.4.

Step 2: (2S, 6R)-4-(4-bromo-2-nitro-5-(trifluoromethyl)phenyl)-l, 2,6-trimethylpiperazine



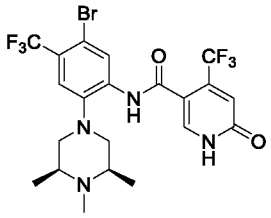
[00302] To a solution of (2S,6R)-l,2,6-trimethyl-4-(2-nitro-5-(trifluoromethyl)phenyl)piperazine (1.150 g, 3.62 mmol) in acetic acid (10 ml) was added bromine (0.467 ml, 9.06 mmol). Slight exothermicity was observed. The resulting dark red solution was stirred at 80°C for 4 h. 52% conversion was observed. 0.2 ml bromine and 3 ml acetic acid were added and the reaction mixture was heated overnight at 80 °C for 22 h. A small amount of starting material was observed. The mixture was allowed to cool to RT, concentrated, the residue was taken up in DCM, neutralized with Satd. $NaHCO_3$ soln., washed with brine, dried over Na_2SO_4 and concentrated to obtain the crude product. It was purified on a 40 g Isco column, eluting with DCM containing 0-2 % MeOH, to yield the desired product as a light brown solid (378 mg, 26 %). LCMS [M+H]+ 396.5

Step 3: 5-bromo-4-(trifluoromethyl)-2-((3S, 5R)-3,4,5-trimethylpiperazin-l-yl)aniline



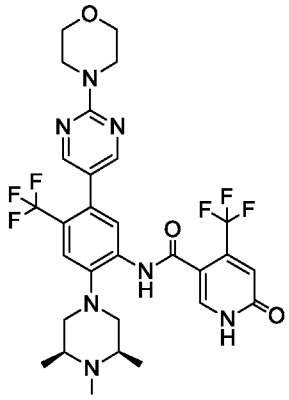
[00303] To a solution of (2S,6R)-4-(4-bromo-2-nitro-5-(trifluoromethyl)phenyl)-1,2,6-trimethylpiperazine (345 mg, 0.871 mmol) in acetic acid (4 ml), was added iron powder, 99% (243 mg, 4.35 mmol). The resulting dark brown solution was stirred at 80 °C. The reaction mixture became a slurry and the conversion was complete in 12 min. The mixture was allowed to cool to RT, concentrated, the residue was taken up in DCM, neutralized with Satd. NaHCCb soln., washed with brine, dried over Na_2SO_4 and concentrated to afford the crude product. It was purified on reverse phase Isco column (15.5), eluting with water containing 0-80 % CH_3CN to collect the title compound as a yellow solid (300 mg, 94 %). LCMS [M+H]+ 366.5

Step 4: N-(5-bromo-4-(trifluoromethyl)-2-((3S, 5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00304] To a 10 mL RBF charged with 6-chloro-4-(trifluoromethyl)nicotinic acid (115 mg, 0.512 mmol), was added thionyl chloride (894 µï, 12.29 mmol) . The resulting suspension was heated at 80 °C for 1 h. It was evaporated to give a light yellow oil which was taken up in DCM (3 mL). 5-bromo-4-(trifluoromethyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (150 mg, 0.410 mmol) and triethylamine (171 µï, 1.229 mmol) were added and the resulting mixture was stirred at RT for 1 h.. After basifying with sat. NaHCCb (5 mL), it was extracted with DCM (5 x 2 mL). The extracts were combined and concentrated to obtain the crude as a pale brown waxy solid. The reaction was combined with HOAc/$H_2$0 (3.6 mL/ 1.2 mL) in a 5 mL microwave vial and was heated in the microwave at 160 °C for 5 h Solvents were removed on a rotovap at 60 °C and the residue was treated with sat. NaHCOs (30 mL). It was extracted with DCM (2 x 45 ml). The extracts were combined, dried over Na_2S0_4, concentrated onto celite and purified on silica gel column (12 G), eluting with DCM containing 0-5 % MeOH. The desired product was obtained as a light purple coloured solid (131 mg, 58 %). LCMS [M+H]+ 555.1

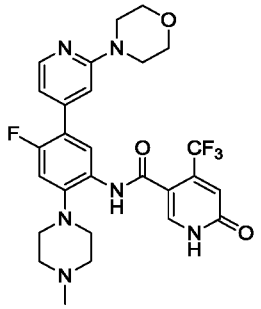
Step 5: N-[5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-4-(Mfluoromethyl)phenyl]-6<>xo-4-(Mfluoromethyl)-lH^yridine-^ -carboxamide



[00305] N-(5-bromo-4-(trifluoromethyl)-2-((3 S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (50 mg, 0.09

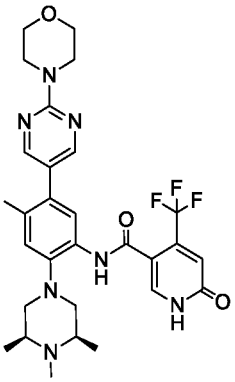
mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (37 mg, .126 mmol), XPhos Pd G2 (14 mg, 0.018 mmol), Xphos (9 mg, 0.018 mmol) and sodium carbonate, anhydrous (95 mg, 0.9 mmol) were taken in a microwave vial. 1,4-Dioxane (4 ml) and water (1 ml) were added and stirred for 5 min. The white suspension was purged with argon and the reaction mixture was heated in the microwave for 60 min at 110 °C. The mixture was concentrated onto celite and purified on preparative column, eluting with water/acetonitrile gradient to isolate the title compound as a white solid (10.5 mg, 17 %). ¹H NMR (500MHz, METHANOL-d4) δ = 8.30 (s, 2H), 8.05 (s, 1H), 7.99 (br. s., 1H), 7.62 (s, 1H), 7.01 - 6.84 (m, 1H), 3.87 - 3.82 (m, 4H), 3.79 - 3.75 (m, 4H), 3.15 (d, *J*=11.7 Hz, 2H), 3.02 (br. s., 2H), 2.90 - 2.81 (m, 2H), 2.66 - 2.64 (m, 3H), 1.29 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+ 640.7.

Example 60: N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholin-4-ylpyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

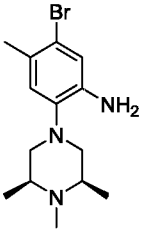


[00306] The title compound was prepared similar to the sequence described for the preparation of Example 3 using 2-morpholinopyridine-4-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.16 (d, *J* = 5.4 Hz, 1H), 7.97 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 12.2 Hz, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.91 (d, *J* = 5.1 Hz, 1H), 3.84 - 3.80 (m, 4H), 3.54 - 3.50 (m, 4H), 3.03 (t, *J* = 4.9 Hz, 4H), 2.68 (s, *J* = 2.0 Hz, 4H), 2.39 (s, 3H); LCMS [M+l]+ = 561.4.

Example 61: N-[4-methyl-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridm^-3-carboxamide

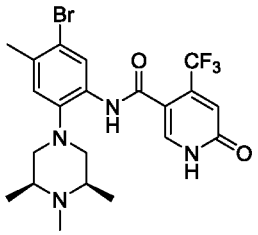


Step 1: 5-bromo-4-methyl-2-((3S,5RJ-3,4,5-trimethylpiperazin-l -yljaniline



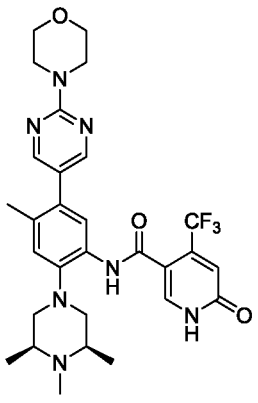
[00307] To a solution of l-bromo-4-fluoro-2-methyl-5-nitrobenzene (2.34g, 10 mmol) in DMSO (5 mL) was added (2S,6R)-l,2,6-trimethylpiperazine (1.35g, 10.5 mmol). The resulting dark red mixture was stirred at 80 °C for 1.5 h. Orange precipitates formed upon cooling. The reaction mixture was diluted with $\mathbf{H_20}$ (60 mL), basified with 1 M aq NaOH (10 mL, 10 mmol) and extracted with EtOAc (60 mL + 30 mL). The combined extracts were concentrated and dried under vacuum to give the $\mathbf{N0_2}$ intermediate as a dark orange solid (3.36 g). LCMS $[M + H]^+$ 342.2.To a solution of the above dark orange solid (3.36 g) and hydrazine monohydrate (1.46 mL, 30 mmol) in MeOH (45 mL) at 60 °C was added a suspension of Raney-Nickel (0.214 g, 2.5 mmol) in MeOH (5 mL) portionwse over 5 min. After addition, the reaction mixture was heated at 60 °C for 30 min. The reaction turned from dark orange red to light brown. It was passed through celite, and rinsed with MeOH (20 mL x 2). The combined filtrate was concentrated to give a light brown oil which was purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-5%) to give the title compound as a pink solid (2.349 g, 74%). LCMS $[M + H]^+$ 312.1.

Step 2: N-(5-bromo-4-methyl-2-((3S, 5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00308] To a 25 mL RBF charged with 6-chloro-4-(trifluoromethyl)nicotinic acid (542 mg, 2.4 mmol) was added thionyl chloride (4.37 mL, 60 mmol). The resulting suspension was heated at 80 °C for 1 h. It was evaporated to give a light yellow oil which was treated with DCM (15 mL), 5-bromo-4-methyl-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (625 mg, 2 mmol) and EtsN (0.84 mL, 6 mmol). The resulting mixture was stirred at rt for 1 h. After basifying with sat. $NaHC0_3$ (30 mL), it was extracted with DCM (30 mL x 2). The combined extracts were concentrated to give a beige solid. LCMS $[M + H]^+$ 519.1. A mixture of the above solid, NaOAc (328 mg, 4 mmol) in HOAc/H_2**0** (10 mL/3mL) in a 20 mL microwave vial was microwaved at 160 °C for 5 h. Solvents were removed and the residue was treated with sat. NaHCCb (30 mL) and extracted with DCM (60 mL + 30 mL). The combined extracts were concentrated and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-15%) and triturated with MeOH (10 mL) to give the title compound as a pale yellow solid (761 mg, 71%). LCMS $[M+ H]^+$ 501.2.

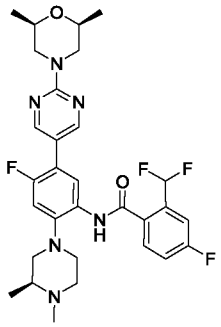
Step 3: N-(4-methyl-5-(2-morpholinopyrimidin-5-yl)-2-(⟨3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6<>xo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00309] The title compound (white solid, 26.4 mg, 45%) was prepared according to a procedure similar to the last step of Example 29 using N-(5-bromo-4-methyl-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50 mg, 0.1 mmol) and 2-(4^ orpηo1iηo)pyrimidiη6-5-

boronic acid pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.37 (s, 2H), 7.96 (s, 1H), 7.74 (s, 1H), 7.16 (s, 1H), 6.91 (s, 1H), 3.86 - 3.76 (m, 8H), 3.01 (d, *J*=11.4 Hz, 2H), 2.71 - 2.62 (m, 2H), 2.61 - 2.53 (m, 2H), 2.40 (s, 3H), 2.30 (s, 3H), 1.18 (d, *J*=1.0 Hz, 6H); LCMS $[M + H]^+$ 586.3.

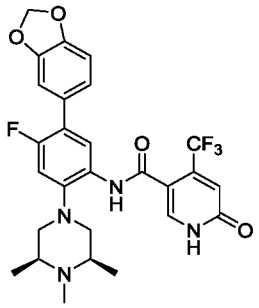
Example 62: 2-(difluoromethyl)-N-(5-(2-((2S, 6R)-2, 6-dimethylmorpholino)pyrimidin-5-yl)-2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluorobenzamide



[00310] A mixture of 2-(difluoromethyl)-4-fluorobenzoic acid (171 mg, 0.9 mmol), HATU (342 mg, 0.9 mmol) and N,N-diisopropylethylamine (0.21 ml, 1.2 mmol) in DMF (2 mL) was heated at 70 °C for 1 min to afford a clear light brown solution before (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (181 mg, 0.6 mmol) was added in one portion. The resulting mixture was heated at 70 °C for 1.5 h. It was diluted with EtOAc (20 mL) and washed with H_20 (30 mL x 2), concentrated and purified by flash chromatography (EtOAc/hex 0-100%, then MeOH/DCM 0-5%) to give (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-2-(difluoromethyl)-4-fluorobenzamide as a light brown solid (265 mg, 92%). LCMS $[M + H]^+$ 474.1. It was redissolved in dioxane (12 mL) and divided equally into 3 portions (each 4 mL, 0.185 mmol). The title compound (formic acid salt, white solid, 38.9 mg, 33%) was prepared according to a method similar to that described in Example 31 using (2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)boronic acid (66 mg, 0.278 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-2-(difluoromethyl)-4-fluorobenzamide in dioxane (0.185 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.37 (br s, 1H), 7.96 (br d, *J*=8.2 Hz, 1H), 7.89 (br dd, *J*=5.6, 8.0 Hz, 1H), 7.56 (dd, *J*=2.3, 9.3 Hz, 1H), 7.51 - 7.25 (m, 2H), 7.18 (d, *J*=11.9 Hz, 1H), 4.65 (dd, *J*=1.3, 13.1 Hz, 2H), 3.71 - 3.63 (m, 2H), 3.39 - 3.35 (m, 1H), 3.31 - 3.23 (m, 2H), 3.14 - 3.06 (m, 1H), 3.02 (br d,

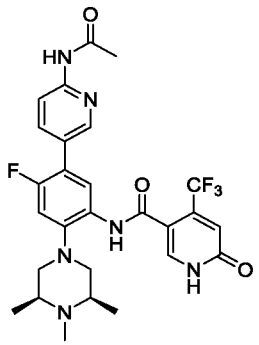
J=10.1 Hz, 2H), 2.86 - 2.79 (m, 1H), 2.73 (s, 3H), 2.64 (dd, *J*=10.7, 13.3 Hz, 2H), 1.30 (d, *J*=6.5 Hz, 3H), 1.25 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 587.4.

Example 63: N-[5-(l, 3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



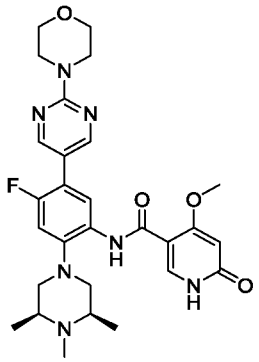
[00311] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 3,4-methylenedioxyphenylboronic acid. ^{1}H NMR (500 MHz, MeOD) δ 7.94 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 5.8 Hz, 3H), 6.92 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.99 (s, 2H), 3.07 (d, *J* = 8.4 Hz, 2H), 2.63 (d, *J* = 7.3 Hz, 4H), 2.42 (s, 3H), 1.18 (d, *J* = 5.4 Hz, 6H); LCMS [M+l]+ = 547.21.

Example 64: N-[5-(5-acetamidopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



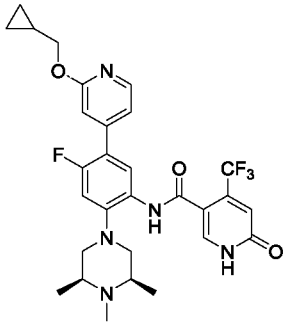
[00312] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 2-acetamidopyridine-5-boronic acid, pinacol ester in as the boronic ester coupling partner. ^{1}H NMR (500 MHz, MeOD) δ 8.47 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.96 - 7.92 (m, 3H), 7.09 (d, *J* = 12.1 Hz, 1H), 6.92 (s, 1H), 3.09 (d, *J* = 10.5 Hz, 2H), 2.67 - 2.59 (m, 4H), 2.41 (s, 3H), 2.20 (s, 3H), 1.18 (d, *J* = 5.8 Hz, 6H); LCMS [M+l]+ = 561.28.

Example 65: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenylJ-4-methoxy-6-oxo-lH-pyridine-3-carboxamide



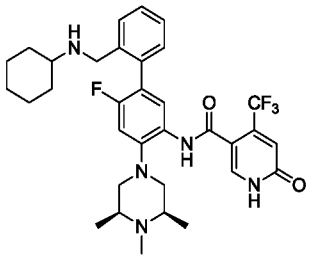
[00313] In a 5 ml microwave vial to a suspension of 4-methoxy-6-oxo-l,6-dihydropyridine-3-carboxylic acid (50.7 mg, 0.300 mmol) in pyridine, anhydrous (364 µï, 4.49 mmol) was added slowly diethyl chlorophosphate (44.4 µï, 0.307 mmol) at rt in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. To this was added 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)aniline (30 mg, 0.075 mmol, preparation described in Example 8) and the reaction was heated at 70 °C for 3 h. The pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, dried over anhydrous Na_2S0_4, and solvent was evaporated in vacuo. The crude product was purified by silica gel chromatography to obtain the title compound (15 mg, 36% yield) as a brown solid. ^{1}H NMR (500 MHz, MeOD) δ 8.55 (d, *J* = 1.1 Hz, 4H), 8.49 (d, *J* = 1.2 Hz, 14H), 8.31 (s, 2H), 7.12 (d, *J* = 11.9 Hz, 2H), 6.84 (dd, *J* = 9.9, 5.9 Hz, 15H), 6.08 (d, *J* = 4.6 Hz, 2H), 4.14 (s, 6H), 3.86 - 3.80 (m, 43H), 3.76 (dd, *J* = 9.0, 4.1 Hz, 43H), 3.19 (s, 7H), 3.02 (d, *J* = 10.7 Hz, 5H), 2.84 (s, 11H), 2.65 - 2.60 (m, 9H), 2.61 - 2.51 (m, 42H), 2.43 (s, 7H), 1.25 (d, *J* = 6.0 Hz, 42H); LCMS [M+l]+ = 552.3.

Example 66: N-[5-[2-(cyclopropylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide

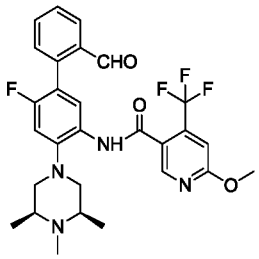


[00314] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 2-(cyclopropylmethoxy)-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine as the boronic ester coupling partner. ^{1}H NMR (500 MHz, MeOD) δ 8.14 (d, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.96 (s, 1H), 7.13 (d, *J* = 5.4 Hz, 1H), 7.07 (d, *J* = 12.3 Hz, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 4.14 (d, *J* = 7.1 Hz, 2H), 3.10 (d, *J* = 11.3 Hz, 2H), 2.62 (t, *J* = 11.2 Hz, 2H), 2.54 (ddd, *J* = 10.3, 6.9, 4.1 Hz, 2H), 2.37 (s, 3H), 1.35 - 1.25 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 6H), 0.61 (q, *J* = 5.9 Hz, 2H), 0.37 (q, *J* = 4.7 Hz, 2H); LCMS [M+l]+ =574.22.

Example 67: N-[5-[2-[(cyclohexylamino)methyl]phenyl]-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridm^ -3-carboxamide



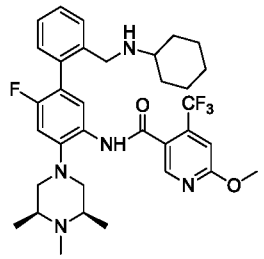
Step 1: N-(6-fluoro-2 '-formyl-4-((3S,5RJ-3,4,5-trimethylpiperazin-l -yl)-[l, 1'-biphenyl]-3-yl)-6-methoxy-4-(trifluoromethyl)nicotinamide



[00315] N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methoxy-4-(trifluoromethyl)nicotinamide (125 mg, 0.241 mmol), 2-

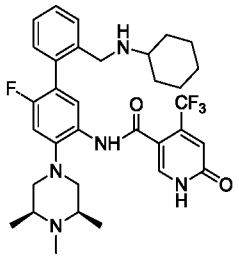
formylphenylboronic acid (50.5 mg, 0.337 mmol), sodium carbonate, anhydrous (255 mg, 2.407 mmol), XPhos Pd G2 (37.9 mg, 0.048mg) and Xphos (22.95 mg, 0.048 mmol) were mixed in a microwave vial. Water (3 ml) and 1,4-dioxane (3 ml) were added and stirred for 5 min. The white suspension was purged with argon and the reaction mixture was heated in the microwave for 30 min at 110 °C. The reaction mixture was concentrated onto celite and purified on Isco (4G) column, eluting with DCM containing 0-2 % MeOH to obtain the desired product as an off white foam. (124 mg, 90%). LCMS [M+H]+ 545.4

Step 2: N-(2'-((cyclohexylamino)methyl)-6-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[lJ'-biphenyl]-3-yl)-6-methoxy-4-(Mfluoromethyl)nicotimmide



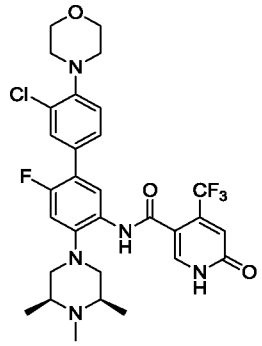
[00316] N-(6-fluoro-2'-formyl-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,l'-biphenyl]-3-yl)-6-methoxy-4-(trifluoromethyl)nicotinamide (70 mg, 0.122 mmol), N-(6-fluoro-2'-foimyl-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,r-biphenyl]-3-yl)-6-methoxy-4-(trifluoromethyl)nicotinamide (70 mg, 0.122 mmol) and acetic acid, glacial, 99.8% (0.028 ml, 0.488 mmol) were mixed in anhydrous DCE. A cloudy solution was obtained. After 5-10 min, sodium triacetoxyborohydride (36.9 mg, 0.174 mmol) was added and the reaction mixture was stirred ovemight at RT. The reaction was complete (by LCMS). The reaction was quenched with sat aq NaHCCb solution (basic). The organic phase was separated, the aqueous phase was extracted with DCM (x2), the combined organic phase was washed with brine, dried over Na_2S0_4 and concentrated to afford the crude product. It was purified by isco column (4G), eluting with DCM containing 0-5% MeOH. The appropriate fractions were combined and concentrated to afford the desired product as a white foam (49 mg, 64 %). LCMS [M+H]+ = 628.6.

Step 3: N-(2'-((cyclohexylamino)methyl)-6-fluoro-4-((3S, 5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamide hydrochloride salt:



[00317] To a solution of N-(2'-((cyclohexylamino)methyl)-6-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,1'-biphenyl]-3-yl)-6-methoxy-4-(trifluoromethyl)nicotinamide (48 mg, 0.076 mmol) in methanol (1.5. ml) was added concentrated HCl (1.0 ml) and the reaction mixture was heated at 80 °C. The reaction was complete after 2.5 h. The reaction mixture was allowed to cool to RT, concentrated to dryness, co-evaporated with MeOH first and then with DCM to yield the desired product as an off white solid (30 mg, 51 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.02 - 7.88 (m, 1H), 7.72 - 7.65 (m, 1H), 7.63 - 7.59 (m, 1H), 7.50 - 7.43 (m, 2H), 7.36 - 7.30 (m, 1H), 7.16 (d, *J*=10.8 Hz, 1H), 6.82 (s, 1H), 4.30 - 4.02 (m, 2H), 3.60 - 3.50 (m, 2H), 3.33 - 3.25 (m, 2H), 3.00 - 2.88 (m, 5H), 1.89 - 1.78 (m, 2H), 1.69(br. s., 2H), 1.56 (d, *J*=12.6 Hz, 1H), 1.44 - 1.31 (m, 6H), 1.23 - 1.15 (m, 5H), 1.12 - 1.04 (m, 1H), 1.12 - 1.04 (m, 1H); LCMS [M+H]+ = 614.6.

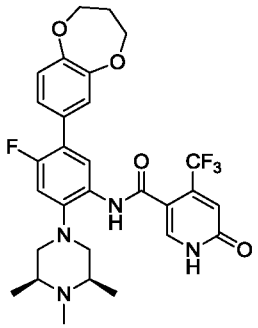
Example 68: N-[5-(3-chloro-4-morpholin-4-ylphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



[00318] The title compound (light brown solid, 50.7 mg, 80%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol, example 31) and 3-chloro-4-(4-morpholinyl)benzeneboronic acid pinacol ester (65 mg, 0.2 mmol). ^{1}H NMR

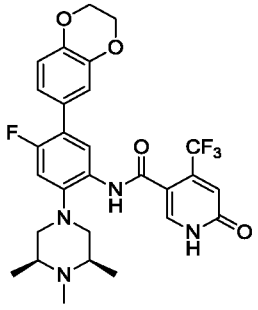
(500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.91 (d, *J*=8.2 Hz, IH), 7.59 (s, IH), 7.48 (d, *J*=8.2 Hz, IH), 7.22 (d, *J*=8.1 Hz, IH), 7.06 (d, *J*=12.1 Hz, IH), 6.92 (s, IH), 3.92 - 3.85 (m, 4H), 3.15 - 3.05 (m, 6H), 2.68 - 2.52 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6. 1 Hz, 6H); LCMS [M + H]$^+$ 622. 1.

Example 69: N-[5-(3,4-dihydro-2H-l, 5-benzodioxepin- 7-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



[00319] The title compound (light beige solid, 44.6 mg, 77%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3,4-dihydro-2H-l,5-benzodioxepin-7-ylboronic acid (38.8 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 7.96 (s, IH), 7.89 (d, *J*=8.3 Hz, IH), 7.19 - 7.15 (m, IH), 7.13 (d, *J*=8.1 Hz, IH), 7.06 - 7.00 (m, 2H), 6.92 (s, IH), 4.25 - 4.19 (m, 4H), 3.06 (d, *J*=ll.l Hz, 2H), 2.67 - 2.52 (m, 4H), 2.39 (s, 3H), 2.23 - 2.17 (m, 2H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS [M+ H]$^+$=575.3.

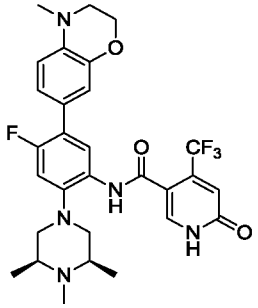
Example 70: N-[5-(2,3-dihydro-l, 4-benzodioxin-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



[00320] The title compound (off white solid, 43.7 mg, 78%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-

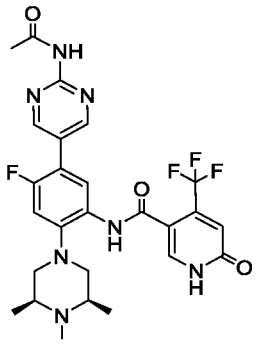
trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 2,3-dihydro-l,4-benzodioxin-6-ylboronic acid (36 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 7.96 (s, 1H), 7.88 (d, *J*=8.3 Hz, 1H), 7.07 - 6.98 (m, 3H), 6.95 - 6.87 (m, 2H), 4.29 (s, 4H), 3.06 (d, *J*=11.2 Hz, 2H), 2.66 - 2.52 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ =561.2.

Example 71: N-[4-fluoro-5-(4-methyl-2, 3-dihydro-l, 4-benzoxazin-7-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



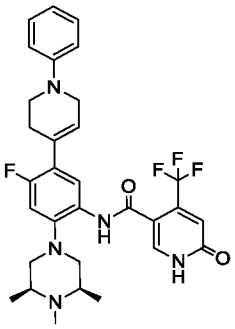
[00321] The title compound (pale beige solid, 28.9 mg, 50%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-methyl-7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-l,4-benzoxazine (55 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.96 (s, 1H), 7.88 (d, *J*=8.3 Hz, 1H), 7.03 (d, *J*=8.4 Hz, 1H), 7.00 (d, *J*=12.2 Hz, 1H), 6.94 - 6.92 (m, 1H), 6.92 (s, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 4.33 - 4.28 (m, 2H), 3.32 - 3.28 (m, 2H), 3.04 (d, *J*=ll.l Hz, 2H), 2.93 (s, 3H), 2.66 - 2.47 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 574.4.

Example 72: N-[5-(2-acetamidopyrimidin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[00322] The title compound was prepared in a manner similar to Example 31 using N-(5-(4,4,5,54etramethyl-l,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)acetamide in place of 2-cyanopyrimidine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.81 (s, 2H), 7.98 (s, 1H), 7.96 (d, *J* = 4.7 Hz, 1H), 7.15 (d, *J* = 12.0 Hz, 1H), 6.93 (s, 1H), 3.16 (d, *J* = 7.0 Hz, 2H), 2.80 (s, 2H), 2.71 (t, *J* = 11.1 Hz, 3H), 2.52 (s, 3H), 2.28 (s, 3H), 1.23 (d, *J* = 5.9 Hz, 6H); LCMS [M+l]+ = 562.2.

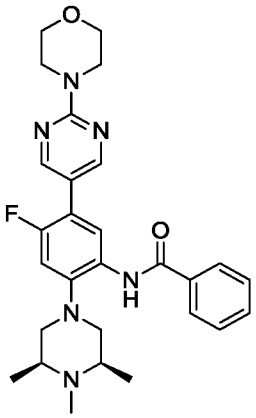
Example 73: N-[4-fluoro-5-(l-phenyl-3, 6-dihydro-2H-pyridin-4-yl)-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00323] The procedure was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (60 mg, 0.099 mmol) and 1,2,3,6-tetrahydro-l-phenyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-pyridine (39.6 mg, 0.139 mmol) to give, after deprotection of the silyloxy intermediate, 20 mg (74% yield) of the title compound as a pale yellow orange powder. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.04 - 7.98 (m, 1H), 7.86 (d, *J*=7.9 Hz, 1H), 7.34 (t, *J*=8.0 Hz, 2H), 7.15 (d, *J*=8.2 Hz, 2H), 7.08 (d, *J*=12.1 Hz, 1H), 7.01 - 6.94 (m, 2H), 6.20 (br. s., 1H), 4.00 - 3.93 (m, 2H),

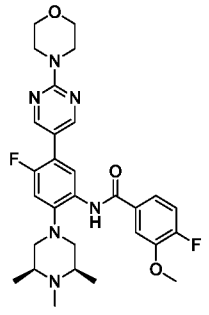
3.62 - 3.57 (m, 2H), 3.55 - 3.48 (m, 2H), 3.37 (br. s., 2H), 3.00 (s, 3H), 2.92 (t, *J*=12.3 Hz, 2H), 2.74 (br. s., 2H), 1.49 - 1.42 (m, 6H); LCMS [M+H]+ 584.6.

Example 74: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[00324] The title compound (pale beige solid, 25.3 mg, 50%) was prepared in a manner similar to Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and benzoyl chloride (17 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.25 (s, 1H), 8.69 (d, *J*=8.2 Hz, 1H), 8.60 (d, *J*=1.2 Hz, 2H), 7.94 (d, *J*=7.1 Hz, 2H), 7.64 - 7.54 (m, 3H), 7.03 (d, *J*=11.4 Hz, 1H), 3.93 - 3.86 (m, 4H), 3.85 - 3.79 (m, 4H), 2.93 (d, *J*=10.9 Hz, 2H), 2.70 (t, *J*=10.9 Hz, 2H), 2.50 - 2.41 (m, 2H), 2.39 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 505.4.

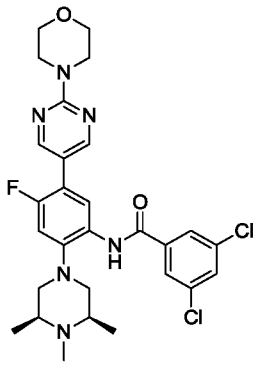
Example 75: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yljphenyl]'-3-methoxybenzamide



[00325] The title compound (beige solid, 4.6 mg, 8%) was prepared in a manner similar to Example 34 using 4-fluoro-3-methoxybenzoic acid (34 mg, 0.2

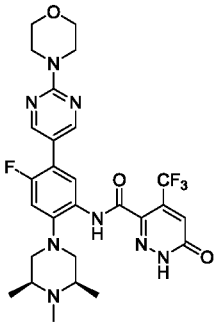
mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.14 (s, IH), 8.57 (d, *J*=8.3 Hz, IH), 8.51 (d, *J*=l.l Hz, 2H), 7.58 (dd, *J*=2.0, 8.1 Hz, IH), 7.31 (t, *J*=5.8 Hz, IH), 7.14 (dd, *J*=8.4, 10.5 Hz, IH), 6.94 (d, *J*=11.2 Hz, IH), 3.93 (s, 3H), 3.83 - 3.78 (m, 4H), 3.74 - 3.71 (m, 4H), 2.82 (d, *J*=10.9 Hz, 2H), 2.61 (t, *J*=10.9 Hz, 2H), 2.36 - 2.30 (m, 2H), 2.29 (s, 3H), 1.08 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 553.3.

Example 76: 3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJbenzamide

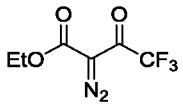


[00326] The title compound (beige solid, 32.4 mg, 55%) was prepared in a manner similar to Example 34 using 3,5-dichlorobenzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, IH), 8.52 (d, *J*=8.2 Hz, IH), 8.50 (d, *J*=1.2 Hz, 2H), 7.71 (s, 2H), 7.50 (s, IH), 6.95 (d, *J*=11.2 Hz, IH), 3.84 - 3.78 (m, 4H), 3.75 - 3.69 (m, 4H), 2.82 (d, *J*=11.0 Hz, 2H), 2.63 (t, *J*=10.9 Hz, 2H), 2.42 - 2.34 (m, 2H), 2.31 (s, 3H), 1.11 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 573.2.

Example 77: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ine-3-carboxamide

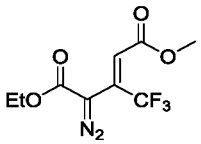


Step 1: ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate



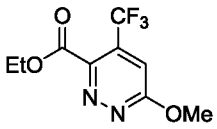
[00327] To a solution of ethyl 2-diazoacetate (50 g, 438 mmol, leq) in DCM (500 mL) was added dropwise a solution of TFAA (70 mL, 482 mmol, 1.1 eq, in DCM) at 0°C under argon, then the reaction mixture was continued for 2 h. TLC analysis indicated formation of polar spot. The reaction mixture was neutralized with sat NaHCCb solution and extracted with DCM (3x300mL). The combined organic layer was washed with **CU2SO4** solution and dried over Na_2S04, then concentrated to give ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate (50g, 55%) as a green oil. TLC: EtOAc : Pet ether (2:8); R_f: 0.4.

Step 2: 5-ethyl 1-methyl (Z)-4-diazo-3-(trifluoromethyl)pent-2-enedioate



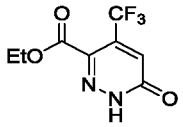
[00328] To a stirred solution of methyl 2-(triphenyl-15-phosphaneylidene)acetate (52.56 g, 157 mmol, 1.5 eq) in diethyl ether (308 mL) was added ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate (22 g, 104 mmol, 1 eq) at 10°C under argon atmosphere, then the reaction mixture was stirred at RT for 24h. TLC analysis indicated formation of polar spot. The reaction mixture was filtered and washed with diethyl ether then the filtrate was concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-10% diethyl ether in pentane as eluent to afford 5-ethyl 1-methyl (Z)-4-diazo-3-(trifluoromethyl)pent-2-enedioate (19 g, 68.19%) as yellow oil. TLC system: diethyl ether : pentane (3:7); R_f: 0.4.

Step 3: ethyl 6-methoxy-4-(trifluoromethyl)pyridazine-3-carboxylate



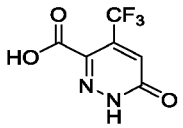
[00329] To a stirred solution of 5-ethyl 1-methyl (Z)-4-diazo-3-(trifluoromethyl)pent-2-enedioate (19 g, 71.42 mmol, leq) in diethyl ether (190 mL) was portion wise added TPP (22.4 g, 85.71 mmol, 1.2 eq) at 10°C then allowed to remain at RT for 16h. TLC analysis indicated formation of polar spot. The reaction mixture was filtered then the filtrate was concentrated to crude residue. The crude residue was purified by column chromatography (silica gel, 230-400mesh) using 0-20% acetone in pet ether as eluent to afford ethyl 6-methoxy-4-(trifluoromethyl)pyridazine-3-carboxylate (5 g, 28.90%) as yellow oil. LCMS: [M+H]+ 251.14.

Step 4: ethyl 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridazine-3-carboxylate



[00330] To a stirred solution of 6-methoxy-4-(trifluoromethyl)pyridazine-3-carboxylate (4.5g, 18mmol, leq) in ACN (80mL) was added Nal (8.1g, 54 mmol, 3eq) and TMS-C1 (5.86 g, 54 mmol, 3 eq) at RT under argon atmosphere, then the reaction mixture was heated to 80°C for 2 h. TLC analysis indicated formation of polar spot. The reaction mixture was concentrated to crude residue, which was diluted with water and extracted with EtOAc (3X 100 mL). The combined organic layer was dried over Na_2S0_4 then concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-5% MeOH in DCM as eluent to afford (3.2 g, 76.20%) as pale yellow solid. LCMS: [M+ H]+ 237.04.

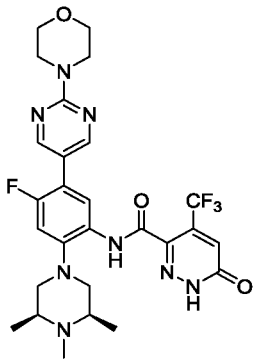
Step 5: 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridazine-3-carboxylic acid



[00331] To a solution of ethyl 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridazine-3-carboxylate (205 mg, 0.923 mmol) in THF (923 µï) was added lithium hydroxide monohydrate (77 mg, 1.846 mmol) dissolved in water (923 µï), and

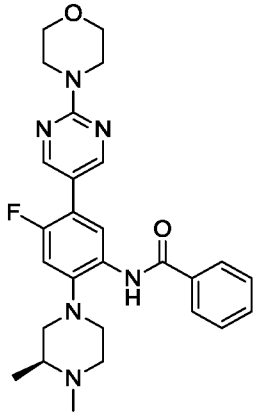
the mixture was stirred for 1 h at room temperature. The reaction was concentrated, adjusted to a pH of 3, and extracted with DCM. The compound was not soluble in DCM. Purification was carried out using an anion exchange column to give the title compound (150 mg, 78% yield). LCMS [M-H] 206.98.

Step 6: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrida zine-3-carboxamide

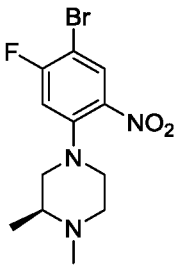


[00332] The title compound was prepared similar to the sequence described above for the preparation of Example 34 using 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridazine-3-carboxylic acid in place of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid. ^{1}H NMR (500 MHz, MeOD) δ 8.57 (d, *J* = 1.1 Hz, 2H), 8.28 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 1H), 7.12 (d, *J* = 11.9 Hz, 1H), 3.86 - 3.83 (m, 4H), 3.78 - 3.75 (m, 4H), 3.08 (d, *J* = 11.5 Hz, 2H), 2.80 (s, 2H), 2.67 (t, *J* = 11.2 Hz, 2H), 2.50 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 6H); LCMS [M+l]+ = 591.4.

Example 78: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl] phenyl] benzamide

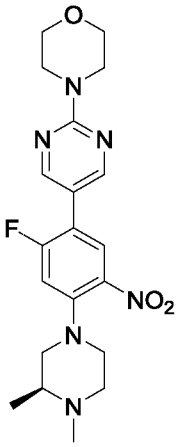


Step 1: (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine



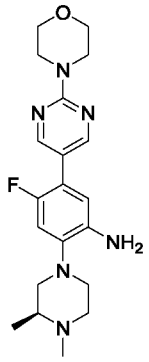
[00333] A solution of l-bromo-2,4-difluoro-5-nitrobenzene (3.85 mL, 30.5 mmol) in toluene (10 mL) was added dropwise to a rapidly stirring mixture of (S)-l,2-dimethylpiperazine dihydrochloride (5.70 g, 30.5 mmol) and potassium carbonate (10.5 g, 76 mmol) in toluene (70 mL) at room temperature. After stirring for 20 minutes the reaction was warmed to 45 °C for 30 minutes. After the reaction was cooled to room temperature the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine (7.41 g, 73 %). LCMS [M+H]+: 332.1.

Step 2: (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-nitrophenyl)pyrimidin-2-yljmorpholine



[00334] A 100 mL round bottomed flask was charged with a mixture of (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine (1.60 g, 4.8 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (1.50 g, 5.2 mmol), XPhos Pd G2 (0.075 g, 0.10 mmol) and XPhos (0.045 g, 0.10 mmol). The flask was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-dioxane (40 mL) and 2 M aqueous sodium carbonate (12 mL) were added via syringe and the flask was evacuated and backfilled an additional time. The reaction was heated to 90 °C for 3 h in an oil bath. After cooling to room temperature the reaction was partitioned between DCM and water. The layers were separated and the aqueous layer was extracted with additional DCM. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] afforded (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-nitrophenyl)pyrirnidin-2-yl)morpholine (2.0 g, >95%). LCMS [M+H]+: 417.2.

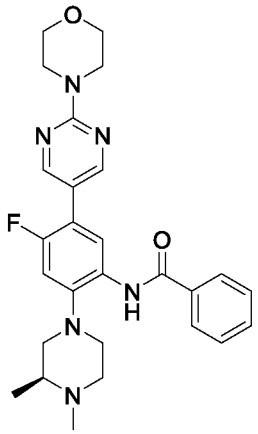
Step 3: Preparation of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline



[00335] A mixture of (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-nitrophenyl)pyrimidin-2-yl)morpholine (2.0 g, 5.0 mmol), iron powder (1.1 g, 20 mmol) and acetic acid (25 mL) was heated to 80 °C for 90 minutes. After cooling to room temperature the reaction was transferred to a large Erlenmeyer flask and diluted with DCM (250 mL). The acetic acid was carefully neutralised by the addition of aqueous sodium bicarbonate. The whole was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with additional DCM. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration, the filtrate was concentrated onto celite. Purification

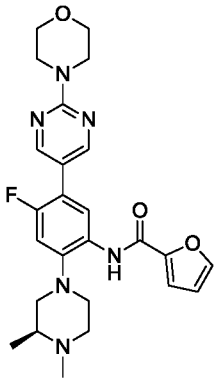
by flash chromatography [0.5-10% DCM/MeOH + 0.5% NH_4OH] afforded (S)-2-(3,4-dimethylpiperazin- 1-yl)-4-fiuoro-5 -(2-morpholinopyrimidin-5-yl)aniline (1.34 g, 70 %). LCMS [M+H]+: 387.3.

Step 4: Preparation of (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide



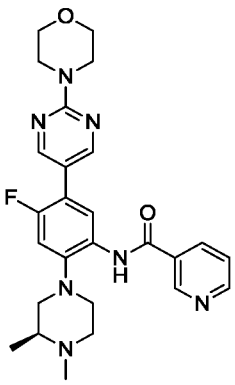
[00336] Benzoyl chloride (0.010 mL, 0.10 mmol) was added dropwise to a stirring solution of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (0.025 g, 0.065 mmol) and triethylamine (0.026 mL, 0.19 mmol) in DCM (3 mL) at room temperature. After stirring for 2 h at room temperature the reaction was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford the title compound (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide (0.028 g, 88 %). ^1H NMR (500MHz, DMSO-d6) δ = 9.57 (s, 1H), 8.57 (s, 2H), 8.04 - 7.93 (m, 3H), 7.67 - 7.53 (m, 3H), 7.18 (d, *J*=12.1 Hz, 1H), 3.79 - 3.75 (m, 4H), 3.71 - 3.67 (m, 4H), 3.06 - 2.98 (m, 2H), 2.91 - 2.78 (m, 4H), 2.22 (br. s., 4H), 0.97 (d, *J*=6.0 Hz, 3H); LCMS [M+H]+: 491.4.

Example 79: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJfuran-2-carboxamide



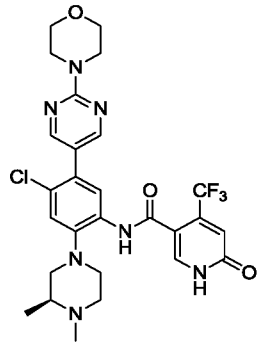
[00337] The title compound was prepared similar to the sequence described above for the preparation of Example 78 using 2-furoyl chloride in place of benzoyl chloride in Step 4. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.37 (s, IH), 8.55 (s, 2H), 8.20 (d, *J*=8.6 Hz, IH), 7.99 (s, IH), 7.30 (d, *J*=3.4 Hz, IH), 7.24 (d, *J*=12.0 Hz, IH), 6.74 (dd, *J*=1.7, 3.5 Hz, IH), 3.79 - 3.75 (m, 4H), 3.72 - 3.66 (m, 4H), 3.00 - 2.82 (m, 5H), 2.27 (br. s., 4H), 1.02 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 481.3.

Example 80: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJpyridine-3-carboxamide

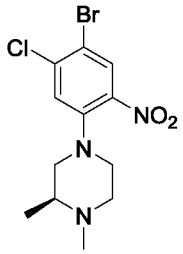


[00338] The title compound was prepared similar to the sequence described above for the preparation of Example 78 using nicotinoyl chloride hydrochloride in place of benzoyl chloride in Step 4. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.82 (s, IH), 9.13 (br. s., IH), 8.78 (d, *J*=4.52 Hz, IH), 8.57 (d, *J*=1.10 Hz, 2H), 8.30 (d, *J*=8.19 Hz, IH), 7.89 (d, *J*=8.31 Hz, IH), 7.61 (dd, *J*=4.89, 7.83 Hz, IH), 7.15 (d, *J*=11.86 Hz, IH), 3.75-3.80 (m, 4H), 3.67-3.71 (m, 4H), 3.05 (br. s., 2H), 2.75-2.91 (m, 2H), 2.21 (br. s., 4H), 0.98 (br. s., 3H); LCMS [M+H]+: 492.4.

Example 81: N-[4-chloro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide

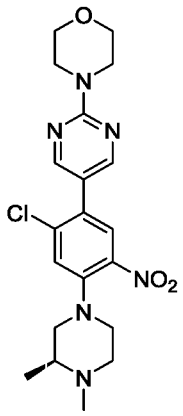


Step 1: (S)-4-(4-bromo-5-chloro-2-nitrophenyl)-l,2-dimethylpiperazine



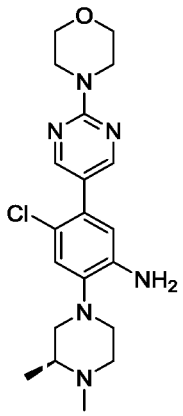
[00339] A solution of l-bromo-2-chloro-4-fluoro-5-nitrobenzene (1.0 g, 3.9 mmol) in toluene (2 mL) was added dropwise to a rapidly stirring mixture of (S)-l,2-dimethylpiperazine dihydrochloride (0.73 g, 3.9 mmol) and potassium carbonate (1.4 g, 9.8 mmol) in toluene (10 mL) at room temperature. After stirring for 20 minutes at room temperature the reaction was warmed to 45 °C for 18 h. After the reaction was cooled to room temperature the reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded (S)-4-(4-bromo-5-chloro-2-nitrophenyl)-l,2-dimethylpiperazine (0.66 g, 48 %). LCMS [M+H]+: 348.0.

Step 2: (S)-4-(5-(2-chloro-4-(3, 4-dimethylpiperazin-l-yl)-5-nitrophenyl)pyrimidin-2-yl)morpholine



[00340] A vial was charged with (S)-4-(4-bromo-5-chloro-2-nitrophenyl)-l,2-dimethylpiperazine (0.40 g, 1.1 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (0.37 g, 1.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.11 mmol). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (7 mL) and 2 M aqueous sodium carbonate (3 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 100 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated onto celite and flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (S)-4-(5-(2-chloro-4-(3,4-dimethylpiperazin-l-yl)-5-nitrophenyl)pyrimidin-2-yl)morpholine (0.28 g, 56 %). LCMS [M+H]+: 433.2.

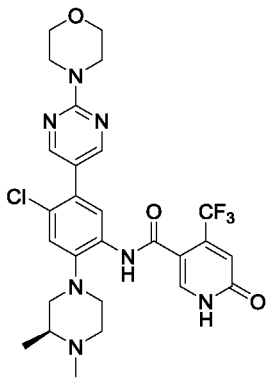
Step 3: (S)-4-chloro-2-(3,4-dimethylpiperazin-1-yl)-5-(2-morpholinopyrimidin-5-yl)aniline



[00341] A mixture of (S)-4-(5-(2-chloro-4-(3,4-dimethylpiperazin-l-yl)-5-nitrophenyl)pyrimidin-2-yl)morpholine (0.12 g, 0.28 mmol), iron powder (0.080 g, 1.4 mmol), hydrochloric acid (0.12 mL, 1.4 mmol), MeOH (5 mL) and water (1 mL) was heated to 85 °C for 1 h. After cooling to room temperature the reaction was

diluted with MeOH and filtered through celite, eluting with additional MeOH. The filtrate was concentrated onto celite and flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] afforded (S)-4-chloro-2-(3,4-dimethylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)aniline (0.046 g, 41 %). LCMS [M+H]+: 403.3.

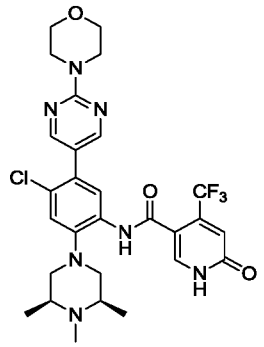
Step 4: (S)-N-(4-chloro-2-(3,4-dimethylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00342] A suspension of 6-chloro-4-(trifluoromethyl)nicotinic acid (0.030 g, 0.13 mmol) and thionyl chloride (0.32 mL, 4.5 mmol) was heated at 80 °C for 1 h. The reaction mixture was concentrated to dryness to afford the acid chloride which was suspended in anhydrous DCM (2 mL) and treated with a solution of (S)-4-chloro-2-(3,4-dimethylpiperazin-l-yl)-5-(2-morpholinopyrimidin-5-yl)aniline (0.045 g, 0.11 mmol) and triethylamine (0.05 mL, 0.3 mmol) in DCM (2 mL) at room temperature. After stirring for 18 h at room temperature the reaction mixture was quenched with a saturated aqueous NaHCCb solution (10 mL) and extracted with DCM. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (S)-6-chloro-N-(4-chloro-2-(3,4-dimethylpiperazin-l-yl)-5-(2-mo rpholinopyrirnidin-5-yl)phenyl)-4-(trifluoromethyl)nicotinamide. A mixture of the prepared amide and sodium acetate (0.018 g, 0.22 mmol) in HOAc/H_2**0** (4 mL/1 mL) was irradiated at 160 °C for 4 h. The reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford the title compound (S)-N-(4-chloro-2-(3,4-dimethylpiperazin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.019 g, 29 %). ^{1}H NMR

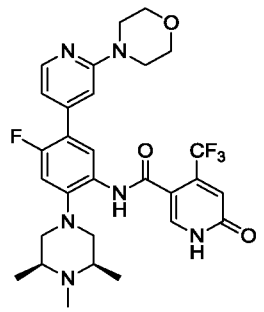
(500MHz, DMSO-d6) δ = 12.58 (br. s., 1H), 9.55 (s, 1H), 8.46 (s, 2H), 8.24 (br. s., 1H), 7.93 (br. s., 1H), 7.80 (s, 1H), 7.28 (s, 1H), 6.88 - 6.79 (m, 2H), 6.64 (s, 1H), 3.78 - 3.75 (m, 4H), 3.70 - 3.68 (m, 4H), 3.06 - 2.99 (m, 3H), 2.84 (d, *J*=11.0 Hz, 3H), 2.25 (br. s., 2H), 1.00 (d, *J*=6.0 Hz, 3H); LCMS [M+H]+: 592.4.

Example 82: N-[4-chloro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00343] The title compound was prepared similar to the sequence described above for the preparation of Example 81 using cis-l,2,6-trimethylpiperazine in place of (S)-l,2-dimethylpiperazine dihydrochloride in Step 1. ^{1}H N-MR (500MHz, DMSO-d6) δ = 12.60 (br. s., 1H), 9.56 (s, 1H), 8.46 (s, 2H), 7.91 (s, 1H), 7.79 (s, 1H), 7.25 (s, 1H), 6.82 (s, 1H), 3.79 - 3.74 (m, 5H), 3.73 - 3.66 (m, 5H), 3.01 (d, *J*=10.6 Hz, 3H), 2.42 - 2.35 (m, 2H), 2.22 (br. s., 3H), 1.02 (d, *J*=5.9 Hz, 6H); LCMS [M+H]+: 606.3.

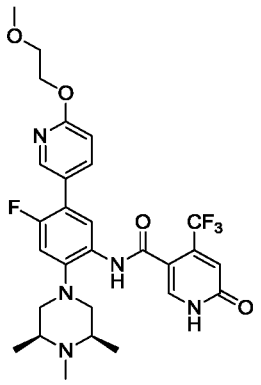
Example 83: N-[4-fluoro-5-(2-morpholin-4-ylpyridin-4-yl)-2-[(3R,5S)-3, 4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00344] The title compound (pale yellow solid, 23.6 mg, 39%) was prepared similar to the procedure of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-

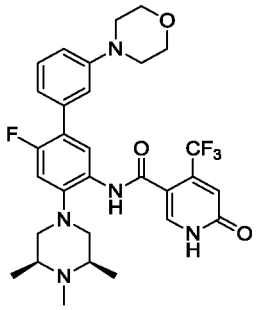
carboxamide (50.5 mg, 0.1 mmol) and 2-morpholinopyridine-4-boronic acid, pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.18 (d, *J*=5.3 Hz, IH), 7.98 (s, IH), 7.95 (d, *J*=7.8 Hz, IH), 7.08 (d, *J*=12.2 Hz, IH), 6.97 (s, IH), 6.95 - 6.90 (m, 2H), 3.86 - 3.80 (m, 4H), 3.58 - 3.49 (m, 4H), 3.11 (d, *J*=11.2 Hz, 2H), 2.64 (t, *J*=11.2 Hz, 2H), 2.60 - 2.53 (m, 2H), 2.39 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 589.4.

Example 84: N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridim-3-carboxamide



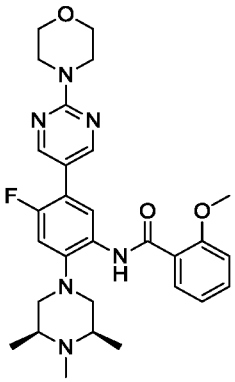
[00345] The title compound (pale yellow solid, 41.2 mg, 68%) was prepared similar to the procedure of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (56 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.31 (s, IH), 7.97 (s, IH), 7.92 (d, *J*=8.2 Hz, IH), 7.89 (d, *J*=8.7 Hz, IH), 7.09 (d, *J*=11.8 Hz, IH), 6.93 (s, IH), 6.92 (d, *J*=7.6 Hz, 2H), 4.51 - 4.44 (m, 2H), 3.79 (dd, *J*=4.1, 5.1 Hz, 2H), 3.44 (s, 3H), 3.08 (d, *J*=ll.l Hz, 2H), 2.67 - 2.54 (m, 4H), 2.40 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 578.4.

Example 85: N-[4-fluoro-5-(3-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridme-3-carboxamide



[00346] The title compound (46.0 mg, 77%) was prepared similar to the procedure of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-[3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl]mo rpholine (58 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.90 (d, *J*=7.9 Hz, IH), 7.34 (t, *J*=7.9 Hz, IH), 7.13 (s, IH), 7.07 - 7.02 (m, 2H), 7.00 (d, *J*=8.3 Hz, IH), 6.92 (s, IH), 3.86 (d, *J*=3.1 Hz, 4H), 3.25 - 3.17 (m, 4H), 3.07 (d, *J*=ll.l Hz, 2H), 2.67 - 2.51 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 588.4.

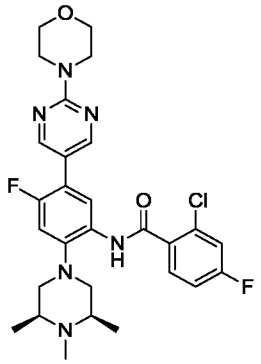
Example 86: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-methoxybenzamide



[00347] The title compound (beige solid, 48.1 mg, 86%) was prepared by a procedure similar to that of Example 34 using 4-fluoro-5-(2-mo φ holinopyrimi σm-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-methoxybenzoyl chloride (22 μL, 0.15 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 10.41 (s, IH), 8.66 (d, *J*=8.4 Hz, IH), 8.59 (s, 2H), 8.33 (d, *J*=7.8 Hz, IH), 7.55 (t, *J*=7.8 Hz, IH), 7.18 (t, *J*=7.5 Hz, IH), 7.09 (d, *J*=8.3 Hz, IH), 6.97 (d, *J*=11.6 Hz, IH), 4.12 (s, 3H), 3.92 - 3.85

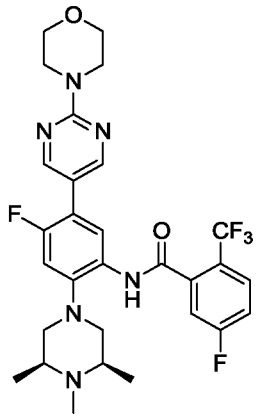
(m, 4H), 3.85 - 3.78 (m, 4H), 3.03 - 2.96 (m, 2H), 2.63 (t, *J*=11.0 Hz, 2H), 2.51 - 2.42 (m, 2H), 2.37 (s, 3H), 1.14 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 535.4.

Example 87: 2-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJbenzamide



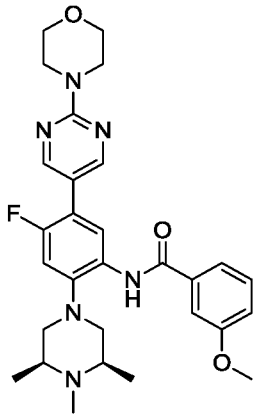
[00348] The title compound (off-white solid, 42.7 mg, 75%) was prepared by a procedure similar to that of Example 34 using 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-chloro-4-fluorobenzoylchloride (20 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.22 (s, IH), 8.69 (d, *J*=8.3 Hz, IH), 8.59 (s, 2H), 7.86 (dd, *J*=6.1, 8.7 Hz, IH), 7.26 (dd, *J*=2.4, 8.4 Hz, IH), 7.16 (t, *J*=8.2 Hz, IH), 7.04 (d, *J*=11.2 Hz, IH), 3.92 - 3.86 (m, 4H), 3.85 - 3.78 (m, 4H), 2.92 - 2.86 (m, 2H), 2.66 (t, *J*=10.9 Hz, 2H), 2.42 - 2.32 (m, 5H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 557.4.

Example 88: 5-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



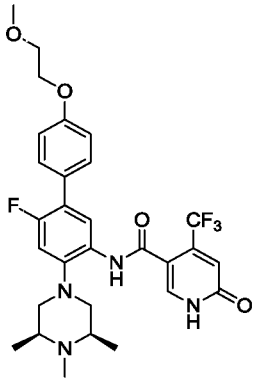
[00349] The title compound (beige solid, 53.4 mg, 87%) was prepared by a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 5-fluoro-2-(trifluoromethyl)benzoyl chloride (23 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.64 - 8.53 (m, 4H), 7.83 (dd, *J*=5.0, 8.7 Hz, 1H), 7.38 - 7.30 (m, 2H), 7.03 (d, *J*=11.2 Hz, 1H), 3.93 - 3.87 (m, 4H), 3.85 - 3.78 (m, 4H), 2.85 (d, *J*=10.9 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.32 - 2.21 (m, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 591.4.

Example 89: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3-methoxybenzamide



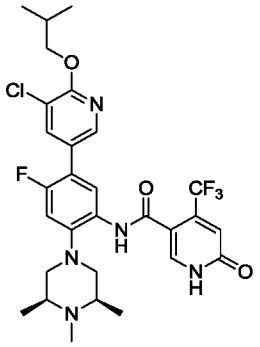
[00350] The title compound (yellow solid, 39.3 mg, 72%) was prepared by a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 3-methoxybenzoyl chloride (21 μL, 0.15 mmol). 'H NMR (500**MHZ**, CHLOROFORM-d) δ = 9.25 (s, 1H), 8.69 (d, *J*=8.3 Hz, 1H), 8.60 (s, 2H), 7.54 - 7.52 (m, 1H), 7.47 - 7.44 (m, 1H), 7.17 - 7.12 (m, 1H), 7.03 (d, *J*=11.2 Hz, 1H), 3.93 (s, 3H), 3.91 - 3.87 (m, 4H), 3.82 (d, *J*=1.0 Hz, 4H), 2.92 (d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=11.0 Hz, 2H), 2.52 - 2.42 (m, 2H), 2.39 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 535.4.

Example 90: N-[4-fluoro-5-[4-(2-methoxyethoxy)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridme-3-carboxamide



[00351] The title compound (grey solid, 37.6 mg, 63%) was prepared by a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-(2-methoxyethoxy)phenylboronic acid (39 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 7.49 (d, *J*=7.6 Hz, 2H), 7.07 - 7.01 (m, 3H), 6.92 (s, 1H), 4.18 (dd, *J*=3.8, 5.4 Hz, 2H), 3.82 - 3.76 (m, 2H), 3.46 (s, 3H), 3.07 (d, *J*=11.0 Hz, 2H), 2.68 - 2.53 (m, 4H), 2.39 (s, 3H), 1.18 (d, *J*=6.0 Hz, 6H); LCMS $[M + H]^+$ 577.4.

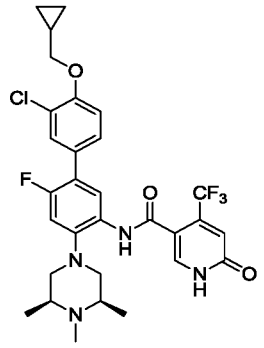
Example 91: N-[5-[5-chloro-6-(2-methylpropoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00352] The title compound (light brown solid, 48.1 mg, 77%) was prepared by a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3-chloro-2-isobutoxypyridine-5-boronic acid (46 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.24 (s, 1H), 7.97 (d,

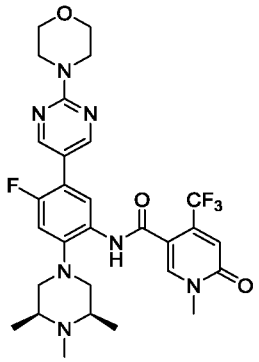
J=7.8 Hz, 2H), 7.92 (d, *J*=8.3 Hz, IH), 7.10 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 4.21 (d, *J*=6.6 Hz, 2H), 3.09 (d, *J*=11.2 Hz, 2H), 2.68 - 2.60 (m, 2H), 2.60 - 2.53 (m, 2H), 2.39 (s, 3H), 2.15 (td, *J*=6.7, 13.4 Hz, IH), 1.18 (d, *J*=6.1 Hz, 6H), 1.08 (d, *J*=6.7 Hz, 6H); LCMS [M + H]$^+$ 610.3.

Example 92: N-[5-[3-chloro-4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

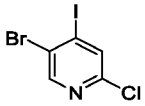


[00353] The title compound (light brown solid, 26.9 mg, 43%) was prepared by a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and (3-chloro-4-(cyclopropylmethoxy)phenyl)boronic acid (45.3 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.90 (d, *J*=8.3 Hz, IH), 7.58 (s, IH), 7.45 (d, *J*=8.7 Hz, IH), 7.13 (d, *J*=8.6 Hz, IH), 7.06 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 3.98 (d, *J*=6.8 Hz, 2H), 3.07 (d, *J*=ll.l Hz, 2H), 2.67 - 2.53 (m, 4H), 2.40 (s, 3H), 1.38 - 1.30 (m, IH), 1.18 (d, *J*=6.0 Hz, 6H), 0.70 - 0.64 (m, 2H), 0.46 - 0.41 (m, 2H); LCMS [M+ H]$^+$ 607.3.

Example 93: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

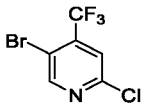


Step 1: 5-bromo-2-chloro-4-iodopyridine



[00354] A stirred solution of DIPA (4.02 niL, 28.8 mmol, l.leq) in dry THF (50 mL) was cooled to -78°C and n-BuLi (10.47 niL, 26.18 mmol, 1.0 eq, 2.5M in hexane) was added dropwise under an argon atmosphere. Then, the reaction mixture was stirred for 30 min. at the same temp., followed by the addition of a solution of 2-chloro-5-bromopyridine (5.0g, 26.178 mmol, 1.0 eq) in dry THF (50mL) and stirred for 1h at the same temp. Then, a solution of iodine (6.64g, 26.178 mmol, l.Oeq) in THF (50mL) was added dropwise at -78°C. After completion of addition the reaction mixture was allowed to warm to RT over 4h. The reaction progress was monitored by TLC. The reaction mixture was quenched with a saturated aqueous solution of sodium thiosulfate, and extracted with EtOAc (3 x lOOmL). The combined organic layer was dried over Na_2S0_4 and concentrated under reduced pressure to obtain the crude compound. The crude compound was recrystallized from ethanol (20 mL) to give the title compound (5 g, 60.3%) as an off white solid. LCMS: [M+H]+ 317.86.

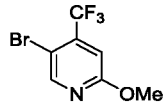
Step 2: 5-bromo-2-chloro-4-(trifluoromethyl)pyridine



[00355] To a stirred solution of 5-bromo-2-chloro-4-iodopyridine (20.0 g, 63.09 mmol, 1.0 eq) in DMF (200 mL), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (16.15 mL, 126.18 mmol, 2.0 eq) and Cul (24.02 g, 126.18 mmol, 2.0 eq) were added at RT under argon atmosphere and the reaction mixture was heated to 100°C for 6h.

TLC analysis indicated a non-polar spot. The reaction mixture was diluted with water (200 mL) and filtered off and washed with w-pentane (1L) and cold water (3L). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure at 30°C. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 5% EtOAc in pet ether as an eluent to afford the title compound (9.0 g, 55.2%) as a liquid compound. TLC: 5% EtOAc in pet ether; R_f: 0.7

Step 3: 5-bromo-2-methoxy-4-(trifluoromethyl)pyridine



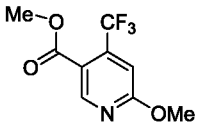
[00356] To a solution of 5-bromo-2-chloro-4-(trifluoromethyl)pyridine (24.0 g, 93.02 mmol, 1.0 eq) in methanol (200 mL), was added 30% NaOMe (33.08 mL, 186.04 mmol, 2.0 eq). Then, the reaction mixture was heated at 70°C for 6 h. TLC analysis indicated formation of a non-polar spot. The reaction mixture was diluted with water and extracted with EtOAc (3 X 200mL). The separated organic layer was dried over sodium sulfate and concentrated under reduced pressure at 30°C. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 5% EtOAc in pet ether as an eluent to give 5-bromo-2-methoxy-4-(trifluoromethyl)pyridine (15g, 63.47%) as an off white solid. TLC: 5% EtOAc in pet ether; R_f: 0.8.

Step 4: 6-methoxy-4-(trifluoromethyl)nicotinic acid

[00357] A solution of w-butyl magnesium chloride (20% in THF; 27.8 mL, 27.79 mmol, 1.2 eq) was added to a solution of w-butyl lithium (2.5M in hexane; 23.16 mL, 92.64 mmol, 4 eq) under argon atm. After 10 min, the reaction mixture was diluted with dry THF (80 mL) and cooled to -78°C. A solution of 5-bromo-2-methoxy-4-(trifluoromethyl)pyridine (6 g, 23.16 mmol, 1.0 eq) in dry THF (30 mL) was added to the above reaction mixture at -78°C and stirred for 1h at the same temperature. Then, crushed dry ice was added at -78°C. After addition, the reaction mixture was allowed to remain at RT for 16h. TLC analysis indicated formation of polar spot. The reaction mixture was concentrated under reduced pressure and acidified with 2N aq. HC1 (20 mL), then the obtained solid was filtered off and

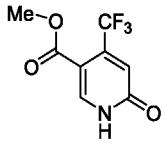
washed with w-pentane to give 6-methoxy-4-(trifluoromethyl)nicotinic acid (3.5g, 67.3%) as an off white solid compound. LCMS: [M+H]+ 221.99, M+H.

Step 5: methyl 6-methoxy-4-(trifluoromethyl)nicotinate



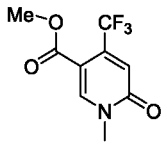
[00358] To a stirred solution of 6-methoxy-4-(trifluoromethyl)nicotinic acid (22 g, 99.5 mmol, 1.0 eq) in acetone (160 mL) was added K_2C0_3 (20.5 g, 149.25 mmol, 1.5 eq) followed by the dropwise addition of dimethylsulphate (16.3g,129.4 mmol, 1.3eq) at 0°C and the reaction mixture was allowed to remain at RT over 2h. TLC analysis indicated formation of a non-polar spot. The reaction mixture was concentrated under reduced pressure to crude residue, which was redissolved in EtOAc (500 mL) and washed with water and brine. The separated organic layer was dried over Na_2S0_4 and concentrated under reduced pressure to give crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-2% EtOAc in pet ether as an eluent to afford methyl 6-methoxy-4-(trifluoromethyl)nicotinate (19 g, 81.5%) as a white solid. [M+H]+ 236.37.

Step 6: methyl 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate



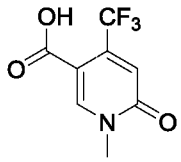
[00359] To a stirred solution of methyl 6-methoxy-4-(trifluoromethyl)nicotinate (3 g, 12.76 mmol, l.Oeq) in ACN (30 mL) was added TMS-Cl (4.54 g, 38.28 mmol, 3.0 eq) and Nal (5.7 g, 38.28 mmol, 3.0 eq) at RT under argon atm. Then, the reaction mixture was heated to reflux for 3h. TLC analysis indicated formation of polar spot. Then, the reaction mixture was diluted with water (500mL) and extracted with EtOAc (3x lOOmL). The combined organic layer was dried over Na_2S0_4 and concentrated under reduced pressure to give crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-5% EtOAc in pet ether as eluent to afford methyl 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate (1.2 g, 42.8%) as an off-white solid. LCMS: [M+H]+ 221.96.

Step 7: methyl l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate



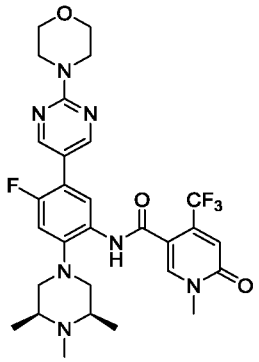
[00360] To a stirred solution of methyl 6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate (13.0 g, 58.82 mmol, 1.0 eq) in DMF (130 mL) was added methyl iodide (4.3 mL, 70.58 mmol, 1.2eq) and cesium carbonate (28.6 g, 88.2 mmol, 1.5eq) at RT under argon atmosphere. Then, the reaction mixture was stirred at RT for lh. TLC analysis indicated formation of a non-polar spot. The reaction mixture was diluted with cold water (1L) and extracted with EtOAc (3x 150mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-30% EtOAc in pet ether as eluent to give methyl l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate (10 g, 72.4% yield) as off-white solid. LCMS: 99.26% with [M+H]+ 235.98.

Step 8: l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid



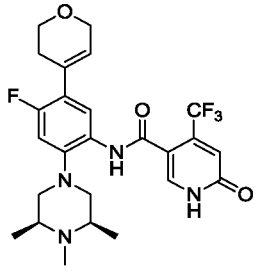
[00361] To a stirred solution of methyl l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylate (9.0 g, 38.29 mmol, l.Oeq) in THF: MeOH: H_20 (220 mL, 3: 1: 2) was added $LiOH.H_20$ (4.7 g, 114.8 mmol, 3.0eq) at RT and the reaction mixture was stirred at RT for 16h. TLC analysis indicated formation of polar spot. The reaction mixture was concentrated under reduced pressure to crude product. The crude product was acidified with aqueous 2N HCl (20mL), the resulting precipitate was filtered off and washed with diethyl to give l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (6.0 g, 71.42%) as an off white solid. LCMS: [M+H]+ 221.95.

Step 9: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-ylj'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



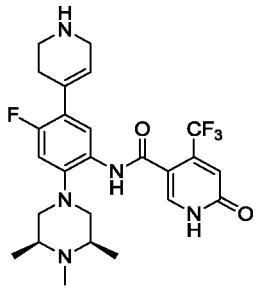
[00362] In a 5 ml microwave vial to a suspension of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (59.6 mg, 0.270 mmol) in pyridine, anhydrous (327 μï, 4.04 mmol) was added slowly diethyl chlorophosphate (59.4 μï, 0.41 1 mmol) at RT in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. The suspension turned brown. To this, 4-fluoro-5-(2-mo ϕ holinopyrimi αm-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)aniline (27 mg, 0.067 mmol) was added and the reaction was heated at 70 °C for 16 h. After completion, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous $Na_2SC>4$. The solvent was evaporated in vacuo yielding the crude product which was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the desired compound. ¾ NMR (500 MHz, MeOD) δ 8.55 (d, *J* = 1.1 Hz, 2H), 8.24 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 12.1 Hz, 1H), 6.94 (s, 1H), 3.85 - 3.82 (m, 4H), 3.78 - 3.75 (m, 4H), 3.64 (s, 3H), 3.04 (d, *J* = 11.3 Hz, 2H), 2.60 (t, *J* = 11.2 Hz, 2H), 2.50 (dd, *J* = 8.3, 5.9 Hz, 2H), 2.34 (s, 3H), 1.15 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 604.24.

Example 94: N-[5-(3, 6-dihydro-2H-pyran-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



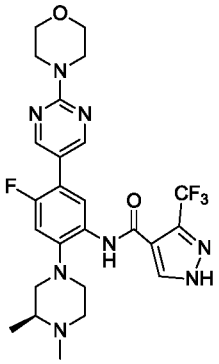
[00363] The procedure followed was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) and 3,6-dihydro-2H-pyran-4-boronic acid, pinacol ester (24.28 mg, 0.116 mmol) followed by deprotection of the intermediate to afford after purification 16 mg (63% for final step) of the title compound as a beige solid. ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 (s, 1H), 7.78 (d, *J*=8.1 Hz, 1H), 6.96 (d, *J*=12.6 Hz, 1H), 6.94 - 6.89 (m, 1H), 6.08 (br. s., 1H), 4.39 - 4.20 (m, 2H), 3.99 - 3.82 (m, 2H), 3.03 (d, *J*=10.6 Hz, 2H), 2.65 - 2.47 (m, 6H), 2.39 (s, 3H), 1.17 (d, *J*=5.9 Hz, 6H); LCMS [M+H]+ 509.7

Example 95: N-[4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yl]-5-(l ,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



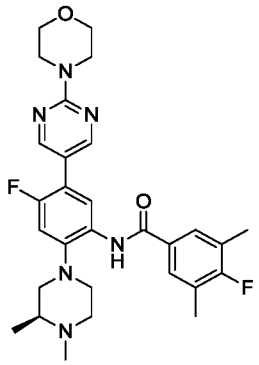
[00364] The product was obtained after TFA deprotection of the intermediate resulting from a reaction between N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(mfluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and tert-butyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-l,2,3,6-tetrahydropyridine-l-carboxylate (35.7 mg, 0.116 mmol) using a method similar to that in Example 39 to give, after deprotection, the title compound in 94% yield for the final step. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.06 (s, 1H), 7.82 (d, *J*=8.1 Hz, 1H), 6.96 (d, *J*=12.5 Hz, 1H), 6.80 (s, 1H), 6.05 (br. s., 1H), 3.66 (d, *J*=2.7 Hz, 2H), 3.24 (t, *J*=5.8 Hz, 2H), 3.02 (d, *J*=ll.l Hz, 2H), 2.65 - 2.47 (m, 6H), 2.36 (s, 3H), 1.16 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 508.6

Example 96: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-3-(trifluoromethyl)-lH-pyrazole-4-carboxamide



[00365] The title compound (white solid, 18.1 mg, 62%) was prepared according to a procedure similar to that used in Example 34 with **3**-(trifluoromethyl)pyrazole-4-carboxylic acid (27 mg, 0.15 mmol) and (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (20 mg, 0.05 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.39 (br. s., 1H), 7.98 (d, *J*=8.2 Hz, 1H), 7.11 (d, *J*=12.0 Hz, 1H), 3.89 - 3.83 (m, 4H), 3.80 - 3.75 (m, 4H), 3.04 (d, *J*=11.4 Hz, 2H), 2.63 (t, *J*=11.2 Hz, 2H), 2.55 - 2.46 (m, 2H), 2.37 (s, 3H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 563.4.

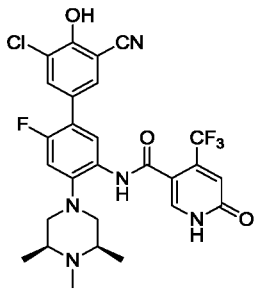
Example 97: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide



[00366] The title compound (pale beige solid, 26.1 mg, 47%) was prepared according to a procedure similar to Example 78 using 4-fluoro-3,5-dimethylbenzoic acid (50 mg, 0.3 mmol) and (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.19 (s, 1H), 8.65 (d, *J*=8.3 Hz, 1H), 8.60 (s, 2H), 7.62 (d, *J*=6.7 Hz, 2H), 7.02 (d, *J*=11.2 Hz, 1H), 3.93 - 3.86 (m, 4H), 3.85 - 3.79 (m, 4H), 2.94

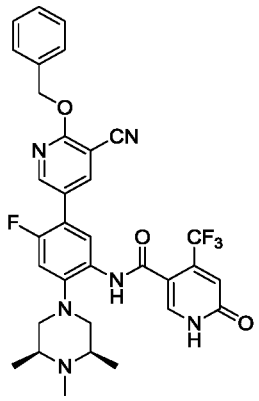
(d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=10.9 Hz, 2H), 2.51 - 2.41 (m, 2H), 2.41 - 2.35 (m, 9H), 1.19 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 551.3.

Example 98: N-[5-(3-chloro-5-cyano-4-hydroxyphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00367] The procedure used was similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) and 3-chloro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2-(2-(trimethylsilyl)ethoxy)benzonitrile (43.9 mg, 0.116 mmol) followed by deprotection of the resulting intermediate using TFA to give the title compound as a tan solid. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.55 (br. s., 1H), 9.45 (s, 1H), 8.16 (s, 1H), 7.94 (s, 1H), 7.67 (d, *J*=8.8 Hz, 1H), 7.39 (br. s., 1H), 7.22 (br. s.,lH), 6.95 (d, *J*=12.8 Hz, 1H), 6.81 (s, 1H), 3.02 (d, *J*=8.7 Hz, 2H), 2.50 - 2.44 (m, 4H), 2.27 (br. s., 3H), 1.04 (d, *J*=5.0 Hz, 6H); LCMS [M+H]+ 578.6

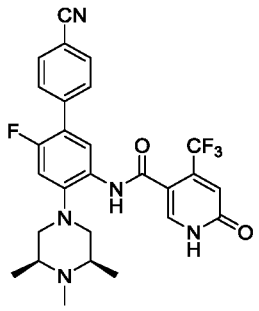
Example 99: N-[5-(5-cyano-6-phenylmethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00368] The procedure used was similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-

6-(2-(trimethylsilyl)ethoxy)nicotinamide (300 mg, 0.495 mmol) and 2-(benzyloxy)-5-(trimethylstannyl)nicotinonitrile (222 mg, 0.595 mmol) to give, after deprotection with TFA, 66 mg (20% yield) of the title compound. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.61 (s, 1H), 8.32 (d, *J*=1.5 Hz, 1H), 8.05 (br. s., 1H), 7.98 (d, *J*=8.1 Hz, 1H), 7.53 (d, *J*=7.3 Hz, 2H),7.41 (t, *J*=7.4 Hz, 2H), 7.38 - 7.32 (m, 1H), 7.24 (d, *J*=11.2 Hz, 1H), 6.95 (s, 1H), 5.69 - 5.56 (m, 2H), 3.69 - 3.49 (m, 2H), 3.48 - 3.36 (m, 2H), 3.11- 2.92 (m, 5H), 1.46 (br. s., 6H); LCMS [M+H]+ 635.7.

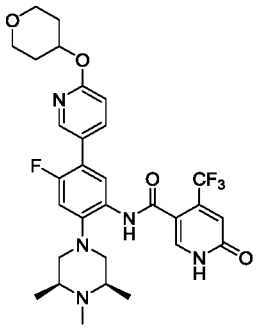
Example 100: N-[5-(4<yanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00369] In a 5 mL microwave vial N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (52.13 mg, 0.086 mmol), 4-cyanophenylboronic acid (18.97 mg, 0.129 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (II) (6.10 mg, 8.61 μηιοΐ) and potassium phosphate tribasic reagent grade (36.5 mg, 0.172 mmol) were dissolved in water (172 μΐ) / 1,4-dioxane (1550 μΐ) (9 : 1 mixture) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 120 °C. The solvent was evaporated and 15 mL of CH2CI2 were added. The suspension was sonicated and extracted from water (15 mL). The solvent was evaporated in vacuo yielding the crude product which was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the protected intermediate. The product was dissolved in 2 mL of DCM and trifluoroacetic acid (132 μΐ, 1.722 mmol) was added. The purple solution was stirred for 1 h and the solvent was evaporated. The residue was purified using a cation exchange column eluting with MeOH:NH_4OH. The residue was freeze dried for 2 days to afford the title compound. ^{1}H

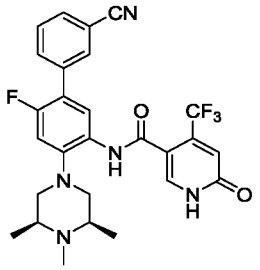
NMR (500 MHz, MeOD) δ 7.96 (d, *J* = 6.7 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 12.3 Hz, 1H), 6.91 (s, 1H), 3.10 (d, *J* = 11.3 Hz, 2H), 2.63 (t, *J* = 11.2 Hz, 2H), 2.55 (dt, *J* = 6.0, 5.1 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.78 (s), -120.23 (s); LCMS [M+l]+ = 528.17.

Example 101: N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R, 5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00370] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-(tetrahydropyran-4-yloxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine as the borolane starting material. ^{1}H NMR (500 MHz, MeOD) δ 8.29 (s, 1H), 7.96 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 9.6 Hz, 1H), 7.07 (d, *J* = 12.0 Hz, 1H), 6.90 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.25 (tt, *J* = 8.4, 4.0 Hz, 1H), 4.01 - 3.94 (m, 2H), 3.63 (ddd, *J* = 11.8, 9.1, 2.9 Hz, 2H), 3.06 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.54 (s, 2H), 2.13 - 2.06 (m, 2H), 1.83 - 1.73 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 604.39.

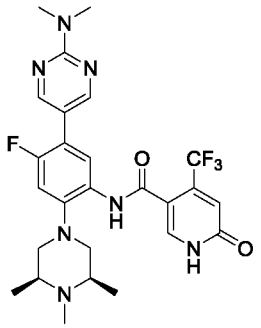
Example 102: N-[5-(3<yanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00371] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 3-cyanophenylboronic acid. ^{1}H NMR

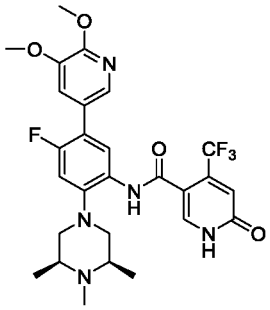
(500 MHz, MeOD) δ 7.96 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 12.2 Hz, 1H), 6.91 (s, 1H), 3.09 (d, *J* = 11.3 Hz, 2H), 2.63 (t, *J* = 11.1 Hz, 2H), 2.55 (s, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 528.32.

Example 103: N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00372] The title compound was prepared according a method similar to that used for the preparation of Example 100 using N,N-dimethyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidin-2-amine. ^{1}H NMR (500 MHz, MeOD) δ 8.51 (d, *J* = 1.1 Hz, 2H), 7.97 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 12.1 Hz, 1H), 6.90 (s, 1H), 3.22 (s, 6H), 3.05 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 11.2 Hz, 2H), 2.53 (d, *J* = 6.0 Hz, 2H), 2.36 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 548.34.

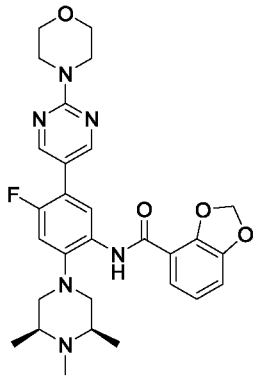
Example 104: N-[5-(5, 6-dimethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00373] The title compound was prepared according a method similar to that used for the preparation of Example 100 with (5,6-dimethoxypyridin-3-yl)boronic acid in place of 4-cyanophenylboronic acid. ^{1}H NMR (500 MHz, MeOD) δ 7.97 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.85 (s, 1H), 7.40 (s, 1H), 7.07 (d, *J* = 12.1 Hz, 1H),

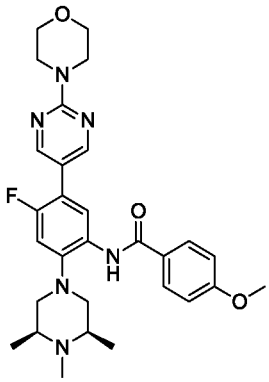
6.91 (s, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 3.06 ***(d, J*** = 11.3 Hz, 2H), 2.62 (**t, *J*** = 11.1 Hz, 2H), 2.54 (s, 2H), 2.37 (s, 3H), 1.16 (d, ***J*** = 6.2 Hz, 6H). ^{19}F NMR (471 MHz, MeOD) δ -63.76 (s), -120.32 (s); LCMS HSS [M+l]+ = 564.29.

Example 105: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-benzodioxole-4-carboxamide



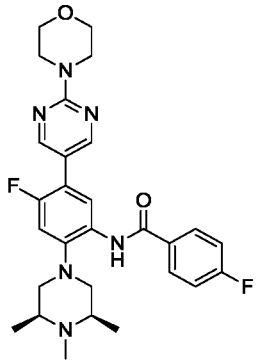
[00374] The title compound (light beige solid, 39.9 mg, 71%) was prepared according to a method similar to that used for Example 34 using l,3-benzodioxole-4-carboxylic acid (33 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.86 (s, 1H), 8.77 (d, ***J***=8.4 Hz, 1H), 8.60 (s, 2H), 7.70 (dd, ***J***=2.4, 7.0 Hz, 1H), 7.08 - 7.00 (m, 3H), 6.22 (s, 2H), 3.92 - 3.85 (m, 4H), 3.84 - 3.79 (m, 4H), 2.96 - 2.89 (m, 2H), 2.66 (t, ***J***=10.9 Hz, 2H), 2.45 - 2.37 (m, 5H), 1.17 (**d, *J***=6.2 Hz, 6H); LCMS $[M + H]^+$ 549.2.

Example 106: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-methoxybenzamide



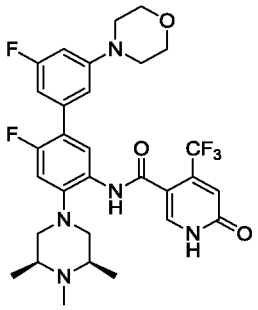
[00375] The title compound (beige solid, 52.4 mg, 96%) was prepared through a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 4-methoxybenzoyl chloride (20 μL, 0.15 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.15 (s, IH), 8.67 (d, *J*=8.3 Hz, IH), 8.60 (d, *J=1.2* Hz, 2H), 7.92 (d, *J*=8.2 Hz, IH), 7.90 (s, IH), 7.04 (d, *J*=8.8 Hz, 2H), 7.02 (d, *J*=11.4Hz, IH), 3.93 (s, 3H), 3.91 - 3.87 (m, 4H), 3.84 - 3.80 (m, 4H), 2.93 (d, *J*=11.0 Hz, 2H), 2.69 (t, *J*=11.0 Hz, 2H), 2.46 (dt, *J*=3.1, 6.6 Hz, 2H), 2.39 (s, 3H), 1.18 (d, *J*=6.2Hz, 6H); LCMS $[M + H]^+$ 535.3.

Example 107: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] benzamide



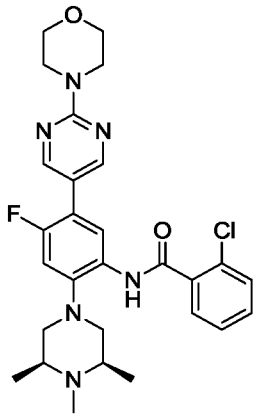
[00376] The title compound (light beige solid, 49.0 mg, 93%) was prepared using a procedure similar to Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 4-fluorobenzoyl chloride (18 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.19 (s, IH), 8.65 (d, *J*=8.2 Hz, IH), 8.59 (s, 2H), 7.95 (t, *J*=6.6 Hz, 2H), 7.27 - 7.22 (m, 2H), 7.03 (d, *J*=11.2 Hz, IH), 3.93 - 3.85 (m, 4H), 3.85 - 3.78 (m, 4H), 2.92 (d, *J*=11.0 Hz, 2H), 2.70 (t, *J*=11.0 Hz, 2H), 2.49 - 2.37 (m, 5H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 523.4.

Example 108: N-[4-fluoro-5-(3-fluoro-5-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[00377] The title compound (brown solid, 28.3 mg, 45%) was prepared through a procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3-fluoro-5-morpholinophenylboronic acid (45 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.90 (d, *J*=8.3 Hz, IH), 7.58 (s, IH), 7.45 (d, *J*=8.7 Hz, IH), 7.13 (d, *J*=8.6 Hz, IH), 7.06 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 3.98 (d, *J*=6.8 Hz, 2H), 3.07 (d, *J*=ll.l Hz, 2H), 2.67 - 2.53 (m, 4H), 2.40 (s, 3H), 1.38 - 1.30 (m, IH), 1.18 (d, *J*=6.0 Hz, 6H), 0.70 - 0.64 (m, 2H), 0.46 - 0.41 (m, 2H); LCMS $[M + H]^+$ 607.3.

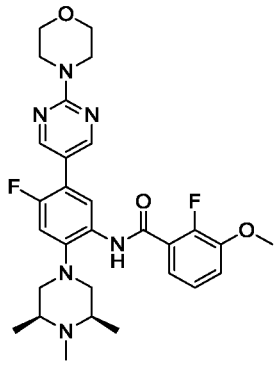
Example 109: 2-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] benzamide



[00378] The title compound (beige solid, 38.2 mg, 70%) was prepared through a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-chlorobenzoyl chloride (19 μL, 0.15 mmol). 'HNMR (500MHZ, CHLOROFORM-d) δ = 9.15 (s, IH), 8.71 (d, *J*=8.3 Hz, IH), 8.61 (s, 2H), 7.81 (dd, *J*=1.8, 7.5 Hz, IH),

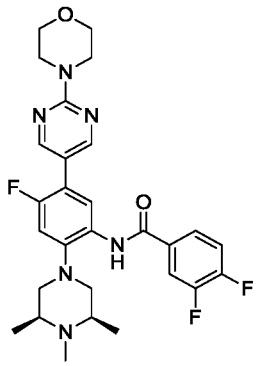
7.54 - 7.41 (m, 3H), 7.04 (d, *J*=11.4 Hz, IH), 3.93 - 3.86 (m, 4H), 3.84 - 3.78 (m, 4H), 2.94 - 2.88 (m, 2H), 2.66 (t, *J*=10.9 Hz, 2H), 2.43 - 2.30 (m, 5H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 539.4.

Example 110: 2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenyl] '-3-methoxybenzamide



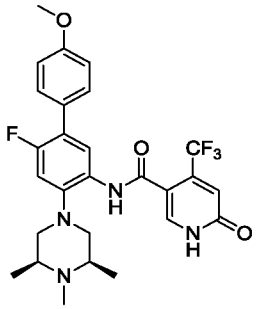
[00379] The title compound (light beige solid, 46.7 mg, 84%) was prepared through a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-fluoro-3-methoxybenzoyl chloride (28 mg, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.73 (d, *J*=12.7 Hz, IH), 8.74 (d, *J*=8.3 Hz, IH), 8.60 (s, 2H), 7.73 (t, *J*=7.2 Hz, IH), 7.26 (t, *J*=8.4 Hz, IH), 7.18 (t, *J*=8.0 Hz, IH), 7.04 (d, *J*=11.4 Hz, IH), 3.98 (s, 3H), 3.92 - 3.86 (m, 4H), 3.85 - 3.78 (m, 4H), 2.92 (d, *J*=10.9 Hz, 2H), 2.67 (t, *J*=10.8 Hz, 2H), 2.54 (br. s., 2H), 2.40 (s, 3H), 1.17 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 553.5.

Example 111: 3,4-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] benzamide



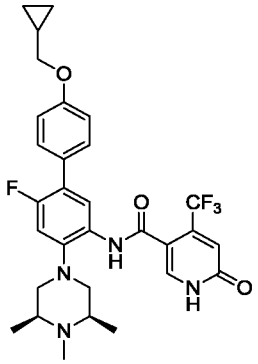
[00380] The title compound (beige solid, 37.5 mg, 67%) was prepared through a procedure similar to that of Example 34 using 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 3,4-difluorobenzoyl chloride (19 μL, 0.15 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.73 (d, *J*=12.7 Hz, IH), 8.74 (d, *J*=8.3 Hz, IH), 8.60 (s, 2H), 7.73 (t, *J*=7.2 Hz, IH), 7.26 (t, *J*=8.4 Hz, IH), 7.18 (t, *J*=8.0 Hz, IH), 7.04 (d, *J*=11.4 Hz, IH), 3.98 (s, 3H), 3.92 - 3.86 (m, 4H), 3.85 - 3.78 (m, 4H), 2.92 (d, *J*=10.9 Hz, 2H), 2.67 (t, *J*=10.8 Hz, 2H), 2.54 (br. s., 2H), 2.40 (s, 3H), 1.17 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 541.3.

Example 112: N-[4-fluoro-5-(4-methoxyphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



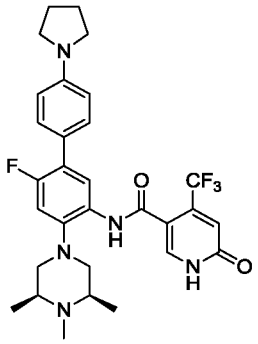
[00381] The title compound (grey solid, 42.7 mg, 79%) was prepared according to a procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-methoxyphenylboronic acid (30 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.96 (s, IH), 7.91 (d, *J*=8.3 Hz, IH), 7.49 (d, *J*=7.5 Hz, 2H), 7.04 (d, *J*=12.2 Hz, IH), 7.01 (d, *J*=8.8 Hz, 2H), 6.93 (s, IH), 3.85 (s, 3H), 3.07 (d, *J*=11.0 Hz, 2H), 2.68 - 2.54 (m, 4H), 2.40 (s, 3H), 1.19 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 533.4.

Example 113: N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00382] The title compound (grey solid, 47.5 mg, 81%) was prepared according to a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-(cyclopropylmethoxy)phenylboronic acid (38 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.96 (s, IH), 7.91 (d, *J*=8.2 Hz, IH), 7.47 (d, *J*=7.6 Hz, 2H), 7.04 (d, *J*=12.1 Hz, IH), 7.00 (d, *J*=8.8 Hz, 2H), 6.93 (s, IH), 3.88 (d, *J*=6.8 Hz, 2H), 3.07 (d, *J*=10.6 Hz, 2H), 2.68 - 2.55 (m, 4H), 2.40 (s, 3H), 1.33 - 1.25 (m, IH), 1.18 (d, *J*=6.0 Hz, 6H), 0.68 - 0.61 (m, 2H), 0.42 - 0.35 (m, 2H); LCMS $[M + H]^+$ 573.3.

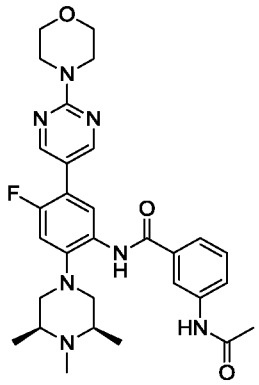
Example 114: N-[4-fluoro-5-(4-pyrrolidin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00383] The title compound (brown solid, 43.2 mg, 74%) was prepared according to a procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and l-[4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine (55 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.95 (s, IH), 7.90 (d, *J*=8.3 Hz, IH), 7.41 (d, *J*=7.7 Hz, 2H),

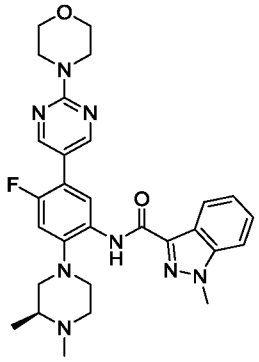
7.00 (d, *J*=12.2 Hz, IH), 6.92 (s, IH), 6.65 (d, *J*=8.7 Hz, 2H), 3.04 (d, *J*=11.0 Hz, 2H), 2.66 - 2.52 (m, 4H), 2.40 (s, 3H), 2.09 - 2.01 (m, 4H), 1.18 (d, *J*=6.0 Hz, 6H); LCMS $[M + H]^+$ 572.4.

Example 115: 3-acetamido-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJbenzamide



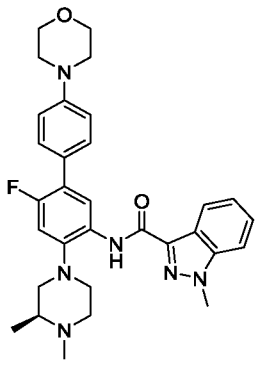
[00384] The title compound (off-white solid, 41.9 mg, 70%) was prepared according to a procedure similar to that of Example 34 using 3-acetylaminobenzoic acid (36 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, IH), 8.57 (d, *J*=8.2 Hz, IH), 8.50 (s, 2H), 8.05 (br. s., IH), 7.71 (d, *J*=8.2 Hz, IH), 7.56 (d, *J*=7.7 Hz, IH), 7.42 (t, *J*=7.9 Hz, IH), 7.23 (br. s., IH), 6.94 (d, *J*=ll.l Hz, IH), 3.83 - 3.77 (m, 4H), 3.75 - 3.69 (m, 4H), 2.83 (d, *J*=11.0 Hz, 2H), 2.59 (t, *J*=10.8 Hz, 2H), 2.46 (br. s., 2H), 2.30 (s, 3H), 2.16 (s, 3H), 1.07 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 562.4.

Example 116: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methylindazole-3-carboxamide



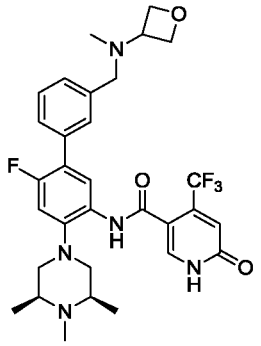
[00385] The title compound was prepared similar to the sequence described above for the preparation of Example 78 using l-methyl-lH-indazole-3-carbonylchloride in place of benzoyl chloride in Step 4. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.94 (s, IH), 8.59 (s, 2H), 8.54 (d, *J*=8.6 Hz, IH), 8.24 (d, *J*=8.2 Hz, IH), 7.82 (d, *J*=8.6 Hz, IH), 7.54 (t, *J*=7.6 Hz, IH), 7.37 (t, *J*=7.5 Hz, IH), 7.29 (d, *J*=11.7 Hz, IH), 4.22 (s, 3H), 3.80 - 3.77 (m, 4H), 3.72 - 3.69 (m, 4H), 3.02 - 2.89 (m, 4H), 2.66 - 2.57 (m, 2H), 2.32 (s, 3H), 1.06 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 545.3.

Example 117: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methylindazole-3-carboxamide

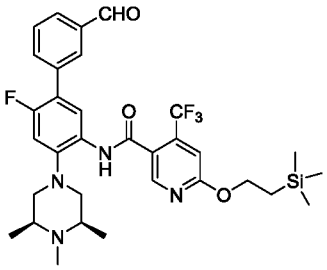


[00386] The title compound was prepared similar to the sequence described above for the preparation of Example 116 using 4-(morpholino)phenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 2. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.94 (s, IH), 8.56 (d, *J*=8.6 Hz, IH), 8.25 (d, *J*=8.2 Hz, IH), 7.82 (d, *J*=8.7 Hz, IH), 7.54 (t, *J*=7.7 Hz, IH), 7.45 (br d, *J*=7.7 Hz, 2H), 7.37 (t, *J*=7.5 Hz, IH), 7.22 (d, *J*=12.1 Hz, IH), 7.08 (d, *J*=8.8 Hz, 2H), 4.21 (s, 3H), 3.80 - 3.75 (m, 4H), 3.21 - 3.17 (m, 4H), 3.00 - 2.89 (m, 5H), 2.67 - 2.58 (m, 4H), 2.32 (s, 3H), 1.07 (d, *J*=6.1 Hz, 3H); LCMS [M+H]+: 543.4.

Example 118: N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

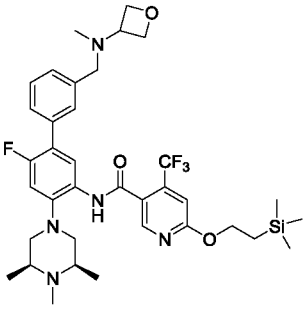


Step 1: N-(6-fluoro-3 '-formyl-4-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)-[1,1'-biphenylJ-3-yl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00387] A procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (130 mg, 0.215 mmol) and **3-**formylphenylboronic acid (45.1 mg, 0.301 mmol) afforded the title compound (84 mg, 62% yield). LCMS [M + H]+: 631.8.

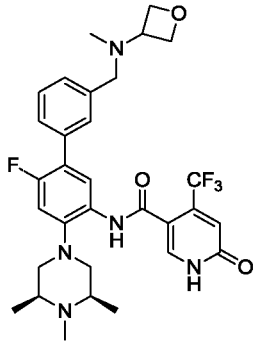
Step 2: N-(6-fluoro-3'-(0nethyl(oxetan-3-yl)amino)methyl)-4-((3S,5R)-3,4,5-Mmethylpiperazin-l-yl)-[lJ'-biphenyl]-3-yl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00388] N-(6-fluoro-3'-formyl-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,1'-biphenyl]-3-yl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg,

0.063 mmol), N-methyl-3-oxetanamine (11.05 mg, 0.127 mmol) and acetic acid, glacial, 99.8% (15.23 mg, 0.254 mmol) were mixed in anhydrous DCE. A cloudy solution was obtained. After 5-10 min, sodium triacetoxyborohydride (40.3 mg, 0.190 mmol) was added and the reaction mixture was stirred at RT. There was no difference observed between 7.5h and overnight at RT. A small amount of the starting material (approx. 5%) of the starting material was observed along with the desired product. The reaction mixture was quenched with sat aq NaHCCb solution (basic). The organic phase was separated, the aqueous phase was extracted with DCM (x2), then the combined organic phase was washed with brine, dried over Na_2S0_4 and concentrated to obtain the crude product. It was purified on reverse phase isco column (5.5G), eluting with water containing 0-60 % acetonitrile. The appropriate fractions were combined and concentrated to afford the desired product as a white foam (31 mg, 70% yield). LCMS [M+H]+ = 700.6.

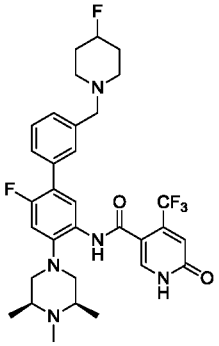
Step 3: N-(6-fluoro-3'-((methyl(oxetan-3-yl)amino)methyl)-4-((3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamide, trifluoroacetic acid salt.



[00389] The product of the foregoing procedure was dissolved in DCM (2 mL) and TFA (0.5 ml) was added. The reaction mixture was stirred at RT. LCMS showed completion of the reaction after 8 min.. The reaction mixture was concentrated to dryness, and the residue was triturated with ether to collect the title compound as a white powder. (32 mg, 82% yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.94 (t, *J*=3.9 Hz, 2H), 7.65 (s, 1H), 7.65 (d, *J*=8.1 Hz, 2H), 7.55 (t, *J*=7.6 Hz, 1H), 7.48 (d, *J*=7.6 Hz, 1H), 7.14 (d, *J*=11.7 Hz, 1H), 6.87 (s, 1H), 4.74 - 4.66 (m, 2H), 4.65 - 4.53 (m, 2H), 4.52 - 4.46 (m,

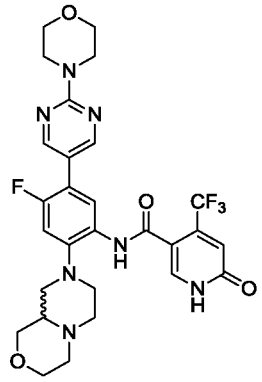
1H), 4.31 (s, 2H), 3.52 - 3.44 (m, 2H), 3.29 (br s, 2H), 2.83 - 2.83 (m, 1H), 2.99 - 2.80 (m, 4H), 2.74 (s, 3H), 1.38 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+ 602.

Example 119: N-[4-fluoro-5-[3-[(4-fluoropiperidin-l-yl)methyl]phenyl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide

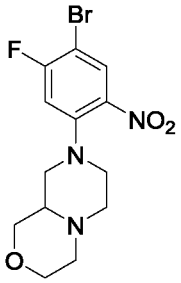


[00390] A sequence similar to that of Example 118 was used with 4-fiuoropiperidine as the amine in the reductive amination step to provide 26 mg (70% yield) of the title compound as the TFA salt. ^{1}H NMR (500MHz, METHANOL-d^ δ = 7.97 - 7.91 (m, 2H), 7.69 - 7.63 (m, 2H), 7.55 (t, *J*=7.6 Hz, 1H), 7.51 - 7.46 (m, 1H), 7.13 (d, *J*=11.7 Hz, 1H), 6.87 (s, 1H), 4.37 (s, 2H), 3.58 - 3.26 (m, 9H), 3.00 - 2.81 (m, 5H), 2.38 - 2.12 (m, 2H), 2.06 - 1.85 (m, 2H), 1.44 - 1.32 (m, 6H). LCMS [M+H]+ 618.7.

Example 120: N-[2-(3,4,6, 7,9,9a-hexahydro-lH-pyrazino[2,l-c][l,4]oxazin-8-yl)-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

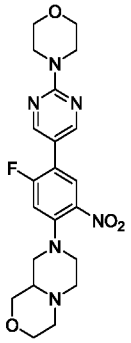


Step 1: 8-(4-bromo-5-fluoro-2-nitrophenyl)octahydropyrazino[2, l-c][l, 4]oxazine



[00391] A suspension of octahydropyrazino[2,1-c][1,4]oxazine (612 mg, 4.30 mmol) and Potassium carbonate (ACS) (297 mg, 2.152 mmol) in toluene (10 ml) was stirred for 5 minutes at room temperature. Then a solution of l-bromo-2,4-difluoro-5-nitrobenzene (1024 mg, 4.30 mmol) in toluene (1ml) was added dropwise from a pipette (2 ml of toluene were used to rinse the vial) and the reaction was stirred at 50 °C for 3h30min. Then the reaction mixture was partitioned into water and DCM and the product was extracted by DCM (3x20mL). The organic phase was dried over $MgSO_4$ and after filtration and solvents removal, the crude material was dry loaded and purified by Flash chromatography [0-10% MeOH/DCM] to afford the desired 8-(4-bromo-5-fluoro-2-nitrophenyl)octahydropyrazino[2,l-c][l,4]oxazine (1.3361 g, 3.67 mmol, 85 % yield) as an orange powder. LCMS $[M+H]^+$: 360.2.

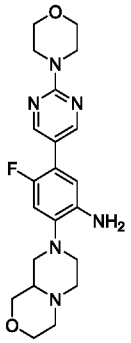
Step 2: 8-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)octahydropyrazino[2,l-c][l, 4]oxazine



[00392] A 30mL vial was charged with a mixture of 8-(4-bromo-5-fluoro-2-nitrophenyl)octahydropyrazino[2,l-c][l,4]oxazine (112 mg, 0.311 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (127 mg, 0.435 mmol), XPhos Pd G2 (4.89 mg, 6.22 μηοΐ) and XPhos (2.96 mg, 6.22 μηοΐ). Then sodium carbonate solution (2molar) (0.777 ml, 1.555 mmol) was added via syringe and the vial was flushed with argon. The reaction was stirred at 90 °C for 2 hours then the reaction

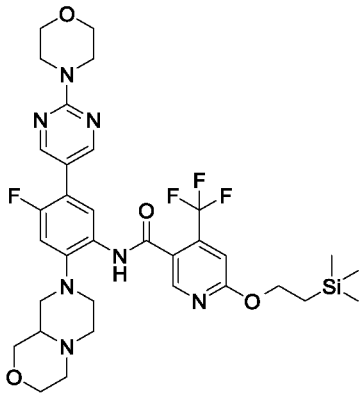
mixture was partitionned into water and DCM and the product was extracted by DCM (3x20mL). The organic phase was dried over MgSC>4 and after filtration and solvents removal, the crude material was dry loaded and purified by flash chromatography [0-10% MeOH/DCM] to afford the desired 8-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)octahydropyrazino[2,l-c][l,4]oxazine (143.6 mg, 0.291 mmol, 94 % yield) as a brown oil. LCMS [M+H]+ 444.9.

Step 3: 4-fluoro-2-(hexahydropyrazino[2, 1-c][l,4]oxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)aniline



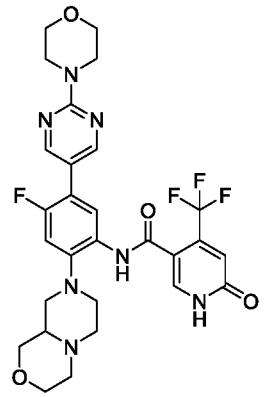
[00393] To a solution of 8-(5-fluoro-4-(2-mo rpholinopyrimidin-5-yl)-2-nitrophenyl)octahydropyrazino[2,l-c][l,4]oxazine (143.6 mg, 0.323 mmol) in a mixture of MeOH (5 ml) and water (1 ml) was added zinc dust (106 mg, 1.615 mmol) followed by 4 drops of hydrochloric acid (ACS) (11.78 mg, 0.323 mmol). The reaction mixture was stirred at 90 °C for 40 minutes then the crude mixture was filtered through a pad of celite using methanol to elute the product. Then the filtrate was concentrated under vacuum and the crude mixture was dry loaded and purified by Flash chromatography [0-10% MeOH/DCM] to afford the desired 4-fluoro-2-(hexahydropyrazino[2,l-c][l,4]oxazin-8(lH)-yl)-5-(2-mo rpholinopyrimidin-5-yl)aniline (53.2 mg, 0.128 mmol, 39.7 % yield) as ayellow oil. LCMS [M+H]+ 415.1.

Step 4: N-(4-fluoro-2-(hexahydropyrazino[2,l-c][l, 4]oxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00394] To a solution of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (51.3 mg, 0.167 mmol) in N,N-dimethylformamide (DMF) (5mL) were added HATU (98 mg, 0.257 mmol) and N,N-diisopropylethylamine (0.133 ml, 0.770 mmol). The reaction mixture was stirred for 5 minutes before adding a solution of 4-fluoro-2-(hexahydropyrazino[2,l-c][l,4]oxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)aniline (53.2 mg, 0.128 mmol) in ImL of DMF (use of 2xlmL of DMF to rinse). Then the reaction mixture was stirred at room temperature overnight. The crude material was dry loaded and purified by flash chromatography [4-100% water/ACN] to afford the desired N-(4-fiuoro-2-(hexahydropyrazino [2, 1-c] [1,4] oxazin-8(lH)-yl)-5 -(2-morpholinopyrimidin-5 -yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (12.7 mg, 0.018 mmol, 13.92 % yield) as a tan solid. LCMS [M+H]+ 704.3.

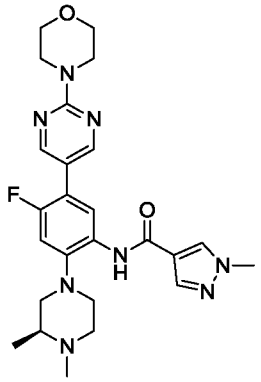
Step 5: N-(4-fluoro-2-(hexahydropyrazino[2,l-cJ[l,4Joxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (TFA salt)



[00395] To a solution of N-(4-fluoro-2-(hexahydropyrazino[2,l-c][l,4]oxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-4-(trifluoromethyl)-6-(2-

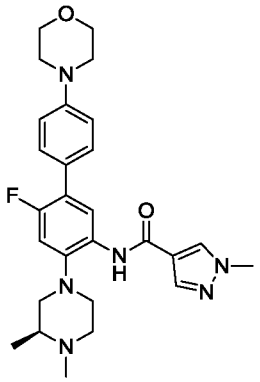
(trimethylsilyl)ethoxy Nicotinamide (12.7 mg, 0.018 mmol) in DCM (3 ml) was added trifluoroacetic acid (2 ml, 26. 1 mmol). The reaction mixture was stirred at 60 °C for 3 hours then the TFA and solvent were removed under vacuum to give the desired N-(4-fluoro-2-(hexahydropyrazino[2,l-c][l,4]oxazin-8(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide TFA salt (15.3 mg, 0.014 mmol, 76 % yield) as a light brown powder. ^{1}H NMR (500 MHz, DMSO-d6) δ = 9.62 (s, 1 H), 8.54 (s, 2 H), 8.02 (s, 1 H), 7.92 (d, *J*=8.31 Hz, 1 H), 7.24 (d, *J*=11.74 Hz, 1 H), 6.85 (s, 1 H), 4.05 (br d, *J*=10.88 Hz, 1 H), 3.96 (br d, *J*=11.13 Hz, 1 H), 3.80 - 3.74 (m, 6 H), 3.71 - 3.65 (m, 6 H), 3.59 - 3.44 (m, 3 H), 3.36 (br d, *J*=11.49 Hz, 1 H), 3.29 (br d, *J*=11.98 Hz, 2 H), 3.23 - 3.06 (m, 2 H), 2.85 (brt , *J*=11.68 Hz, 1 H); LCMS [M+H]+ 604.31.

Example 121: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl] phenyl] -l-methylpyrazole-4-carboxamide



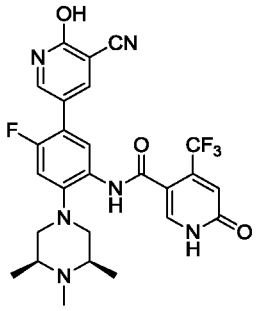
[00396] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using 1-methyl- lH-pyrazole-4-carboxylic acid in place of 3-(trifluoromethyl)pyrazole-4-carboxylic acid for Step 4. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.07 (s, 1H), 8.55 (d, *J*=1.0 Hz, 2H), 8.30 (s, 1H), 7.98 (s, 1H), 7.86 (d, *J*=8.6 Hz, 1H), 7.11 (d, *J*=12.2 Hz, 1H), 3.91 (s, 3H), 3.77 - 3.75 (m, 4H), 3.70 - 3.67 (m, 4H), 3.06 - 2.94 (m, 2H), 2.85 - 2.75 (m, 2H), 2.36 (dd, *J*=2.3, 10.6 Hz, 1H), 2.30 - 2.20 (m, 4H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 495.3.

Example 122: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl] phenyl] -l-methylpyrazole-4-carboxamide

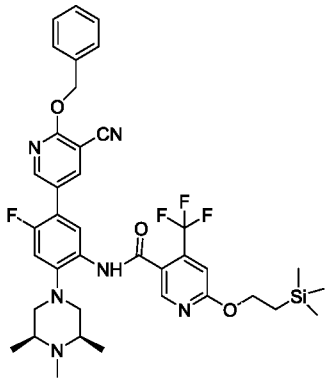


[00397] The title compound was prepared similar to the sequence described above for the preparation of Example 78 using 4-(morpholino)phenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 2. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.01 (s, 1H), 8.29 (s, 1H), 7.97 (s, 1H), 7.88 (d, *J*=8.7 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.09 - 7.00 (m, 3H), 3.91 (s, 3H), 3.79 - 3.74 (m, 4H), 3.19 - 3.15 (m, 4H), 3.03 - 2.92 (m, 2H), 2.85 - 2.76 (m, 2H), 2.40 - 2.35 (m, 1H), 2.31 - 2.21 (m, 4H), 0.98 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 493.4.

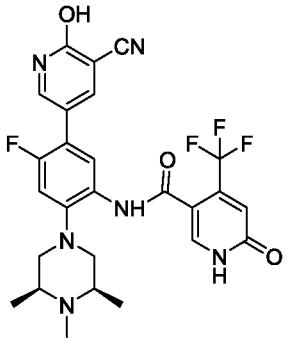
Example 123: N-[5-(5-cyano-6-hydroxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



Step 1: N-(5-(5-(benzyloxy)-5-cyanopyridin-3-yl)-4-fluoro-2-(⌜3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



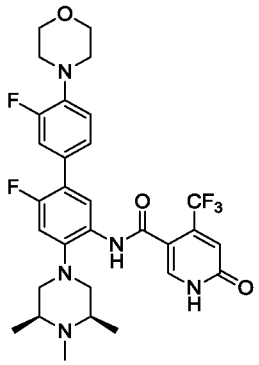
[00398] To a solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (300 mg, 0.495 mmol) and 2-(benzyloxy)-5-(trimethylstannyl)nicotinonitrile (222 mg, 0.595 mmol) in dry DMF (2 ml) at RT under N_2, was added CsF (151 mg, 0.991 mmol), copper(I) iodide (9.44 mg, 0.050 mmol) and tetrakis(triphenylphosphine)palladium(0) polymer bound (573 mg, 0.495 mmol). The reaction mixture was stirred overnight at 60°C. The major product was the deprotected one. The mixture was concentrated to dryness, partitioned between EtOAc and satd. aq citric acid solution. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3X). The combined organic phase was washed with sodium bicarbonate solution (8 ml), dried over Na_2S04 and concentrated to obtain the crude product which was adsorbed on celite and purified on isco (12 g), eluting with DCM containing 0-10 % MeOH. The deprotected product was isolated as a beige solid (66 mg, 20 %). LCMS [M+H]+ 635.7



[00399] N-(5-(6-(benzyloxy)-5-cyanopyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (20 mg) was dissolved in MeOH and subjected to hydrogenolysis at 45°C in an H-cube. The reaction was complete in lh. The solution was concentrated

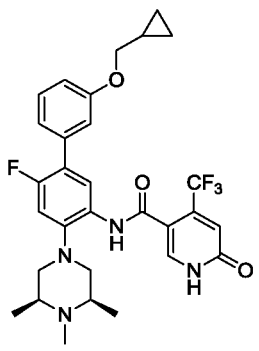
and purified on a preparatory column, eluting with water/acetonitrile gradient. The desired product was isolated as a white solid. (5 mg, 26 %). ^{1}H NMR (500MHz, METHANOL-d4)) δ ppm 1.24 - 1.30 (m, 6 H) 2.68 - 2.87 (m, 5 H) 3.13 - 3.19 (m, 2 H) 3.22 - 3.32 (m, 2 H) 6.83 (br s, 1 H) 7.07 (br d, *J*=11.86 Hz, 1 H) 7.79 (d, *J*=8.31 Hz, 1 H) 7.87 (br s, 1 H) 7.91 (s, 1 H) 8.24 (br s, 1 H). LCMS [M+H]+ 545.7

Example 124: N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



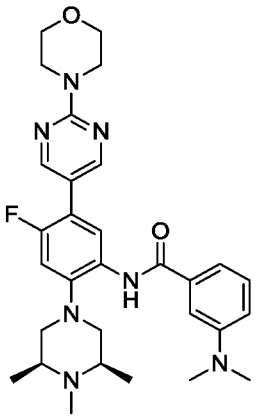
[00400] The title compound (brown solid, 37.4 mg, 61%) was prepared by a procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3-fluoro-4-morpholinophenylboronic acid (45 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d^ δ = 7.97 (s, IH), 7.92 (d, *J*=8.3 Hz, IH), 7.33 (d, *J*=8.7 Hz, IH), 7.30 (d, *J*=14.2 Hz, IH), 7.12 (t, *J*=8.7 Hz, IH), 7.05 (d, *J*=12.4 Hz, IH), 6.93 (s, IH), 3.92 - 3.83 (m, 4H), 3.18 - 3.11 (m, 4H), 3.08 (br d, *J*=10.9 Hz, 2H), 2.69 - 2.54 (m, 4H), 2.40 (s, 3H), 1.19 (d, *J*=6.0Hz, 6H); LCMS [M+H] $^{+}$ 606.3.

Example 125: N-[5-[3-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



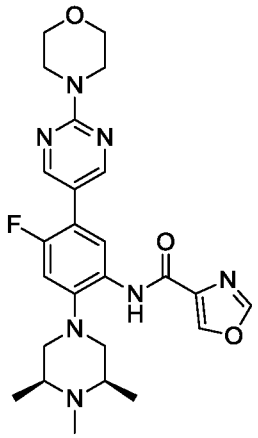
[00401] The title compound (light brown solid, 47.3 mg, 82%) was prepared according to a procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3-(cyclopropylmethoxy)phenylboronic acid (38 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOLS) δ = 7.97 (s, IH), 7.92 (d, *J*=8.2 Hz, IH), 7.34 (t, *J*=8.0 Hz, IH), 7.11 (d, *J*=7.7 Hz, IH), 7.09 (s, IH), 7.05 (d, *J*=12.0 Hz, IH), 6.92 (s, IH), 6.93 (d, *J*=6.6 Hz, 2H), 3.88 (d, *J*=6.8 Hz, 2H), 3.08 (br d, *J*=ll.l Hz, 2H), 2.68 - 2.54 (m, 4H), 2.40 (s, 3H), 1.33 - 1.24 (m, IH), 1.19 (d, *J*=6.0 Hz, 6H), 0.67 - 0.61 (m, 2H), 0.42 - 0.35 (m, 2H); LCMS $[M + H]^+$ 573.4.

Example 126: 3-(dimethylamino)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5SJ-3, 4, 5-trimethylpiperazin-l-ylJphenylJbenzamide



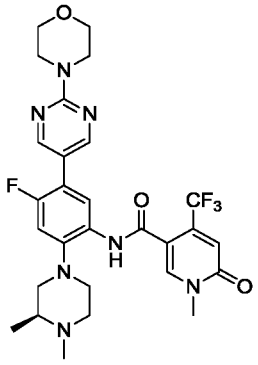
[00402] The title compound (light pink solid, 30.8 mg, 55%) was prepared according to a procedure similar to Example 34 using 3-(dimethylamino)benzoic acid (33 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.21 (d, *J*=8.3 Hz, IH), 7.38 (t, *J*=8.0 Hz, IH), 7.29 (s, IH), 7.22 (d, *J*=7.6 Hz, IH), 7.11 (d, *J*=11.9 Hz, IH), 7.01 (dd, *J*=2.4, 8.3 Hz, IH), 3.88 - 3.83 (m, 4H), 3.80 - 3.76 (m, 4H), 3.05 (s, 7H), 2.64 (t, *J*=ll.l Hz, 2H), 2.56 - 2.48 (m, 2H), 2.37 (s, 3H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 548.3.

Example 127: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -l,3-oxazole-4-carboxamide

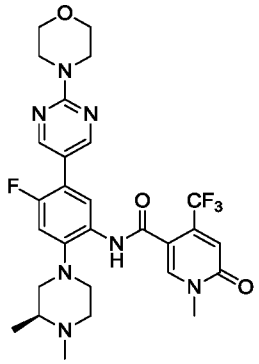


[00403] The title compound (light beige solid, 30.7 mg, 61%) was prepared according to a procedure similar to that of Example 34 using oxazole-4-carboxylic acid (23 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.78 (s, 1H), 8.61 (d, *J*=8.3 Hz, 1H), 8.58 (d, *J*=1.2 Hz, 2H), 8.35 (s, 1H), 7.97 (s, 1H), 7.28 (s, 1H),6.98 (d, *J*=11.4 Hz, 1H), 3.92 - 3.85 (m, 4H), 3.84 - 3.79 (m, 4H), 2.96 (d, *J*=9.7 Hz, 2H), 2.72 - 2.58 (m, 4H), 2.41 (s, 3H), 1.17 (d, *J*=5.5 Hz, 6H); LCMS $[M + H]^{+}$ 496.4.

Example 128: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

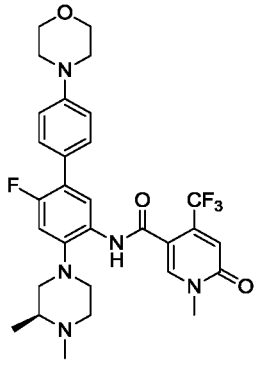


Step 2: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00404] The title compound was prepared according to a procedure similar to Example 78 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (obtained as described in Example 93, Step 8) as the acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.40 (s, 1H), 8.45 (s, 2H), 8.23 (s, 1H), 7.67 (d, *J*=8.7 Hz, 1H), 7.02 (d, *J*=12.2 Hz, 1H), 6.80 (s, 1H), 3.71 - 3.66 (m, 4H), 3.63 - 3.59 (m, 4H), 3.46 (s, 3H), 3.01 - 2.91 (m, 2H), 2.78 - 2.66 (m, 2H), 2.35 - 2.27 (m, 2H), 2.20 - 2.09 (m, 4H), 0.90 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 590.3.

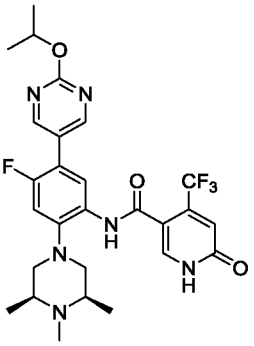
Example 129: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6<>xo-4-(trifluoromethyl)pyridine-3-carboxamide



[00405] The title compound was prepared similar to the sequence described above for the preparation of Example 128 using (S)-4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-4'-morpholino-[l ,l'-biphenyl]-3-amine which was derived from a sequence using 4-(morpholino)phenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 2 of Example 78. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.34 (s, 1H), 8.24 (s, 1H), 7.68 (d, J=8.8 Hz, 1H), 7.31 (br s, 1H), 7.30 (br s, 1H), 7.00 - 6.94 (m, 3H), 6.80 (s, 1H), 3.70 - 3.67 (m, 4H), 3.45 (s, 3H), 3.11 - 3.07 (m,

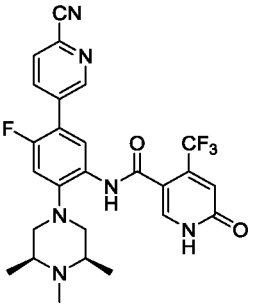
4H), 2.98 - 2.90 (m, 2H), 2.79 - 2.66 (m, 2H), 2.36 - 2.27 (m, 3H), 2.18 - 2.11 (m, 4H), 0.91 (d, J=6.2 Hz, 3H); LCMS [M+H]+: 588.4.

Example 130: N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00406] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using (2-isopropoxypyrimidin-5-yl)boronic acid in place of 4-cyanophenylboronic acid. ^{1}H NMR (500 MHz, MeOD) δ 8.73 (s, 2H), 7.97 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 12.0 Hz, 1H), 6.90 (s, 1H), 5.37 (dt, *J* = 12.3, 6.1 Hz, 1H), 3.08 (d, *J* = 11.3 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.54 (d, *J* = 6.1 Hz, 2H), 2.36 (s, 3H), 1.41 (d, *J* = 6.2 Hz, 6H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 563.39.

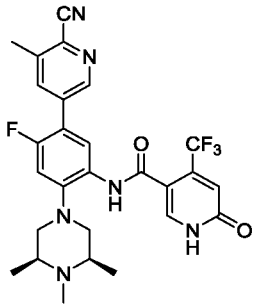
Example 131: N-[5-(5<yanopyridin-3-yl)-4-fluoro-2-[(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00407] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-cyanopyridine-5-boronic acid pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.91 (s, 1H), 8.19 (d, *J* = 9.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.96 (t, *J* = 4.0 Hz, 2H), 7.13 (d, *J* = 12.3 Hz, 1H), 6.91 (s,

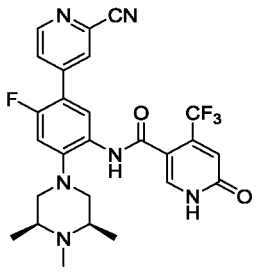
IH), 3.12 (d, *J* = 11.4 Hz, 2H), 2.64 (t, *J* = 11.2 Hz, 2H), 2.55 (dd, *J* = 13.2, 7.0 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 529.38.

Example 132: N-[5-(5-cyano-5-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



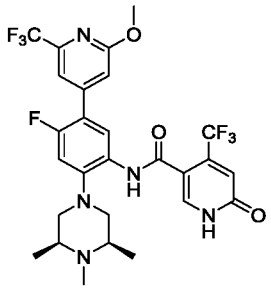
[00408] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-cyano-3-methylpyridine-5-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.72 (s, IH), 8.07 (s, IH), 7.98 (d, *J* = 8.2 Hz, IH), 7.97 (s, IH), 7.12 (d, *J* = 12.3 Hz, IH), 6.91 (s, IH), 3.12 (d, *J* = 11.4 Hz, 2H), 2.64 (d, *J* = 10.9 Hz, 2H), 2.62 (s, 3H), 2.54 (dd, *J* = 9.0, 5.2 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.75 (s), -119.92 (s); LCMS HSS [M+l]+ = 543.30.

Example 133: N-[5-(2<yanopyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



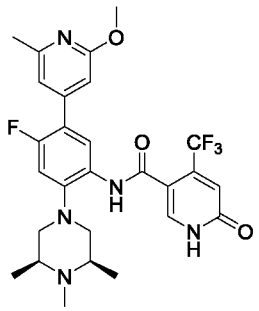
[00409] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-cyanopyridine-4-boronic acid pinacol ester in place of 4-cyanophenylboronic acid. ^{1}H NMR (500 MHz, MeOD) δ 8.75 (d, *J* = 5.3 Hz, IH), 8.12 (s, IH), 8.03 (d, *J* = 8.2 Hz, IH), 7.98 (s, IH), 7.88 (d, *J* = 5.2 Hz, IH), 7.12 (d, *J* = 12.6 Hz, IH), 6.91 (s, IH), 3.14 (d, *J* = 11.7 Hz, 2H), 2.63 (t, *J* = 11.2 Hz, 2H), 2.58 - 2.50 (m, 2H), 2.36 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 529.38.

Example 134: N-[4-fluoro-5-[2-methoxy-6-(trifluoromethyl)pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



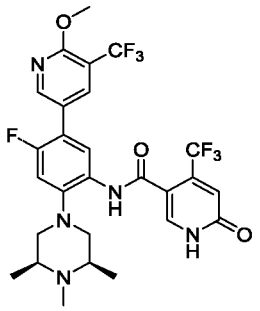
[00410] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-methoxy-6-trifluoromethylpyridine-4-boronic acid. ^{1}H NMR (500 MHz, MeOD) δ 7.97 (s, 2H), 7.53 (s, 1H), 7.19 (s, 1H), 7.10 (d, *J* = 12.5 Hz, 1H), 6.91 (s, 1H), 4.01 (s, 3H), 3.12 (d, *J* = 11.5 Hz, 2H), 2.63 (t, *J* = 11.2 Hz, 2H), 2.58 - 2.52 (m, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l]+ = 602.06.

Example 135: N-[4-fluoro-5-(2-methoxy-6-methylpyridin-4-yl)-2-[(3R,5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridme-3-carboxamide



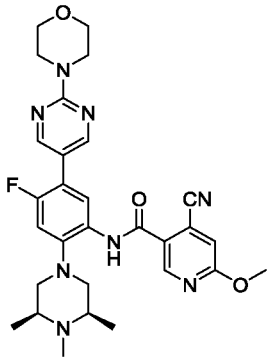
[00411] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 6-methoxy-2-picoline-4-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 7.95 (s, 2H), 7.07 (d, *J* = 12.2 Hz, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.76 (s, 1H), 3.93 (s, 3H), 3.12 (d, *J* = 8.1 Hz, 2H), 2.65 (d, *J* = 7.1 Hz, 4H), 2.48 (s, 3H), 1.19 (d, *J* = 5.5 Hz, 6H); LCMS [M+l]+ = 548.04.

Example 136: N-[4-fluoro-5-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

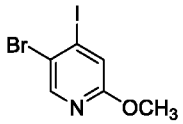


[00412] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 2-methoxy-3-(trifluoromethyl)pyridine-5-boronic acid. ^{1}H NMR (500 MHz, MeOD) δ 8.54 (s, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 4.08 (s, 3H), 3.08 (d, *J* = 11.3 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.55 (dd, *J* = 8.1, 6.1 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS [M+l]+ = 602.3.

Example 137: 4-cyano-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxypyridine-3-carboxamide



Step 1: 5-bromo-4-iodo-2-methoxypyridine

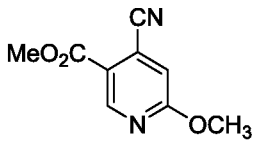


[00413] A solution of DIPA (14.8 niL, 117.6 mmol, and l.leq) in dry THF (150mL) was cooled to -78 °C, and n-BuLi (42 niL, 106.95 mmol, 1 eq, 2.5 M) was added dropwise. Then, the reaction mixture was stirred for 30 min, 5-bromo-2-methoxypyridine (20.0 g, 106.95 mmol, 1.0 eq) in dry THF (115mL) was added dropwise, then the reaction mixture was stirred at -78°C for lh. The reaction mixture was quenched with iodine (27.6 g, 106.95 mmol, and leq) in THF (80 mL) added dropwise and the reaction mixture was stirred for 16h.TLC analysis indicated a non-polar spot. The reaction was quenched with sodium thiosulfate solution (500 mL), extracted with EtOAc (1000 mL) and the separated organic layers were combined and dried over Na_2S04. Concentration under reduced pressure gave crude compound; which was recrystallized from ethanol (120mL) to give 5-bromo-4-iodo-2-methoxypyridine (12 g, 35.9%) as an off white solid. LCMS: [M+H]+ 315.83.

Step 2: 5-bromo-2-methoxyisonicotinonitrile

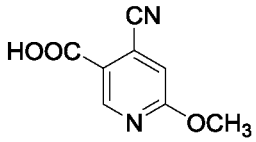
[00414] To a suspension of 5-bromo-4-iodo-2-methoxypyridine (10 g, 31.85 mmol, leq) in DMF (100 mL) was added CuCN (5.7 g, 63.7 mmol, 2.0 eq). The reaction mixture was heated at 100°C for 16 h. TLC analysis indicated polar spot. The reaction mixture was diluted with water (200 mL) and filtered off and washed with EtOAc (500 mL) and cold water (300 It). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure at 30°C. This was purified by column chromatography using silica (100-200 mesh) eluting with 5% EtOAc in pet ether to give 5-bromo-2-methoxyisonicotinonitrile (4g, 59.7% yield) as a solid compound. GCMS: [M+H]+ 213.

Step 3: methyl 4-cyano-6-methoxynicotinate



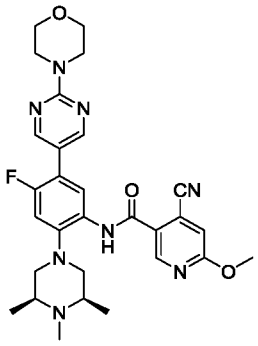
[00415] To a stirred solution of 5-bromo-2-methoxyisonicotinonitrile (4 g, 18.86 mmol, leq) in MeOH (33 mL) was added TEA (33 mL, 226.32 mmol, 12 eq) and $Pd_2(dppf)Cl_2$.DCM (1.5 g, 1.89 mmol, 0.1 eq) at RT and the reaction mixture was de-gassed with argon for 5min. Then the reaction mixture was heated to 90°C for 16 h under CO gas (250psi) in a sealed bomb. TLC analysis indicated formation of polar spot. The reaction mixture was filtered through a celite pad then the filtrate was concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-2000 mesh) using 20% EtOAc in Pet ether as eluent to afford methyl 4-cyano-6-methoxynicotinate (2 g, 55.5% yield) as solid. LCMS: [M+H] 193.0.

Step 4: 4-cyano-6-methoxynicotinic acid



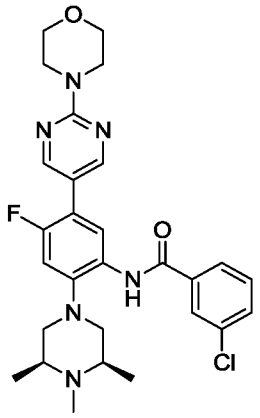
[00416] To a suspension of methyl 4-cyano-6-methoxynicotinate (2 g, 10.36 mmol, leq) in THF: MeOH: **H_20** (9 mL: 3 mL: 6 mL) (33mL), lithium hydroxide monohydrate (248 mg, 249.2 mmol, 4.0 eq) was added. The reaction mixture was stirred at RT for 16 h. TLC analysis of indication of polar spot. The reaction was concentrated under reduced pressure gave crude compound. This was acidified with 2N HC1 (20 mL), precipitate was formed and filtered off and washed with diethyl ether (50mL) and filtered off and dried on vacuum to give 4-cyano-6-methoxynicotinic acid (0.9mg, 48.6% yield) as an off white solid compound. LCMS: [M+]H+ 177.17.

Step 5: 4-cyano-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxypyridine-3-carboxamide



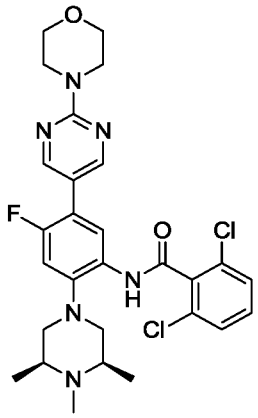
[00417] The title compound was prepared in a manner similar to the preparation of Example 34 using 4-cyano-6-methoxynicotinic acid in place of 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid. ^{1}H NMR (500 MHz, MeOD) δ 8.76 (d, *J* = 10.2 Hz, 1H), 8.56 (s, 2H), 7.50 (s, 1H), 7.46 (dd, *J* = 12.0, 8.2 Hz, 1H), 7.14 (t, *J* = 12.6 Hz, 1H), 4.10 (d, *J* = 1.4 Hz, 3H), 3.82 (dd, *J* = 6.4, 2.9 Hz, 4H), 3.77 - 3.73 (m, 4H), 2.89 (d, *J* = 12.1 Hz, 1H), 2.67 (t, *J* = 11.0 Hz, 1H), 2.64 (dt, *J* = 30.5, 11.2 Hz, 2H), 2.57 - 2.51 (m, 1H), 2.57 - 2.44 (m, 2H), 2.20 (s, 3H), 1.04 (dd, *J* = 22.7, 6.3 Hz, 6H); **Major rotamer reported:** LCMS [M+l] $^{+}$ = 561.43.

Example 138: 3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] benzamide



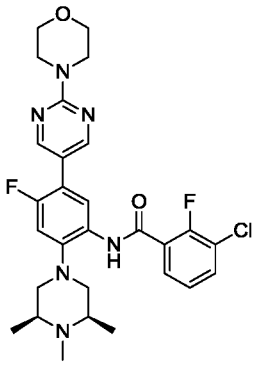
[00418] The title compound (beige solid, 32.4 mg, 55%) was prepared according to a procedure similar to Example 34 using 3,5-dichlorobenzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, 1H), 8.52 (d, *J*=8.2 Hz, 1H), 8.50 (d, *J*=1.2 Hz, 2H), 7.71 (s, 2H), 7.50 (s, 1H), 6.95 (d, *J*=11.2 Hz, 1H), 3.84 - 3.78 (m, 4H), 3.75 - 3.69 (m, 4H), 2.82 (d, *J*=11.0 Hz, 2H), 2.63 (t, *J*=10.9 Hz, 2H), 2.42 - 2.34 (m, 2H), 2.31 (s, 3H), 1.11 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^{+}$ 573.2.

Example 139: 2,6-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJ benzamide



[00419] The title compound (beige solid, 32.4 mg, 55%) was prepared according to a procedure similar to Example 34 using 3,5-dichlorobenzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, IH), 8.52 (d, *J*=8.2 Hz, IH), 8.50 (d, *J*=1.2 Hz, 2H), 7.71 (s, 2H), 7.50 (s, IH), 6.95 (d, *J*=11.2 Hz, IH), 3.84 - 3.78 (m, 4H), 3.75 - 3.69 (m, 4H), 2.82 (d, *J*=11.0 Hz, 2H), 2.63 (t, *J*=10.9 Hz, 2H), 2.42 - 2.34 (m, 2H), 2.31 (s, 3H), 1.11 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^{+}$ 573.2.

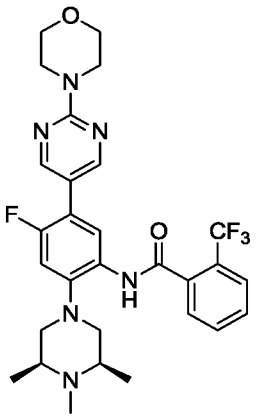
Example 140: 3-chloro-2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJbenzamide



[00420] The title compound (light yellow solid, 46.9 mg, 82%) was prepared by a procedure similar to Example 34 using 3-chloro-2-fluorobenzoic acid (35 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.78 (d, *J*=12.5 Hz, IH), 8.71 (d, *J*=8.3 Hz, IH), 8.58 (s, 2H), 8.08 (t, *J*=7.3 Hz, IH), 7.61 (t,

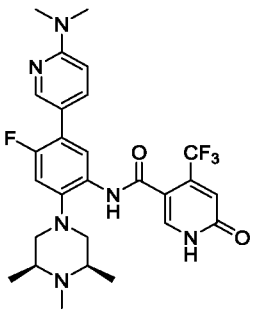
J=7.5 Hζ,IH), 7.29 (t, *J*=7.6 Hz, 1H), 7.04 (d, *J*=\ 1.4 Hz, 1H), 3.91 - 3.84 (m, 4H), 3.83 - 3.78 (m, 4H), 2.89 (t, *J*=7.0 Hz, 2H), 2.67 (t, *J*=10.9 Hz, 2H), 2.56 - 2.47 (m, 2H), 2.38 (s, 3H), 1.16 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^+$ 557.3.

Example 141: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



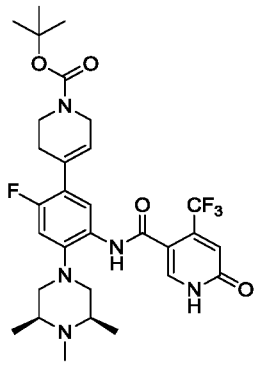
[00421] The title compound (beige solid, 51.7 mg, 89%) was prepared by a procedure similar to Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-(trifluoromethyl)benzoyl chloride (22 µï¸, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.62 - 8.53 (m, 4H), 7.80 (d, *J*=7.6 Hz, 1H), 7.69 (t, *J*=7.6 Hz, 1H), 7.64 (t, *J*=6.8 Hz, 2H), 7.00 (d, *J*=11.2 Hz, 1H), 3.92 - 3.84 (m, 4H), 3.84 - 3.76 (m, 4H), 2.85 (d, *J*=11.0 Hz, 2H), 2.62 (t, *J*=10.9 Hz, 2H), 2.31 - 2.17 (m, 5H), 1.11 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 573.4.

Example 142: N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbomm ide

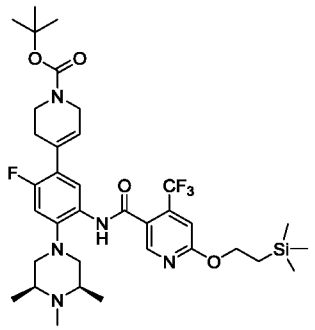


[00422] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 6-(dimethylarmno)pyridine-3-boronic acid pinacol ester. ¾ NMR (500 MHz, MeOD) δ 8.25 (s, 1H), 7.95 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.74 (dd, *J* = 9.0, 0.8 Hz, 1H), 7.04 (d, *J* = 12.2 Hz, 1H), 6.91 (s, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 3.12 (s, 6H), 3.04 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.57 - 2.50 (m, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l]+ = 547.28.

Example 143: tert-butyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate

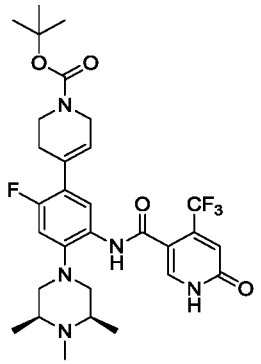


Step 1: tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4-(〈3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate



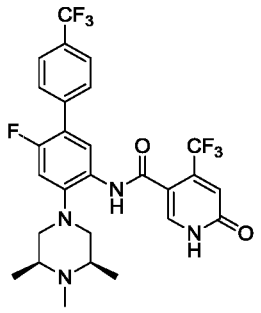
[00423] A procedure similar to Example 39 was employed using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (250 mg, 0.413 mmol), tert-butyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-l,2,3,6-tetrahydropyridine-l-carboxylate (191 mg, 0.619 mmol to give the title compound. LCMS [M+H] = 708.7.

Step 2: tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4-((3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate



[00424] TFA (0.6 ml) was added to a solution of tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinanudo)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate in DCM (20 ml) at RT and the reaction mixture was stirred at RT. LCMS after 10 min showed completion of the reaction. The reaction mixture was concentrated to dryness (bath temperature <25°C), the residue was dissolved in MeOH and passed through a cation exchange resin cartridge (Porapak Rxn CX 60 cc) to collect the title compound as an off white powder. (706 mg, 91%). ¾ NMR (500MHz, METHANOL-d^ δ = 8.01 - 7.93 (m, 1H), 7.84 - 7.73 (m, 1H), 7.01 - 6.93 (m, 1H), 6.92 - 6.86 (m, 1H), 6.10 - 5.93 (m, 1H), 4.17 - 4.02 (m, 2H), 3.71 - 3.58 (m, 2H), 3.06 - 2.99 (m, 2H), 2.65 - 2.49 (m, 6H), 2.43 - 2.36 (m, 3H), 1.62 - 1.43 (m, 9H), 1.17 (br d, J=5.7 Hz, 6H); LCMS [M+H]+ 608.6

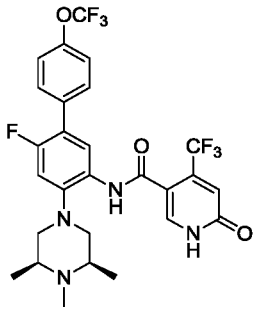
Example 144: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(trifluoromethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide



[00425] The title compound (tan solid, 43.8 mg, 75%) was prepared using a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-

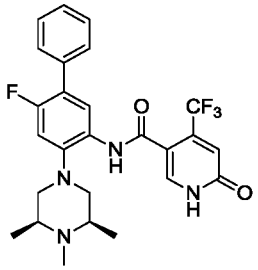
trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-(trifluoromethyl)phenylboronic acid (38 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.66 (s, IH), 8.50 (d, *J*=8.1 Hz, IH), 7.88 (s, IH), 7.70 (s, 4H), 7.04 (d, *J*=11.6 Hz, IH), 7.01 (s, 1H),2.85 (br d, *J*=11.0 Hz, 2H), 2.68 (br t, *J*=10.9 Hz, 2H), 2.41 - 2.27 (m, 5H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 571.1.

Example 145: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(trifluoromethoxy)phenyl]phenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



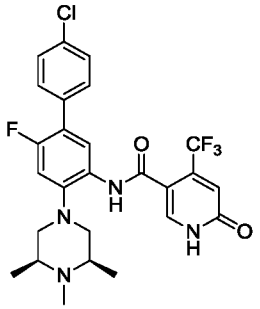
[00426] The title compound (light solid, 37.6 mg, 64%) was prepared by a procedure similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-(trifluoromethoxy)phenylboronic acid (41 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.67 (s, IH), 8.47 (d, *J*=8.2 Hz, IH), 7.86 (s, IH), 7.60 (d, *J*=7.8 Hz, 2H), 7.29 (br d, *J*=8.4 Hz, 2H), 7.05 - 6.99 (m, 2H), 2.84 (br d, *J*=10.9 Hz, 2H), 2.67 (br t, *J*=10.9 Hz, 2H), 2.40 - 2.29 (m, 5H), 1.15 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 587.2.

Example 146: N-[4-fluoro-5-phenyl-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



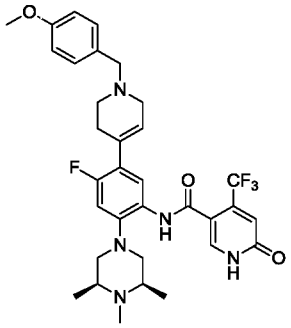
[00427] The title compound (grey solid, 29.4 mg, 56%) was prepared by a procedure similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and phenylboronic acid (24 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.67 (s, 1H), 8.48 (d, *J*=8.1 Hz, 1H), 7.87 (s, 1H), 7.58 (d, *J*=8.1 Hz, 2H), 7.44 (t, *J*=7.6 Hz, 2H), 7.39 - 7.34 (m, 1H), 7.04 - 6.98 (m, 2H), 2.85 (br d, *J*=10.9 Hz, 2H), 2.67 (br t, *J*=10.9 Hz, 2H), 2.42 - 2.29 (m, 5H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 503.2.

Example 147: N-[5-(4-chlorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



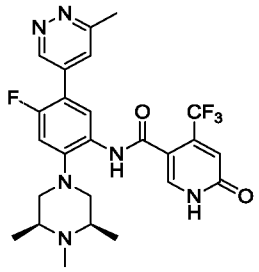
[00428] The title compound (grey solid, 31.5 mg, 57%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 4-chlorophenylboronic acid (31 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.66 (s, 1H), 8.46 (d, *J*=8.1 Hz, 1H), 7.87 (s, 1H), 7.51 (d, *J*=7.7 Hz, 2H), 7.44 - 7.39 (m, 2H), 7.04 - 6.98 (m, 2H), 2.84 (br d, *J*=11.0 Hz, 2H), 2.67 (br t, *J*=10.8 Hz, 2H), 2.40 - 2.30 (m, 5H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 537.3.

Example 148: N-[4-fluoro-5-[l-[(4-methoxyphenyl)methyl]-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



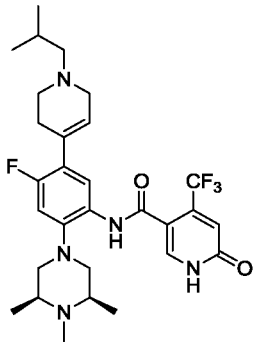
[00429] N-(4-Fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (15 mg, 0.030 mmol), 4-methoxybenzaldehyde (8.05 mg, 0.059 mmol) and acetic acid, glacial, 99.8% (7.10 mg, 0.118 mmol) were mixed in anhydrous DCE. A cloudy solution was obtained. After 5-10 min, sodium triacetoxyborohydride (18.79 mg, 0.089 mmol) was added and the reaction mixture was stirred at RT for 18 h. LCMS showed complete disappearance of the starting material and formation of the desired product. The reaction was quenched with sat aq NaHCCb solution (basic). The organic phase was separated, the aqueous phase was extracted with DCM (2X), then the combined organic phase was washed with brine, dried over Na_2S0_4 and concentrated to obtain the crude product. It was purified on isco column (4 G), eluting with DCM containing 0-8 % DCM. The appropriate fractions were combined and concentrated to afford the title compound as a white foam (11 mg, 56%). ¾ NMR (500MHz, METHANOL-d4) δ = 7.97 - 7.89 (m, 1H), 7.81 - 7.70 (m, 1H), 7.35 - 7.27 (m, 2H), 6.98 - 6.83 (m, 4H), 6.03 - 5.95 (m, 1H), 3.83 - 3.76 (m, 3H), 3.69 - 3.62 (m, 2H), 3.25 - 3.17 (m, 2H), 3.05 - 2.95 (m, 2H), 2.84 - 2.73 (m, 2H), 2.61 - 2.48 (m, 6H), 2.35 (s, 3H), 1.17 - 1.12 (m, 6H); LCMS [M+H]+ 628.4

Example 149: N-[4-fluoro-5-(5-methylpyridazin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



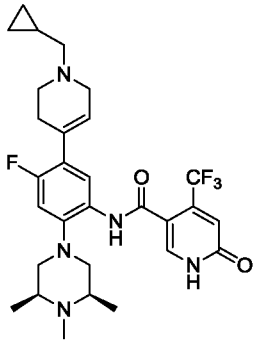
[00430] N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and 3-methylpyridazine-5-boronic acid, pinacol ester (25.4 mg, 0.116 mmol) using a procedure similar to Example 39 afforded the silyl ether intermediate, which was deprotected using TFA and isolated to give the title compound in 61% yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.32 - 9.20 (m, 1H), 8.12 - 8.03 (m, 1H), 8.01 - 7.95 (m, 1H), 7.86 - 7.80 (m, 1H), 7.23 - 7.10 (m, 1H),6.98 - 6.88 (m, 1H), 3.21 - 3.12 (m, 2H), 2.78 - 2.74 (m, 3H), 2.72 - 2.61 (m, 4H), 2.49 - 2.38 (m, 3H), 1.20 (br d, *J*=4.6 Hz, 6H); LCMS [M+H]+ 519.5

Example 150: N-[4-fluoro-5-[l-(2-methylpropyl)-3, 6-dihydro-2H-pyridin-4-yl]-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



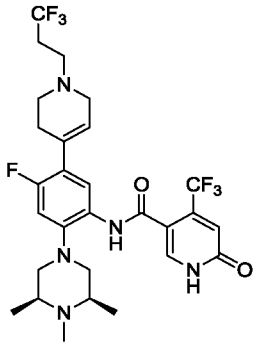
[00431] A procedure similar to Example 148 was used with N-(4-fluoro-5-(1,2,3, 6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide and isobutyraldehyde to give the desired product. ¾ NMR (500 MHz, METHANOL-d4) δ = 7.87 - 7.76 (m, 1H), 7.74 - 7.62 (m, 1H), 6.87 - 6.81 (m, 1H), 6.81 - 6.77 (m, 1H), 5.96 - 5.84 (m, 1H), 3.29 - 3.22 (m, 2H), 2.95 - 2.86 (m, 2H), 2.80 - 2.71 (m, 2H), 2.56 - 2.50 (m, 2H), 2.50 - 2.45 (m, 2H), 2.45 - 2.37 (m, 2H), 2.37 - 2.30 (m, 2H), 2.29 - 2.23 (m, 3H), 1.94 - 1.83 (m, 1H), 1.08 - 1.01 (m, 6H), 0.91 - 0.86 (m, 6H); LCMS [M+H]+ 564.4

Example 151: N-[5-[1-(cyclopropylmethyl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



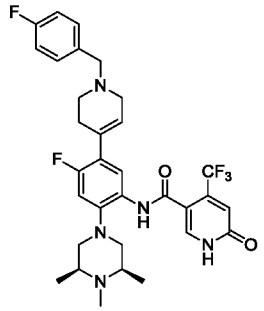
[00432] A procedure similar to Example 148 was used with cyclopropylbutyraldehyde to give the title compound in 77% yield. ^{1}H NMR (500MHz, METHANOLS) δ = 7.96 - 7.90 (m, 1H), 7.88 - 7.82 (m, 1H), 7.04 - 6.97 (m, 1H), 6.96 - 6.91 (m, 1H), 6.11 - 6.03 (m, 1H), 3.86 - 3.74 (m, 2H), 3.40 - 3.35 (m, 2H), 3.11 - 3.02 (m, 2H), 2.98 - 2.90 (m, 2H), 2.86 - 2.77 (m, 2H), 2.69 - 2.57 (m, 4H), 2.48 - 2.38 (m, 3H), 1.22 - 1.17 (m, 6H), 1.16 - 1.09 (m, 1H), 0.78 - 0.73 (m, 2H), 0.44 - 0.37 (m, 2H); LCMS [M+H]+ 562.5

Example 152: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[l-(3,3,3-trifluoropropyl)-3,6-dihydro-2H-pyridin-4-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



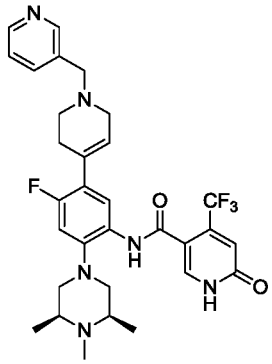
[00433] A procedure similar to that used for Example 148 was employed using 4,4,4-trifluorobutanal to give the title compound in 83% yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 - 7.91 (m, 1H), 7.83 - 7.73 (m, 1H), 6.98 - 6.93 (m, 1H), 6.93 - 6.91 (m, 1H), 6.06 - 5.98 (m, 1H), 3.27 - 3.22 (m, 2H), 3.07 - 3.01 (m, 2H), 2.83 - 2.75 (m, 4H), 2.63 - 2.49 (m, 8H), 2.40 - 2.37 (m, 3H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 604.5

Example 153: N-[4-fluoro-5-[l-[(4-fluorophenyl)methyl]-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00434] A procedure similar to that used for Example 148 with 4-fluorobenzaldehyde gave the title compound in 73 % yield. ^{1}H NMR (500MHz, METHANOLS) δ = 7.97 - 7.90 (m, 1H), 7.83 - 7.73 (m, 1H), 7.49 - 7.37 (m, 2H), 7.15 - 7.05 (m, 2H), 6.99 - 6.88 (m, 2H), 6.05 - 5.96 (m, 1H), 3.73 - 3.67 (m, 2H), 3.25 - 3.19 (m, 2H), 3.08 - 2.99 (m, 2H), 2.81 - 2.75 (m, 2H), 2.63 - 2.53 (m, 6H), 2.42 - 2.37 (m, 3H), 1.21 - 1.16 (m, 6H); LCMS [M+H]+ 616.6.

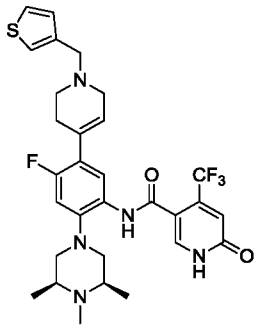
Example 154: N-[4-fluoro-5-[l-(pyridin-3-ylmethyl)-3, 6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00435] A procedure similar to Example 148 using nicotinaldehyde afforded the title compound in 38 % yield. ^{1}H NMR (500MHz, METHANOLS) δ = 8.49 - 8.45 (m, 1H), 8.40 - 8.33 (m, 1H), 7.84 - 7.77 (m, 2H), 7.70 - 7.60 (m, 1H), 7.37 - 7.33 (m, 1H), 6.86 - 6.78 (m, 2H), 5.94 - 5.86 (m, 1H), 3.67 - 3.60 (m, 2H), 3.13 -

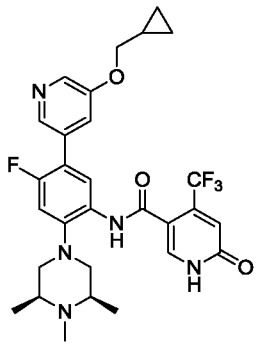
3.08 (m, 2H), 2.96 - 2.87 (m, 2H), 2.69 - 2.63 (m, 2H), 2.54 - 2.45 (m, 6H), 2.32 - 2.28 (m, 3H), 1.08 - 1.05 (m, 6H); LCMS [M+H]+ 599.5

Example 155: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[l-(thiophen-3-ylmethyl)-3,6-dihydro-2H-pyridin-4-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00436] A procedure similar to Example 148 using thiophene-3-carbaldehyde afforded the title compound in 73 % yield. ^{1}H NMR (500MHz, METHANOLS) δ = 7.99 - 7.90 (m, 1H), 7.83 - 7.73 (m, 1H), 7.42 (dd, *J*=3.1, 4.6 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.23 - 7.15 (m, 1H), 6.99 - 6.86 (m, 2H), 6.08 - 5.95 (m, 1H), 3.82 - 3.71 (m, 2H), 3.28 - 3.20 (m, 2H), 3.02 (br d, *J*=10.9 Hz, 2H), 2.85 - 2.74 (m, 2H), 2.63 - 2.50 (m, 6H), 2.41 - 2.35 (m, 3H), 1.20 - 1.14 (m, 6H); LCMS [M+H]+ 604.5

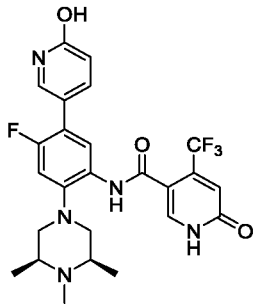
Example 156: N-[5-[5-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ne-3-carboxamide



[00437] A procedure similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide and 3-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine afforded the silyoxy intermediate which

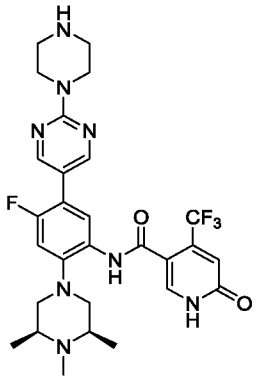
was deprotected using TFA to give the title compound in 71% yield for the last step. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.22 - 8.17 (m, 1H), 8.16 - 8.08 (m, 1H), 7.93 - 7.88 (m, 1H), 7.87 - 7.80 (m, 1H), 7.50 - 7.44 (m, 1H), 7.10 - 7.00 (m, 1H), 6.86 - 6.79 (m, 1H), 3.90 - 3.83 (m, 2H), 3.16 - 3.08 (m, 2H), 3.01 - 2.81 (m, 2H), 2.73 - 2.65 (m, 2H), 2.63 - 2.43 (m, 3H), 1.23 - 1.18 (m, 7H), 0.59 - 0.52 (m, 2H), 0.33 - 0.27 (m, 2H); LCMS [M+H]+ 574.6

Example 157: N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(ᵗrifluoromethyl)-lH-pyridine-3-carboxamide



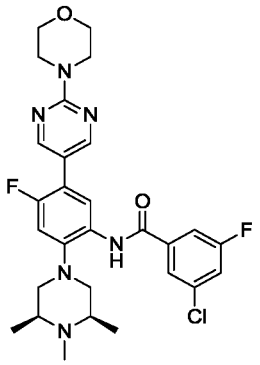
[00438] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine. This compound was isolated during the purification step as a side product. ¾ NMR (500 MHz, DMSO) δ 9.50 (s, 1H), 7.91 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 9.6 Hz, 1H), 7.49 (s, 1H), 7.00 (d, *J* = 12.6 Hz, 1H), 6.80 (s, 1H), 6.44 (d, *J* = 9.5 Hz, 1H), 3.00 (d, *J* = 10.9 Hz, 2H), 2.44 (t, *J* = 11.0 Hz, 2H), 2.36 - 2.31 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J* = 6.1 Hz, 6H); ^{19}F NMR (471 MHz, DMSO) δ -61.34 (s), -119.33 (s); LCMS HSS [M+l]+ = 520.35. **Major rotamer reported**

Example 158: N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00439] The title compound was prepared similar to the sequence described above for the preparation of Example 31 using 2-(4-boc-piperazino)pyrimidine-5-boronic acid pinacol ester and deprotecting the intermediate Boc-protected piperidine with TFA. ^{1}H NMR (500 MHz, MeOD) δ 8.56 (d, *J* = 0.9 Hz, 2H), 7.97 (s, IH), 7.90 (d, *J* = 8.2 Hz, IH), 7.08 (d, *J* = 12.1 Hz, IH), 6.89 (s, IH), 3.97 - 3.92 (m, 4H), 3.07 - 3.02 (m, *J* = 10.8, 5.6 Hz, 6H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.57 - 2.48 (m, 2H), 2.36 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS HSS [M+l]+ = 589.34.

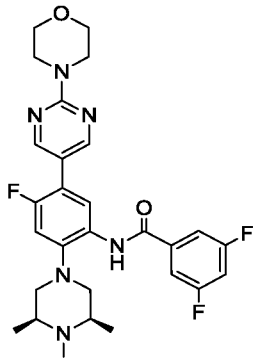
Example 159: 3-chloro-5-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJbenzamide



[00440] The title compound (beige solid, 42.5 mg, 74%) was prepared by a procedure similar to Example 34 using 3-chloro-5-fiuorobenzoic acid (35 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ¾I NMR (500MHz, CHLOROFORM-d) δ = 9.26 (s, IH), 8.60 (d, *J*=8.1 Hz, IH), 8.57 (d, *J*=l.l Hz, 2H), 7.68 (s, IH), 7.54 (td, *J*=1.8, 8.7 Hz, IH), 7.32 (td, *J*=2.1, 8.0 Hz, IH), 7.03 (d, *J*=\ 1.2 Hz, IH), 3.92 - 3.85 (m, 4H), 3.83 - 3.78 (m,

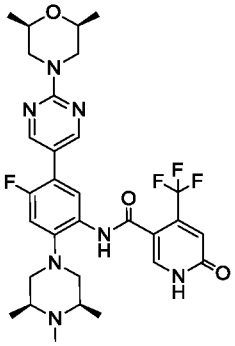
4H), 2.90 (br d, *J*=\ 1.0 Hz, 2H), 2.71 (br t, *J*=10.9 Hz, 2H), 2. 49 - 2.41 (m, 2H), 2.38 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]+ 557.4.

Example 160: 3,5-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJbenzamide

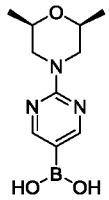


[00441] The title compound (beige solid, 41.5 mg, 74%) was prepared by a procedure similar to Example 34 using 3,5-difluorobenzoic acid (32 mg, 0.2 mmol) and 4-fluoro-5-(2-mo ϕ holinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.23 (s, 1H), 8.61 (d, *J*=8.1 Hz, 1H), 8.57 (d, *J*=1.0 Hz, 2H), 7.46 - 7.40 (m, 2H), 7.08 - 7.00 (m, 2H), 3.92 - 3.85 (m, 4H), 3.83 - 3.78 (m, 4H), 2.89 (br d, *J*=11.0 Hz, 2H), 2.70 (t, *J*=10.9 Hz, 2H), 2.46 - 2.40 (m, 2H), 2.38 (s, 3H), 1.17 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]+ 541.4.

Example 161: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3S, 5R)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

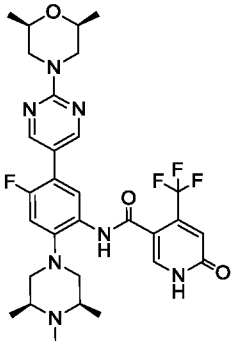


Step 1: Preparation of (2-((2S, 6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid



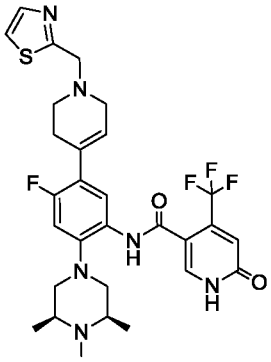
[00442] To a mixture of 2-chloropyrimidine-5-boronic acid (1.584 g, 10 mmol) and cis-2,6-dimethylmorpholine (1.29 mL, 10.5 mmol) in EtOH (5 mL) was added triethylamine (1.54 mL, 11 mmol). The resulting suspension was stirred at 60 °C for 1 h. Solvents were removed and the residue oil solidified to a crystalline pale yellow solid. It was triturated with $\mathbf{H_20}$ (20 mL), suction filtered, rinsed with $\mathbf{H_20}$ (20 mL), air dried and dried under vacuum to give the title compound as a pale yellow solid (827 mg, 35%). LCMS $[M + H]^+$ 238.14.

Step 2: Preparation of N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide



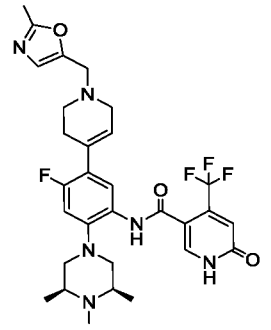
[00443] The title compound (brown solid, 39.1 mg, 60%) was prepared by a procedure similar to Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and (2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (47 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.54 (s, 2H), 7.98 (s, IH), 7.90 (d, *J*=8.2 Hz, IH), 7.09 (d, *J*=12.0 Hz, IH), 6.93 (s, IH), 4.64 (dd, *J*=1.3, 13.1 Hz, 2H), 3.67 (ddd, *J*=2.3, 6.3, 10.5 Hz, 2H), 3.07 (br d, *J*=11.0 Hz, 2H), 2.66 - 2.55 (m, 6H), 2.40 (s, 3H), 1.25 (d, *J*=6.1 Hz, 6H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 618.4.

Example 162: N-[4-fluoro-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-yl]-5-[l-(1,3-thiazol-2-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00444] The procedure was similar to Example 148 using thiazole-2-carbaldehyde and N-(4-fluoro-5-(l,2,3,64etrahydropyridin-4-yl)-2<(3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide to give the title compound in 81 % yield. ¾ NMR (500MHz, METHANOLS) δ = 7.97 - 7.91 (m, 1H), 7.83 - 7.73 (m, 2H), 7.62 - 7.57 (m, 1H), 6.99 - 6.90 (m, 2H), 6.06 - 5.97 (m, 1H), 4.07 - 4.02 (m, 2H), 3.37 - 3.34 (m, 2H), 3.07 - 2.99 (m, 2H), 2.88 - 2.81 (m, 2H), 2.63 - 2.53 (m, 6H), 2.39 (s, 3H), 1.19 - 1.14 (m, 6H); LCMS [M+H]+ 605.4

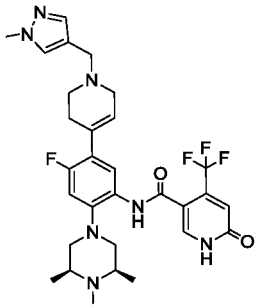
Example 163: N-[4-fluoro-5-[l-[(2-methyl-l, 3-oxazol-5-yl)methyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00445] The procedure was similar to Example 148 using 2-methyloxazole-5-carbaldehyde and N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide to give the title compound in 35 % yield. ¾ NMR (500MHz,

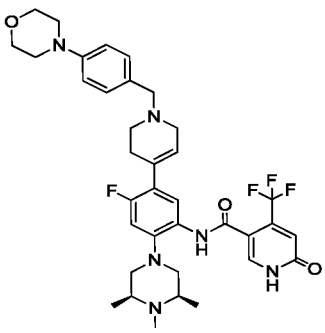
METHANOL-d4) δ = 7.96 - 7.91 (m, 1H), 7.82 - 7.74 (m, 1H), 6.99 - 6.97 (m, 1H), 6.96 - 6.93 (m, 1H), 6.93 - 6.91 (m, 1H), 6.05 - 5.99 (m, 1H), 3.80 - 3.75 (m, 2H), 3.28 - 3.21 (m, 2H), 3.06 - 2.99 (m, 2H), 2.81 (t, *J*=5.7 Hz, 2H), 2.62 - 2.53 (m, 6H), 2.49 - 2.45 (m, 3H), 2.41 - 2.38 (m, 3H), 1.19 - 1.16 (m, 6H); LCMS [M+H]+ 603.5

Example 164: N-[4-fluoro-5-[1-[(1-methylpyrazol-4-yl)methyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



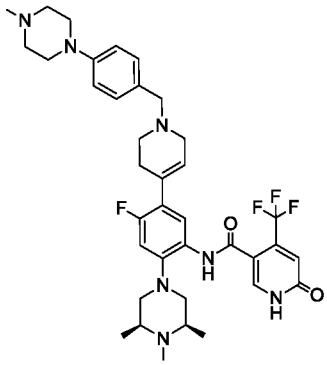
[00446] The procedure was similar to Example 148 using 1-methyl-lH-pyrazole-4-carbaldehyde and N-(4-fluoro-5-(l ,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide to give the title compound in 68 % yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 (s, 1H), 7.77 (br d, *J*=8.1 Hz, 1H), 7.62 (s, 1H), 7.50 (s, 1H), 6.96 - 6.92 (m, 1H), 6.91 (s, 1H), 6.02 (br s, 1H), 3.90 (s, 3H), 3.64 (s, 2H), 3.26 - 3.20 (m, 2H), 3.05 - 2.98 (m, 2H), 2.83 - 2.76 (m, 2H), 2.62 - 2.50 (m, 6H), 2.37 (s, 3H), 1.16 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 602.5.

Example 165: N-[4-fluoro-5-[l -[(4-morpholin-4-ylphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



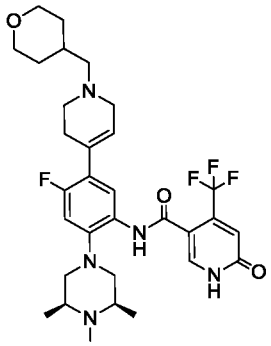
[00447] The procedure was similar to Example 148 using 4-morpholinobenzaldehyde and N-(4-fluoro-5-(l ,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide to give the title compound in 45 % yield. ^{1}H NMR (500MHz, METHANOLS) δ = 7.98 - 7.91 (m, 1H), 7.83 - 7.74 (m, 1H), 7.35 - 7.26 (m, 2H), 7.01 - 6.97 (m, 2H), 6.96 - 6.92 (m, 1H), 6.91 - 6.89 (m, 1H), 6.11 - 5.92 (m, 1H), 3.87 - 3.83 (m, 4H), 3.69 - 3.63 (m, 2H), 3.27 - 3.21 (m, 2H), 3.19 - 3.15 (m, 4H), 3.05 - 2.98 (m, 2H), 2.83 - 2.76 (m, 2H), 2.62 - 2.50 (m, 6H), 2.39 - 2.36 (m, 3H), 1.18 - 1.14 (m, 6H); LCMS [M+H]+ 683.5

Example 166: N-[4-fluoro-5-[l-[[4-(4-methylpiperazin-l-yl)phenyl]methyl]-3, 6-dihydro-2H-pyridin-4-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



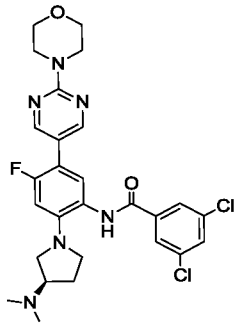
[00448] The procedure was similar to Example 148 using 4-(4-methylpiperazin-l-yl)benzaldehyde and N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide to give the title compound in 22 % yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.01 - 7.89 (m, 1H), 7.82 - 7.72 (m, 1H), 7.34 - 7.27 (m, 2H), 7.02 - 6.98 (m, 2H), 6.96 - 6.92 (m, 1H), 6.92 - 6.88 (m, 1H), 6.07 - 5.94 (m, 1H), 3.73 - 3.66 (m, 2H), 3.28 - 3.22 (m, 6H), 3.06 - 2.98 (m, 2H), 2.85 - 2.78 (m, 2H), 2.70 - 2.65 (m, 4H), 2.62 - 2.50 (m, 6H), 2.38 (d, *J*=8.9 Hz, 6H), 1.18 - 1.14 (m, 6H); LCMS [M+H]+ 696.5

Example 167: N-[4-fluoro-5-[1-(oxan-4-ylmethyl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

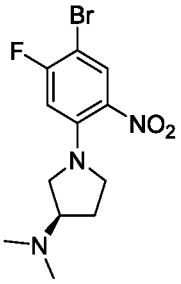


[00449] The procedure was similar to Example 148 using tetrahydro-2H-pyran-4-carbaldehyde and N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide to give the title compound in 88 % yield. ¾ NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.90 (m, 1H), 7.85 - 7.74 (m, 1H), 6.98 - 6.93 (m, 1H), 6.93 - 6.89 (m, 1H), 6.08 - 5.95 (m, 1H), 4.00 - 3.93 (m, 2H), 3.51 - 3.43 (m, 2H), 3.28 - 3.22 (m, 2H), 3.07 - 2.98 (m, 2H), 2.84 - 2.77 (m, 2H), 2.65 - 2.52 (m, 6H), 2.46 - 2.42 (m, 2H), 2.40 - 2.36 (m, 3H), 2.02 - 1.90 (m, 1H), 1.79 - 1.73 (m, 2H), 1.34 - 1.30 (m, 2H), 1.18 - 1.15 (m, 6H); LCMS [M+H]+ 606.5.

Example 168: 3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]benzamide

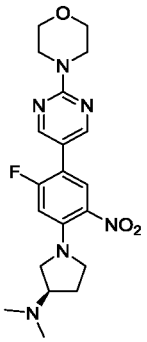


Step 1: Preparation of (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



[00450] A solution of l-bromo-2,4-difluoro-5-nitrobenzene (2.7 mL, 21 mmol) in toluene (5 mL) was added dropwise to a rapidly stirring mixture of (3R)-(+)-3-(dimethylamino)pyrrolidine (2.4 g, 21 mmol) and potassium carbonate (1.4 g, 10 mmol) in toluene (50 mL) at room temperature. After stirring for 20 minutes the reaction was warmed to 45 °C for 30 minutes. After the reaction was cooled to room temperature the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)-1-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (6.4 g, 91 %). LCMS [M+H]+: 332.1.

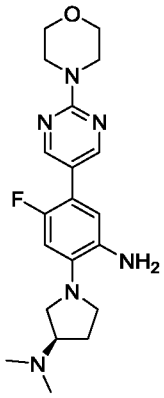
Step 2: Preparation of (R)-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



[00451] A vial was charged with (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.50 g, 1.50 mmol), 2-(4^ orpho1ηo)pyπimidiη6-5-boronic acid pinacol ester (0.48 g, 1.66 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.15 mmol). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (12 mL) and 2 M aqueous sodium carbonate (4 mL) were added via syringe and the vial was evacuated

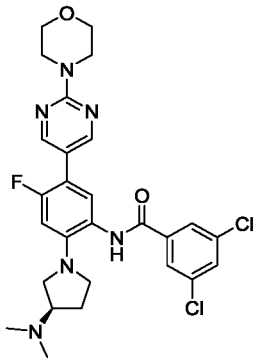
and backfilled an additional time. The reaction was heated to 85 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated onto celite and flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.61 g, 97 %). LCMS [M+H]+: 417.3.

Step 3: Preparation of (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine



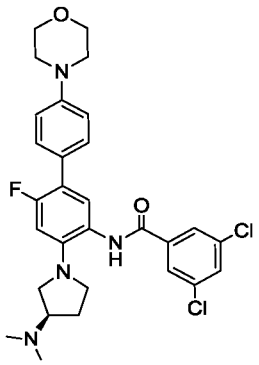
[00452] A mixture of (R)-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.61 g, 1.5 mmol) and tin(II) chloride (0.93 g, 4.9 mmol) in ethanol (12 mL) was heated to 75 °C for 1 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3 -amine (0.54 g, 90 %). LCMS [M+H]+: 387.2.

Step 4: Preparation of (R)-3,5-dichloro-N-(2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide



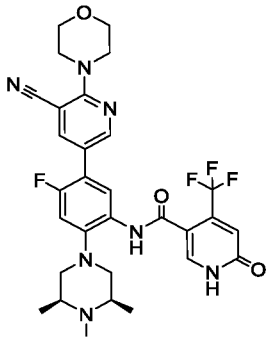
[00453] To a solution of 3,5-dichlorobenzoic acid (0.025 g, 0.13 mmol) in DCM (1 mL) was added propylphosphonic anhydride (50% solution) (0.08 mL, 0.13 mmol) and triethylamine (0.03 mL, 0.19 mmol). After mixing the clear solution was transferred by pipette to a suspension of (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3 -amine (0.025 g, 0.07 mmol) in DCM (1 mL) at room temperature. After stirring for 18 h at room temperature the reaction was concentrated onto celite and purified by flash chromatography [0.5 - 10% MeOH/DCM + 0.5% NH_4OH] to afford the title compound (R)-3,5-dichloro-N-(2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide (0.021 g, 55 %). ^1H NMR (500MHz, DMSO-d6) δ = 10.17 (s, 1H), 8.52 (s, 2H), 7.99 (d, *J*=1.8 Hz, 2H), 7.89 (t, *J*=1.8 Hz, 1H), 7.31 (d, *J*=8.8 Hz, 1H), 6.67 (d, *J*=14.1 Hz, 1H), 3.75 - 3.72 (m, 4H), 3.70 - 3.66 (m, 4H), 3.44 - 3.40 (m, 1H), 3.19 (t, *J*=8.7 Hz, 1H), 2.65 - 2.61 (m, 1H), 2.13 - 2.05 (m, 7H), 1.71 - 1.62 (m, 1H); LCMS [M+H]+: 559.3.

Example 169: 3,5-dichloro-N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]benzamide



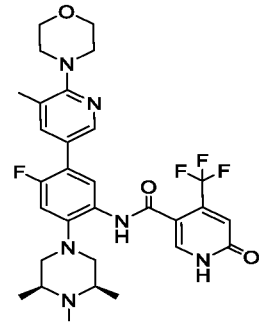
[00454] The title compound was prepared similar to the sequence described above for the preparation of Example 168 using 4-(morpholino)phenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 2. ^1H NMR (500MHz, DMSO-d6) δ = 10.13 (s, 1H), 7.99 (s, 2H), 7.89 (s, 1H), 7.37 (br d, *J*=8.3 Hz, 2H), 7.23 (d, *J*=8.8 Hz, 1H), 7.00 (d, *J*=8.8 Hz, 2H), 6.81 (br s, 1H), 6.68 - 6.56 (m, 2H), 3.78 - 3.73 (m, 4H), 3.41 - 3.39 (m, 2H), 3.19 (br t, *J*=8.9 Hz, 1H), 3.16 - 3.12 (m, 4H), 2.13 - 2.05 (m, 9H), 1.72 - 1.62 (m, 1H); LCMS [M+H]+: 557.3.

Example 170: N-[5-(5-cyano-6-morpholin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00455] The title compound was prepared according a procedure similar to Example 31 using 3-cyano-2-mo rpholinopyridine-5-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.57 (s, IH), 8.15 (d, *J* = 2.2 Hz, IH), 7.96 (s, IH), 7.91 (d, *J* = 8.3 Hz, IH), 7.09 (d, *J* = 12.2 Hz, IH), 6.91 (s, IH), 3.85 - 3.82 (m, 4H), 3.76 - 3.73 (m, 4H), 3.07 (d, *J* = 11.2 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.55 (dt, *J* = 6.4, 4.2 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l]+ = 614.39.

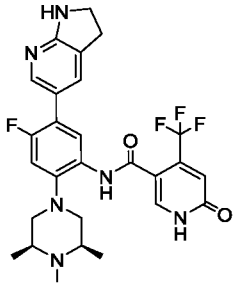
Example 171: N-[4-fluoro-5-(5-methyl-6-morpholin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbomm ide



[00456] The title compound was prepared using a procedure similar to Example 31 using 4-(3-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine. ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, IH), 7.96 (s, IH), 7.91 (d, *J* = 8.2 Hz, IH), 7.74 (s, IH), 7.07 (d, *J* = 12.1 Hz, IH), 6.91 (s, IH), 3.87 - 3.84 (m, 4H), 3.20 - 3.17 (m, 4H), 3.07 (d, *J* = 11.2 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.55 (ddd, *J*

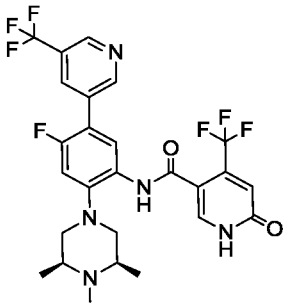
= 10.4, 6.2, 3.1 Hz, 2H), 2.37 (s, 6H), 1.16 (d, *J* = 6.1 Hz, 6H); $^{1\hat{y}}$F NMR (471 MHz, MeOD) δ -63.78, -120.54; LCMS HSS [M+l]+ = 603.26.

Example 172: N-[5-(2,3-dihydro-lH-pyrrolo[2,3-b]pyridin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00457] The title compound was prepared by a procedure similar to Example 31 using 2,3-dihydropyrrolo[2,3-b]pyridine-5-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 7.95 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.83 (s, 1H), 7.50 (s, 1H), 7.03 (d, *J* = 12.1 Hz, 1H), 6.90 (s, 1H), 3.65 (t, *J* = 8.5 Hz, 2H), 3.12 (t, *J* = 8.4 Hz, 2H), 3.04 (d, *J* = 10.9 Hz, 2H), 2.60 (t, *J* = 11.1 Hz, 2H), 2.54 (ddd, *J* = 9.8, 7.5, 2.5 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.78 (s), -120.60 (s); LCMS HSS [M+l]+ = 545.33.

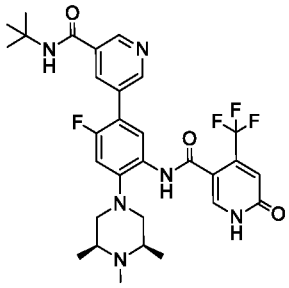
Example 173: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[5-(Mfluoromethyl)pyridin-3-yl]phenyl]-6<>xo-4-(Mfluoromethyty-1H-pyridine-3-carboxamide



[00458] The procedure followed was similar to that used in Example 39 to give, after deprotection of the silyloxy intermediate, the title compound in 91% yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.07 - 9.00 (m, 1H), 8.94 - 8.86 (m, 1H), 8.37 - 8.32 (m, 1H), 8.03 - 7.96 (m, 2H), 7.20 - 7.12 (m, 1H), 6.97 - 6.91 (m, 1H),

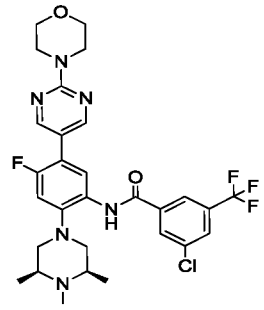
3.17 - 3.11 (m, 2H), 2.70 - 2.63 (m, 2H), 2.62 - 2.54 (m, 2H), 2.42 - 2.37 (m, 3H), 1.22 - 1.16 (m, 6H); LCMS [M+H]+ 572.5.

Example 174: N-[5-[5-(tert-butylcarbamoyl)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00459] The procedure followed was similar to that used in Example 39 to give, after deprotection of the silyloxy intermediate, the title compound in 84% yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.90 - 8.81 (m, 2H), 8.35 - 8.30 (m, 1H), 8.04 - 7.93 (m, 2H), 7.18 - 7.08 (m, 1H), 6.96 - 6.87 (m, 1H), 3.16 - 3.05 (m, 2H), 2.70 - 2.61 (m, 2H), 2.61 - 2.52 (m, 2H), 2.41 - 2.35 (m, 3H), 1.51 - 1.47 (m, 9H), 1.21 - 1.15 (m, 6H); LCMS [M+H]+ 603.7

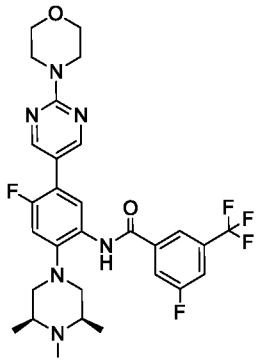
Example 175: 3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide



[00460] The title compound (beige solid, 36.8 mg, 59%) was prepared using a procedure similar that of Example 34 using 3-chloro-5-(trifluoromethyl)benzoic acid (45 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.45 (s, 1H), 8.65 (d, *J*=8.2 Hz, 1H), 8.60 (d, *J*=0.7 Hz, 2H), 8.17 (s, 1H), 8.03 (s, 1H), 7.85 (s, 1H), 7.06 (d, *J*=ll.l Hz, 1H), 3.94 - 3.86 (m, 4H),

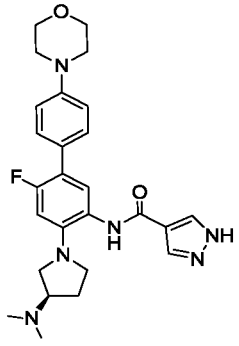
3.86 - 3.79 (m, 4H), 2.92 (br d, *J*=ll.l Hz, 2H), 2.74 (br t, *J*=10.9 Hz, 2H), 2.52 - 2.42 (m, 2H), 2.39 (s, 3H), 1.20 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 607.3.

Example 176: 3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide



[00461] The title compound (beige solid, 38.4 mg, 63%) was prepared by a procedure similar to Example 34 using 3-fluoro-5-trifluoromethylbenzoic acid (42 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^1H NMR (500MHz, CHLOROFORM-d) δ = 9.44 (s, 1H), 8.66 - 8.63 (m, 1H), 8.58 (d, *J*=1.5 Hz, 2H), 7.94 - 7.88 (m, 2H), 7.56 (br d, *J*=7.7 Hz, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 3.91 - 3.86 (m, 4H), 3.82 - 3.78 (m, 4H), 2.90 (br d, *J*=11.0 Hz, 2H), 2.72 (t, *J*=11.0 Hz, 2H), 2.47 - 2.40 (m, 2H), 2.37 (s, 3H), 1.18 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 591.4.

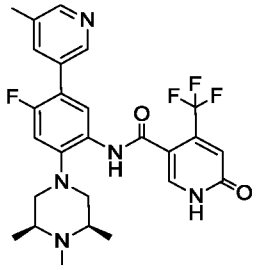
Example 177: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-lH-pyrazole-4-carboxamide



[00462] The title compound was prepared similar to the sequence described above for the preparation of Example 168 using lH-pyrazole-4-carboxylic acid in place of 3,5-

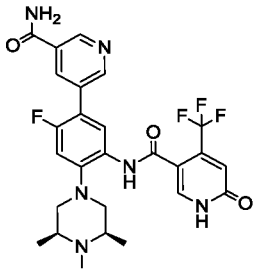
dichlorobenzoic acid in Step 4. ¾ NMR (500MHz, DMSO-d6) δ = 13.21 (br s, 1H), 9.47 (s, 1H), 8.38 - 8.25 (m, 1H), 8.15 - 7.97 (m, 1H), 7.36 (d, *J*=7.9 Hz, 2H), 7.17 (d, *J*=9.0 Hz, 1H), 7.00 (d, *J*=8.9 Hz, 2H), 6.81 (s, 1H), 6.66 - 6.59 (m, 2H), 3.78 - 3.73 (m, 4H), 3.23 (t, *J*=8.7 Hz, 1H), 3.16 - 3.12 (m, 4H), 2.63 - 2.59 (m, 1H), 2.12 (s, 3H), 2.11 - 2.02 (m, 7H), 1.73 - 1.61 (m, 1H), 1.57 - 1.46 (m, 1H); LCMS [M+H]+: 479.3.

Example 178: N-[4-fluoro-5-(5-methylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00463] The procedure used was similar to Example 39 to give, after deprotection of the silyloxy intermediate, the title compound in 91% yield. ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.07 - 9.00 (m, 1H), 8.94 - 8.86 (m, 1H), 8.37 - 8.32 (m, 1H), 8.03 - 7.96 (m, 2H), 7.20 - 7.12 (m, 1H), 6.97 - 6.91 (m, 1H), 3.17 - 3.11 (m, 2H), 2.70 - 2.63 (m, 2H), 2.62 - 2.54 (m, 2H), 2.42 - 2.37 (m, 3H), 1.22 - 1.16 (m, 6H); LCMS [M+H]+ 572.5.

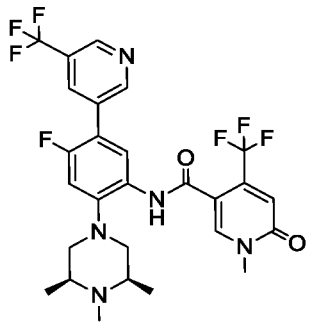
Example 179: N-[5-(5-carbamoylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carb oxamide



[00464] TFA (2 ml) was added to a solution of N-(5-(5-(tert-butylcarbamoyl)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (Example 174) in DCM (2 ml) at RT and the mixture was heated at 50 °C for 30 min. The reaction

mixture was concentrated and heated with methylsulfonic acid (10 eq) in toluene at 100 °C. Complete disappearance of the intermediate and formation of the desired product was observed after 30 min. The reaction mixture was concentrated to dryness, the residue was dissolved in MeOH and passed through a cation exchange resin cartridge (Isolute SCX-2 500 mg, 6ml) to collect the title compound as a beige powder (6.5 mg, 27 %). ¾ NMR (500MHz, METHANOL-d4) δ = 8.95 - 8.88 (m, 1H), 8.83 - 8.74 (m, 1H), 8.38 - 8.32 (m, 1H), 7.93 - 7.83 (m, 2H), 7.09 - 7.01 (m, 1H), 6.86 - 6.79 (m, 1H), 3.10 - 2.99 (m, 2H), 2.66 - 2.54 (m, 4H), 2.42 - 2.30 (m, 3H), 1.15 - 1.07 (m, 6H); ^{19}F NMR (471MHz, METHANOL-d4) δ = -63.78 (s, IF), -120.49 (s, IF)

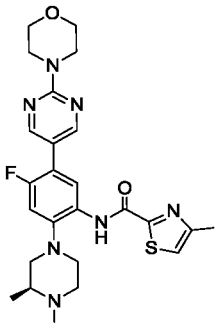
Example 180: N-[4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]-5-[5-(trifluoromethyl)pyridin-3-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethy l)pyridine-3-carboxamide



[00465] Cesium carbonate (8.55 mg, 0.026 mmol) was added to a solution of N-(4-fluoro-5-(5-(trifluoromethyl)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (Example 173, 15 mg, 0.026 mmol) and iodomethane (2.451 µï, 0.039 mmol) in DMF (l.ml) at RT. The reaction mixture was continuously stirred at RT. After 10 min, complete conversion was observed. One minor less polar peak with the same mass was observed. While not wishing to be limited by theory, it could be the O-methylated by-product. Mass (600) corresponding to the dimethyl substituted by-product was also observed in trace amounts. The mixture was diluted with DCM (4 ml) and washed with water (6 ml). The aqueous phase was extracted with DCM (2x5ml) and the combined organic phase was washed with water, and brine, then dried with Na_2S0_4 and concentrated onto celite. Purification by flash column chromatography on Isco (4G) column, eluting with DCM containing 0-3 % MeOH afforded the title compound as a white solid. (6 mg,

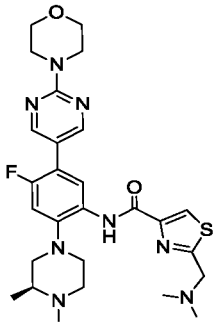
37% yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.97 - 8.87 (m, IH), 8.83 - 8.73 (m, IH), 8.25 - 8.19 (m, IH), 8.19 - 8.14 (m, IH), 7.93 - 7.84 (m, IH), 7.11 - 7.03 (m, IH), 6.88 - 6.80 (m, IH), 3.58 - 3.54 (m, 3H), 3.09 - 2.99 (m, 2H), 2.62 - 2.45 (m, 4H), 2.37 - 2.27 (m, 3H), 1.12 - 1.07 (m, 6H); LCMS [M+H]+ 586.4.

Example 181: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-4-methyl-l,3-thiazole-2-carboxamide



[00466] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using 4-methylthiazole-2-carboxylic acid in place of 6-chloro-4-(trifluoromethyl)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 10.19 (s, IH), 8.56 (s, 2H), 8.38 (d, *J*=8.3 Hz, IH), 7.76 (s, IH), 7.31 (d, *J*=11.7 Hz, IH), 3.80 - 3.75 (m, 4H), 3.71 - 3.67 (m, 4H), 2.98 - 2.86 (m, 5H), 2.59 (br d, *J*=9.5 Hz, 3H), 2.28 (s, 3H), 1.04 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 512.4.

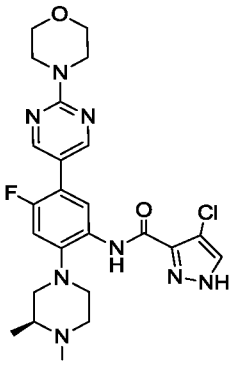
Example 182: 2-[(dimethylamino)methyl]-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-l ,3-thiazole-4-carboxamide



[00467] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using 2-[(dimethylamino)methyl]-l,3-thiazole-4-carboxylic acid in place of 6-chloro-4-(trifluoromethyl)nicotinic acid. ^{1}H

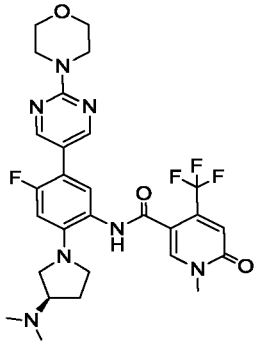
NMR (500MHz, DMSO-d6) δ = 10.24 (s, IH), 8.56 (s, 2H), 8.49 (br d, *J*=8.2 Hz, IH), 8.45 (s, IH), 7.28 (br d, *J*=11.7 Hz, IH), 3.90 - 3.81 (m, 2H), 3.77 (br d, *J*=4.2 Hz, 4H), 3.70 (br d, *J*=4.4 Hz, 4H), 2.94 - 2.86 (m, 4H), 2.34 - 2.28 (m, 8H), 1.02 (br d, *J*=6.0 Hz, 3H); LCMS [M+H]+: 555.4.

Example 183: 4-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-lH-pyrazole-3-carboxamide



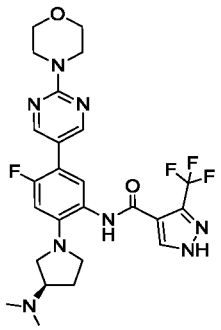
[00468] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using 4-chloro-lH-pyrazole-3-carboxylic acid in place of 3,5-dichlorobenzoic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.63 (s, IH), 8.49 (d, *J*=1.0 Hz, 2H), 8.37 (d, *J*=8.4 Hz, IH), 8.05 (br s, IH), 7.18 (d, *J*=11.7 Hz, IH), 3.71 - 3.68 (m, 4H), 3.63 - 3.60 (m, 4H), 2.89 - 2.75 (m, 4H), 2.40 - 2.34 (m, 2H), 2.28 - 2.23 (m, IH), 2.19 (s, 3H), 0.94 (d, *J*=6.1 Hz, 3H); LCMS [M+H]+: 515.2.

Example 184: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00469] l-Methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (29 mg, 0.13 mmol) was activated with HATU (49 mg, 0.13 mmol) and N,N-diisopropylethylamine (0.023 niL, 0.13 mmol) in DMF (0.5 mL) at room temperature. This solution of activated acid was added to a stirring solution of (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrirnidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine (25 mg, 0.065 mmol) [Example 168, Step C] in DMF (1 mL) at room temperature. The reaction was warmed to 40 °C for 1 h and then to 55 °C for an additional 1 h. An additional portion of activated acid was prepared and added to the reaction mixture and the reaction was heated at 55 °C overnight. The reaction mixture was concentrated onto celite and purified by flash chromatography [1-10% MeOH/DCM + 1%, NH_4OH] followed by reverse phase chromatography [5-95% MeCN/water; C18 column] to afford (R)-N-(2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.020 g, 52%). ^{1}H NMR (500MHz, DMSO-d6) δ = 13.95 (br. s., 1H), 9.29 (br. s., 1H), 8.59 (br. s., 1H), 8.55 (s, 2H), 7.82 (d, *J*=8.4 Hz, 1H), 7.14 (d, *J*=12.0 Hz, 1H), 3.78 - 3.75 (m, 4H), 3.70 - 3.67 (m, 4H), 3.01 (br. s., 2H), 2.88 (br. s, 2H), 2.23 (br. s., 3H), 1.00 (br. s, 3H); LCMS [M+H]+: 590.5.

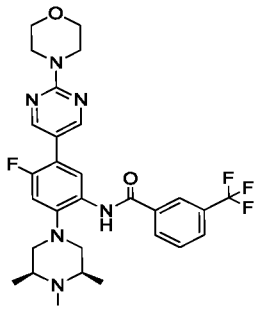
Example 185: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-3-(trifluorom ethyl)-1H-pyrazole-4-carboxamide



[00470] The title compound was prepared similar to the procedure described above for the preparation of Example 184 using 3-(trifluoromethyl)pyrazole-4-carboxylic acid in place of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.60 (s, 1H), 8.46 (s, 1H), 8.44 (s, 2H), 7.17 (d, *J*=8.7 Hz, 1H), 6.60 (d, *J*=14.1 Hz, 1H), 3.68 - 3.64 (m, 4H), 3.62 -

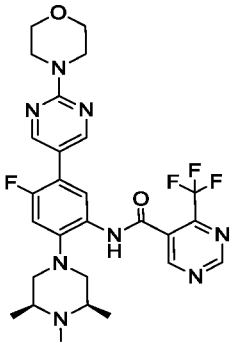
3.59 (m, 4H), 3.30 (br dd, *J*=3.2, 6.7 Hz, 4H), 3.14 (t, *J*=8.8 Hz, IH), 2.55 - 2.49 (m, 4H), 2.02 (s, 6H), 2.00 - 1.95 (m, IH), 1.64 - 1.55 (m, IH); LCMS [M+H]+: 549.4.

Example 186: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-(trifluoromethyl)benzamide



[00471] The title compound (beige solid, 51.0 mg, 87%) was prepared by a procedure similar to Example 34 using 3-(trifluoromethyl)benzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-txiimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.41 (s, IH), 8.67 (d, *J*=8.2 Hz, IH), 8.58 (d, *J=1.2* Hz, 2H), 8.18 (d, *J*=7.8 Hz, IH), 8.14 (s, IH), 7.86 (d, *J*=7.8 Hz, IH), 7.70 (t, *J*=7.8 Hz, IH), 7.03 (d, *J*=11.2 Hz, IH), 3.91 - 3.85 (m, 4H), 3.83 - 3.77 (m, 4H), 2.91 (br d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=11.0 Hz, 2H), 2.49 - 2.40 (m, 2H), 2.37 (s, 3H), 1.17 (d, *J*=6.2Hz, 6H); LCMS $[M + H]^+$ 573.3.

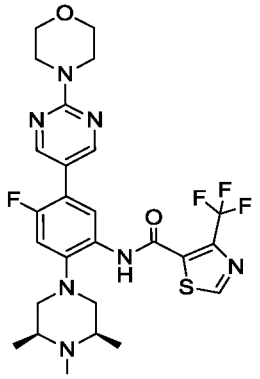
Example 187: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



[00472] The title compound (beige solid, 39.0 mg, 65%) was prepared through a procedure similar to Example 34 using 44rifluoromethyl-pyrimidine-5-carboxylic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-

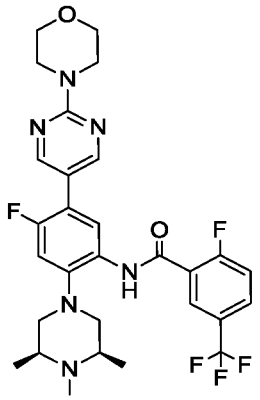
trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.50 (s, 1H), 9.15 (s, 1H), 8.83 (s, 1H), 8.61 - 8.54 (m, 3H), 7.06 (d, *J*=ll.l Hz, 1H), 3.90 - 3.85 (m, 4H), 3.83 - 3.78 (m, 4H), 2.81 (br d, *J*=10.9 Hz, 2H), 2.65 (br t, *J*=10.8 Hz, 2H), 2.33 - 2.21 (m, 5H), 1.12 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 575.4.

Example 188: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenylJ-4-(trifluoromethyl)-l,3-thiazole-5-carboxamide



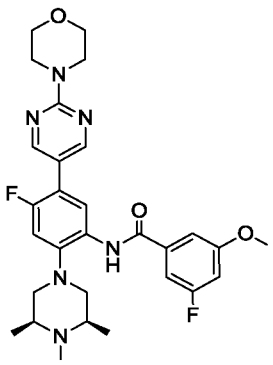
[00473] The title compound (beige solid, 42.3 mg, 72%) was prepared by a procedure similar to Example 34 using 4-(trifluoromethyl)-l,3-thiazole-5-carboxylic acid (39 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFODR-d) δ = 9.19 (br s, 1H), 8.94 (s, 1H), 8.60 - 8.54 (m, 3H), 7.07 (d, *J*=ll.l Hz, 1H), 3.92 - 3.84 (m, 4H), 3.83 - 3.77 (m, 4H), 2.82 (br d, *J*=10.8 Hz, 2H), 2.66 (br t, *J*=10.8 Hz, 2H), 2.43 - 2.30 (m, 5H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^+$ 580.3.

Example 189: 2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide



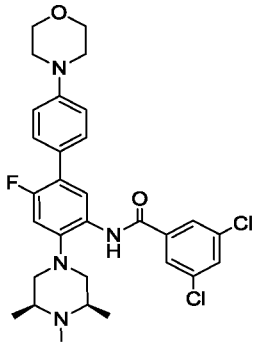
[00474] The title compound (pale beige solid, 53.6 mg, 89%) was prepared by a procedure similar to Example 34 using 2-fluoro-5-(trifluoromethyl)benzoic acid (42 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.84 (br d, *J*=12.7 Hz, IH), 8.73 (d, *J*=8.3 Hz, IH), 8.59 (d, *J*=*l.l* Hz, 2H), 8.54 (dd, *J*=2.0, 6.9 Hz, IH), 7.86 - 7.80 (m, IH), 7.38 (dd, *J*=8.9, 10.9 Hz, IH), 7.05 (d, *J*=11.2 Hz, IH), 3.91 - 3.86 (m, 4H), 3.83 - 3.77 (m, 4H), 2.89 (br d, *J*=10.8 Hz, 2H), 2.67 (br t, *J*=10.8 Hz, 2H), 2.53 - 2.45 (m, 2H), 2.38 (s, 3H), 1.16 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 591.4.

Example 190: 3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenyl]'-5-methoxybenzamide



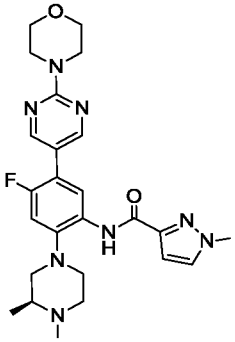
[00475] The title compound (beige solid, 48.4 mg, 87%) was prepared by a procedure similar to Example 34 using 3-fluoro-5-methoxybenzoic acid (34 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimiώn-5-yl)-2-((3S,5R)-3,4,5-tximethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, IH), 8.63 (d, *J*=8.2 Hz, IH), 8.57 (s, 2H), 7.28 (br s, IH), 7.16 (br d, *J*=8.7 Hz, IH), 7.01 (d, *J*=11.2 Hz, IH), 6.83 (td, *J*=2.1, 10.1 Hz, IH), 3.90 (s, 3H), 3.89 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.90 (br d, *J*=11.0 Hz, 2H), 2.68 (t, *J*=10.9 Hz, 2H), 2.49 - 2.39 (m, 2H), 2.37 (s, 3H), 1.16 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 553.4.

Example 191: 3,5-dichloro-N-[4-fluoro-5-(4-morpholin-4-ylphenyl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] benzamide



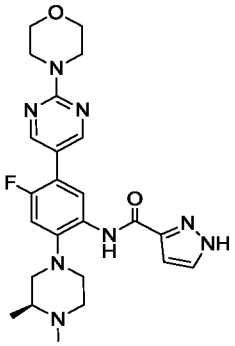
[00476] The title compound (pale beige solid, 43.1 mg, 75%) was prepared by a procedure similar to Example 34 using 3,5-dichlorobenzoic acid (38 mg, 0.2 mmol) substituting 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline as the aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.30 (s, 1H), 8.63 (d, *J*=8.3 Hz, 1H), 7.80 (d, *J*=1.7 Hz, 2H), 7.59 - 7.51 (m, 3H), 7.02 - 6.94 (m, 3H), 3.93 - 3.85 (m, 4H), 3.28 - 3.18 (m, 4H), 2.90 (br d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=10.9 Hz, 2H), 2.52 - 2.41 (m, 2H), 2.38 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^{+}$ 571.3.

Example 192: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-l-methylpyrazole-3-carboxamide



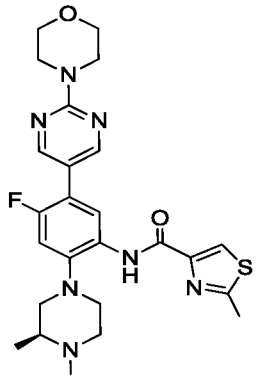
[00477] The title compound was prepared similar to the procedure described for the preparation of Example 78 using 1-methyl- lH-pyrazole-3-carboxylic acid as the acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.75 (br s, 1H), 8.55 (br s, 2H), 8.47 - 8.41 (m, 1H), 7.90 (br s, 1H), 7.30 - 7.21 (m, 1H), 6.77 (br s, 1H), 3.97 (br s, 3H), 3.79 - 3.75 (m, 4H), 3.71 - 3.68 (m, 4H), 2.91 (br s, 5H), 2.29 (br s, 3H), 1.04 (br s, 3H); LCMS [M+H]+: 495.4.

Example 193: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-lH-pyrazole-3-carboxamide



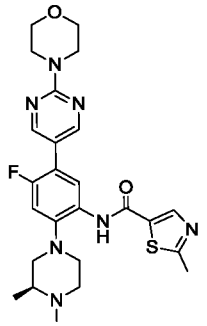
[00478] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using lH-pyrazole-3-carboxylic acid in place of 3-(trifluoromethyl)pyrazole-4-carboxylic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 13.70 - 13.36 (m, IH), 9.72 (br s, IH), 8.56 (br s, 2H), 8.48 (br d, *J*=4.0 Hz, IH), 7.93 (br s, IH), 7.25 (br d, *J*=ll.l Hz, IH), 6.80 (br s, IH), 3.80 - 3.76 (m, 4H), 3.71 - 3.67 (m, 4H), 2.97 - 2.85 (m, 5H), 2.28 (br s, 3H), 1.03 (br s, 3H); LCMS [M+H]+: 481.4.

Example 194: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-4-carboxamide



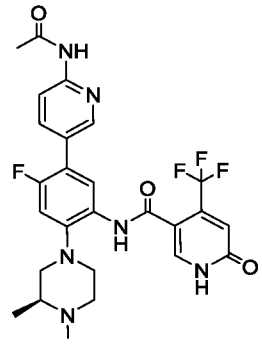
[00479] The title compound was prepared similar to the procedure described for Example 78 using 2-methyl-l,3-thiazole-4-carboxylic acid hydrochloride as the carboxylic acid acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 10.27 (s, IH), 8.56 (s, 2H), 8.50 (d, *J*=8.6 Hz, IH), 8.32 (s, IH), 7.28 (d, *J*=l 1.6 Hz, IH), 3.79 - 3.76 (m, 4H), 3.71 - 3.68 (m, 4H), 2.95 - 2.87 (m, 4H), 2.78 (s, 3H), 2.56 (br d, *J*=ll.l Hz, 4H), 2.29 (s, 3H), 1.04 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 512.2.

Example 195: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-5-carboxamide

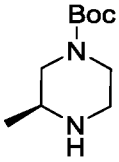


[00480] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using 2-methyl-l,3-thiazole-5-carboxylic acid as acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.59 (s, 1H), 8.48 (s, 2H), 8.31 (br s, 1H), 7.69 (d, *J*=8.6 Hz, 1H), 7.03 (d, *J*=12.3 Hz, 1H), 3.70 - 3.67 (m, 4H), 3.62 - 3.59 (m, 4H), 2.99 - 2.90 (m, 2H), 2.79 - 2.68 (m, 2H), 2.64 (s, 3H), 2.27 - 2.21 (m, 1H), 2.13 (s, 3H), 0.89 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 512.2.

Example 196: N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



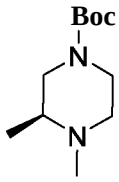
Step 1: tert-butyl (S)-3-methylpiperazine-l-carboxylate



[00481] To a stirred solution of 2- methyl piperazine (lOg, lOOmmol, leq) in ethanol (200mL) was added DIPEA (43.5mL, 250mmol, and the reaction mixture stirred for 10 min.. To this Boc anhydride (21.8mL, lOOmmol, leq) was added at 0°C

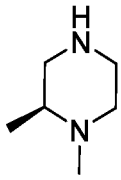
and the resulting reaction mixture was stirred at room temperature overnight. The progress of reaction was monitored by TLC, which indicated formation of nonpolar spot. The reaction mixture was concentrated and dissolved in DCM (200mL) then washed with water (2 x 80mL) followed by brine solution. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude tert-butyl (S)-3-methylpiperazine-l-carboxylate (20g, crude yield 100%) as a yellow liquid. TLC: MeOH : DCM (0.5: 9.5); R,= 0.3.

Step 2: tert-butyl (S)-3,4-dimethylpiperazine-l-carboxylate



[00482] To a stirred solution of tert-butyl (S)-3-methylpiperazine-l-carboxylate (50 g, 250 mmol, leq) in DCM: AcOH (10: 3, 500 mL) was added 37% HCHO (40.5 mL, 500 mmol, 2 eq) at 0°C and the resulting reaction mixture was stirred at room temperature for 3h. $NaCNBH_3$ (31.5 g, 500 mmol, 2 eq) was added portion wise at 0°C and the resulting reaction mixture was stirred at room temperature for 2h. The progress of reaction was monitored with TLC, which indicated formation of nonpolar spot. The reaction mixture was basified with sat. aq, $NaHCO_3$ solution and extracted with DCM (2 x 150 mL). The combined organic layer was washed with water, followed by brine solution and dried over $\mathbf{Na_2S0_4}$ then concentrated under reduced pressure to afford tert-butyl (S)-3,4-dimethylpiperazine-l-carboxylate (55g, crude) as colorless liquid. TLC system: MeOH : DCM (1: 9); R_f: 0.4.

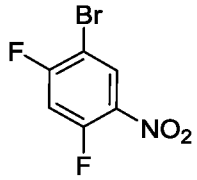
Step 3: (S)-l,2-dimethylpiperazine



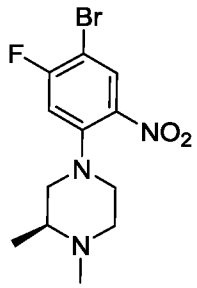
[00483] To a stirred solution of tert-butyl (S)-3,4-dimethylpiperazine-l-carboxylate (50 g, 233 mol, 1 eq) in DCM (500 mL) was added TFA (156 mL, 2097.3 mmol, 9 eq) at 0°C and the resulting reaction mixture was stirred at room temperature for 16h. The progress of reaction was monitored with TLC, which indicated formation of

polar spot. The reaction mixture was evaporated under reduced pressure to crude residue, which was basified with NH_3 in THF and excess THF then was concentrated under reduced pressure, followed by dilution with DCM (150 mL) and filtration. The filtrate was concentrated under reduced pressure to afford crude (S)-l,2-dimethylpiperazine (55 g, crude) as a colorless liquid. TLC system: MeOH: DCM (1: 5); R_f :0.1.

Step 4: l-bromo-2,4-difluoro-5-nitrobenzene



[00484] To a stirred suspension of 1-bromo-2,4-difluorobenzene (50 g, 259 mmol, leq) in cold H_2SO_4 (187.6 mL) was added cone. HNO_3 (165.5 mL) in a dropwise manner keeping the internal temp 20°C then stirred for 10 min. at 0°C. Then the reaction mixture was poured into a mixture of diethyl ether (250 mL) and ice water (250 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was again extracted with **Et_20** (250 mL). The combined organic layer was washed with sat. sodium bicarbonate (2X 200 mL) followed by sat. brine (2X 200 mL) solution. The separated organic layer was dried over **Na_2S0_4** and concentrated under reduced pressure to give crude product which was purified by column chromatography (silica gel, 100-200 mesh) using 0-15% EtOAc in pet ether as an eluent to afford l-bromo-2,4-difluoro-5-nitrobenzene (52 g, 72%) as a yellow color liquid. TLC System: EtOAc: pet ether (3: 7); R_f: 0.4

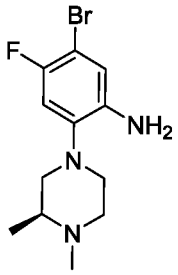


Step 5: (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine

[00485] To a stirred solution of (S)-l, 2-dimethylpiperazine (45g, 190.6mmol, leq) in EtOH (450mL) was added TEA (106.9mL, 762.7mmol, 4eq) under argon for 20min., then followed by addition of l-bromo-2,4-difluoro-5-nitrobenzene (47.8g,

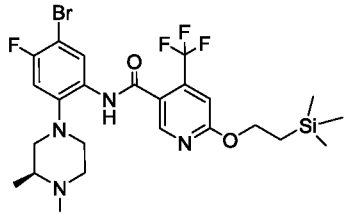
286.0mmol, 1.5eq) at RT under argon atm and heated to 85°C for 16h. TLC analysis indicated formation of less polar spot, then the reaction mixture was cooled to RT and solvent was evaporated under reduced pressure to give crude product, which was purified by column chromatography (silica gel, 100-200 mesh) using 0-30% EtOAc in pet ether as an eluent to afford (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine (42g, 92%) as a yellow solid. LCMS: [M+H]+ 332.0.

Step 6: (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline



[00486] To a stirred solution of (S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2-dimethylpiperazine (32 g, 96.67 mmol, leq) in EtOH: water (1:1, 640 mL) was added NH_4C1 (31g, 96.67mmol, 6eq) followed by Fe powder (32.3 g, 96.67 mmol, 6 eq) at RT under argon atm., and heated to 80°C for 16h. TLC analysis indicated formation of polar spot, then the reaction mixture was cooled to RT then filtered through a celite pad and washed with MeOH (2X lOOmL). The filtrate was concentrated under reduced pressure to crude product. The crude compound was purified by column chromatography (neutral alumina) using 100% DCM as an eluent affording (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (10.5 g, 48% yield) as pale yellow semi-solid. LCMS: [M+H]+ 302.17.

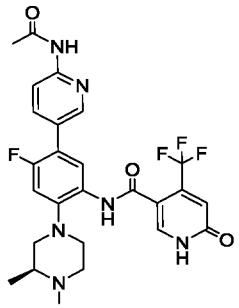
Step 7: (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00487] Propylphosphonic anhydride solution (2.81 ml, 4.71 mmol) was added dropwise to a mixture of (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (0.890 g, 2.95 mmol) and pyridine (0.949 ml, 11.78 mmol) in dry tetrahydrofuran

(THF) (14.73 ml) under N_2 at RT. After 1.5 h of stirring, a pale yellow solution was obtained. Then (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (0.890 g, 2.95 mmol) was added as a solid and the reaction mixture was heated at 50 °C. The crude product was allowed to cool to RT, THF was removed and the residue was partitioned between ethyl acetate (25 mL) and sodium bicarbonate sat solution (25 mL). The organic phase was separated and the aqueous phase was extracted with additional ethyl acetate (25 mL). The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the desired compound (1.36 g, 89%). LCMS $[M+l]^+$ = 591.22 g/mol.

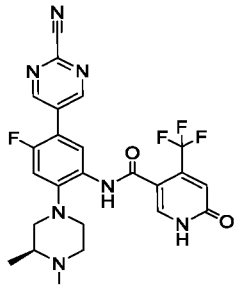
Step 8: N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00488] In a 5 mL microwave vial 2-acetamidopyridine-5-boronic acid, pinacol ester (0.034 g, 0.131 mmol), (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.05183 g, 0.088 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (6.20 mg, 8.76 μmoï) and potassium phosphate tribasic reagent grade (0.037 g, 0.175 mmol) were dissolved in water (0.175 ml) / 1,4-dioxane (1.577 ml) (9 : 1 mixture) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 110 °C. The solvent was evaporated and 15 mL of CH_2Cl_2 were added. The suspension was sonicated and extracted from water (15 mL). The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the protected intermediate. The product was dissolved in 2 mL of DCM and trifiuoroacetic acid (0.101 ml, 1.314 mmol) was added. The purple solution was stirred

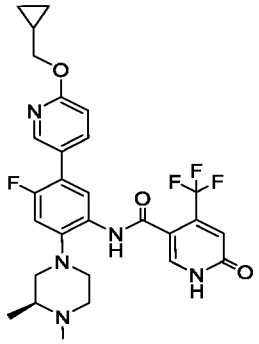
for 1 h and the solvent was evaporated. The residue was purified using a cation exchange column eluting with MeOH:NH_4OH. ^1H NMR (500 MHz, MeOD-d4) δ 8.37 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.87 (s, 1H), 7.84 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 12.1 Hz, 1H), 6.81 (s, 1H), 3.02 (dq, *J* = 11.6, 2.0 Hz, 1H), 2.97 (dt, *J* = 11.6, 2.2 Hz, 1H), 2.87 - 2.80 (m, 2H), 2.50 - 2.42 (m, 2H), 2.32 (ddd, *J* = 9.4, 6.4, 2.7 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); LCMS [M+l]+ = 547.28.

Example 197: N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



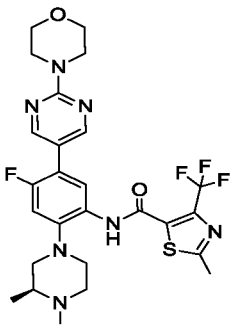
[00489] The title compound was prepared similar to the sequence described above for the preparation of Example 196 using 2-cyanopyrimidine-5-boronic acid pinacol ester in place of 2-acetamidopyridine-5-boronic acid, pinacol ester. ^1H NMR (500 MHz, MeOD) δ 9.14 (d, *J* = 0.7 Hz, 2H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.97 (s, 1H), 7.18 (d, *J* = 12.2 Hz, 1H), 6.92 (s, *J* = 4.4 Hz, 1H), 3.21 - 3.17 (m, 1H), 3.14 (dt, *J* = 12.0, 2.7 Hz, 1H), 2.98 - 2.91 (m, 2H), 2.61 - 2.52 (m, 2H), 2.42 (ddd, *J* = 9.6, 6.3, 2.9 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 3H); LCMS [M+l]+ = 516.29.

Example 198: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



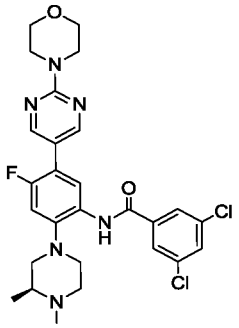
[00490] The title compound was prepared similar to the sequence described above for the preparation of Example 196 using 2-cyanopyrimidine-5-boronic acid pinacol ester in place of 2-acetamidopyridine-5-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.17 (s, 1H), 7.86 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.76 (dq, *J* = 8.7, 0.8 Hz, 1H), 6.99 (d, *J* = 12.0 Hz, 1H), 6.82 (s, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 4.05 (d, *J* = 7.1 Hz, 2H), 3.01 (dq, *J* = 11.3, 2.0 Hz, 1H), 2.96 (dt, *J* = 11.4, 2.1 Hz, 1H), 2.87 - 2.82 (m, 2H), 2.49 - 2.42 (m, 2H), 2.33 (ddd, *J* = 9.6, 6.5, 3.0 Hz, 1H), 2.28 (s, 2H), 1.21 (ddd, *J* = 12.9, 7.7, 4.1 Hz, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.53 - 0.49 (m, 2H), 0.27 (q, *J* = 4.7 Hz, 2H); LCMS [M+l]+ = 560.30.

Example 199: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-2-methyl-4-(trifluoromethyl)-l,3-thiazole-5-carboxamide



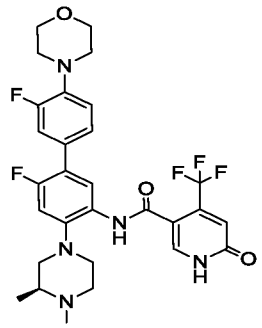
[00491] The title compound was prepared according to a procedure similar to Example 78 using 2-methyl-4-(trifluoromethyl)-l,3-thiazole-5-carbonyl chloride as acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.96 (s, 1H), 8.46 (s, 2H), 7.70 (br d, *J*=7.0 Hz, 1H), 7.05 (br d, *J*=11.5 Hz, 1H), 3.71 - 3.67 (m, 4H), 3.63 - 3.59 (m, 4H), 2.98 - 2.86 (m, 2H), 2.81 - 2.67 (m, 5H), 2.36 (br t, *J*=10.5 Hz, 1H), 2.31 - 2.24 (m, 1H), 2.19 - 2.12 (m, 4H), 0.93 (d, *J*=6.1 Hz, 3H); LCMS [M+H]+: 580.2.

Example 200: 3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJbenzamide



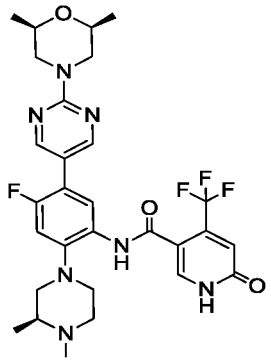
[00492] The title compound was prepared using a procedure similar to Example 78 with 3,5-dichlorobenzoic acid as acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.79 (s, IH), 8.49 (d, *J*=l.l Hz, 2H), 7.92 - 7.80 (m, 3H), 7.73 (d, *J*=8.6 Hz, IH), 7.05 (d, *J*=12.3 Hz, IH), 3.71 - 3.66 (m, 4H), 3.63 - 3.59 (m, 5H), 2.96 (br t, *J*=9.0 Hz, 2H), 2.82 - 2.66 (m, 2H), 2.20 (dt, *J*=2.8, 11.0 Hz, IH), 2.16 - 2.07 (m, 4H), 0.90 (d, *J*=6.4 Hz, 3H); LCMS [M+H]+: 559.1.

Example 201: N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine -3-carboxamide



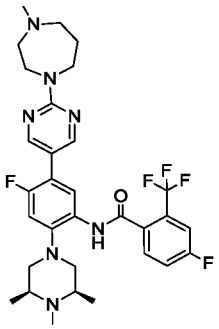
[00493] The title compound (brown solid, 37.4 mg, 61%) was prepared through a procedure similar to that of Example 40 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 3-fluoro-4-morpholinophenylboronic acid (45 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.92 (d, *J*=8.3 Hz, IH), 7.33 (d, *J*=8.7 Hz, IH), 7.30 (d, *J*=14.2 Hz, IH), 7.12 (t, *J*=8.7 Hz, IH), 7.05 (d, *J*=12.4 Hz, IH), 6.93 (s, IH), 3.92 - 3.83 (m, 4H), 3.18 - 3.11 (m, 4H), 3.08 (br d, *J*=10.9 Hz, 2H), 2.69 - 2.54 (m, 4H), 2.40 (s, 3H), 1.19 (d, *J*=6.0 Hz, 6H); LCMS $[M + H]^+$ 606.3.

Example 202: N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00494] The title compound (light brown solid, 48.3 mg, 77%) was prepared in a manner similar to that described in Example 40 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-6-oxo-4-(tafluoromethyl)- 1,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol) and (2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)boronic acid (47 mg, 0.2 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.71 (s, IH), 8.57 (d, *J*=1.0 Hz, 2H), 8.47 (d, *J*=8.2 Hz, IH), 7.89 (s, IH), 7.06 (d, *J*=ll.l Hz, IH), 7.02 (s, IH), 4.64 (dd, *J*=1.5, 13.2 Hz, 2H), 3.69 (ddd, *J*=2.4, 6.3, 10.5 Hz, 2H), 3.02 - 2.87 (m, 3H), 2.83 (br d, *J*=ll.l Hz, IH), 2.68 (dd, *J*=10.6, 13.2 Hz, 2H), 2.61 (br t, *J*=10.6 Hz, IH), 2.42 - 2.32 (m, 4H), 2.28 - 2.18 (m, IH), 1.30 (d, *J*=6.2 Hz, 6H), 1.11 (d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^+$ 604.3.

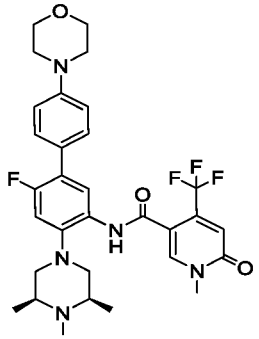
Example 203: 4-fluoro-N-[4-fluoro-5-[2-(4-methyl-l, 4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



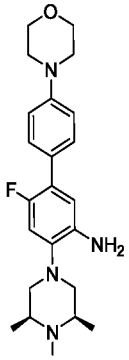
[00495] To a mixture of 2-chloropyrimidine-5-boronic acid (48 mg, 0.3 mmol) and 1-methylhomopiperazine (0.039 mL, 0.315 mmol) in EtOH (2 mL) was added

triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C for 1.5 h. Solvents were removed to give crude (2-(4-methyl-l,4-diazepan-l-yl)pyrimidin-5-yl)boronic acid as a yellow oil. LCMS $[M + H]^+$ 237.4. The title compound (off white solid, 31.4 mg, 50%) was prepared using a procedure similar to that of Example 29 using crude (2-(4-methyl-l,4-diazepan-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.60 - 8.52 (m, 4H), 7.66 (dd, *J*=5.3, 8.4 Hz, IH), 7.50 (dd, *J*=2.4, 8.8 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.00 (d, *J*=ll.l Hz, IH), 4.02 - 3.95 (m, 2H), 3.87 (t, *J*=6.4 Hz, 2H), 2.83 (br d, *J*=11.0 Hz, 2H), 2.76 - 2.69 (m, 2H), 2.65 - 2.56 (m, 4H), 2.40 (s, 3H), 2.30 - 2.18 (m, 5H), 2.08 - 2.00 (m, 2H), 1.10 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 618.6.

Example 204: N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6<>xo-4-(trifluoromethyl)pyridine-3-carboxamide



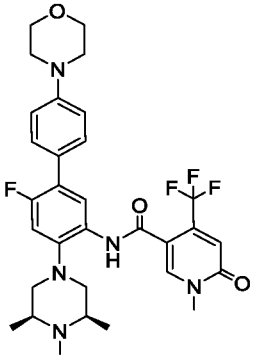
Step 1: Preparation of 6-fluoro-4'-morpholino-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl] -3-amine



[00496] To a 20 mL microwave vial charged with 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (1.265 g mg, 4 mmol), 4-

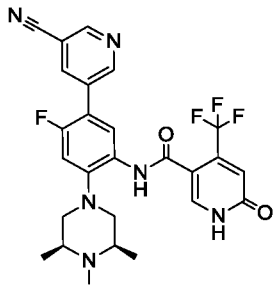
(morpholino)phenylboronic acid (1.242 g, 6.0 mmol), and $Pd(dppf)Cl_2$ (220 mg, 0.3 mmol, 7.5 mol%) was added dioxane (12 mL), followed by 1 M aq K_3PO_4 (6 mL, 6 mmol). The resulting mixture was irradiated in a microwave at 110 °C for 2 h. After quenching with sat. brine (20 mL), it was extracted with EtOAc (30 mL x 2). The combined extracts were concentrated and purified by Biotage SNAP KP-Sil 50 g (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-8%). Fractions showing product gave light brownish clear needle crystals (1.320 g, yield 82%) of the desired product. LCMS$[M + H]^+$ 399.3.

Step 2: N-(6-fluoro-4'-morpholino-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,1'-biphenyl]-3-yl)-l-methyl-6<>xo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



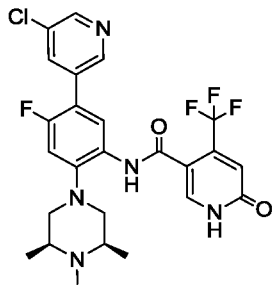
[00497] The title compound (yellow solid, 19.9 mg, 32%) was prepared through a procedure similar to Example 34 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (44 mg, 0.2 mmol) and 6-fluoro-4'-morpholino-4-((3 S,5R)-3,4,5-trimethylpiperazin- 1-yl)-[1,1'-biphenyl]-3-amine (40 mg, 0.1 mmol). ^1H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (s, 1H), 8.48 (d, *J*=8.3 Hz, 1H), 7.87 (s, 1H), 7.52 (d, *J*=7.5 Hz, 2H), 7.02 - 6.94 (m, 4H), 3.92 - 3.85 (m, 4H), 3.64 (s, 3H), 3.26 - 3.19 (m, 4H), 2.81 (br d, *J*=11.0 Hz, 2H), 2.65 (br t, *J*=10.8 Hz, 2H), 2.33 (s, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 602.4.

Example 205: N-[5-(5-cyanopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00498] The title compound was prepared using a procedure similar to that described in Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-mme thylpiperazin-l-yl)phenyl)-4-(mfluoromethyl)-6-(2-(ta methylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol), 3-cyanopyridine-5-boronic acid pinacol ester (19.00 mg, 0.083 mmol) and [I,Γ-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12.10 mg, 0.017 mmol) to give, after deprotection of the silyoxy intermediate, 25.5 mg (94% yield for the last step) of the title compound. ¾ NMR (500 MHz, METHANOL-d4) δ = 9.15 - 8.83 (m, 2H), 8.52 - 8.30 (m, 1H), 8.14 - 7.90 (m, 2H), 7.27 - 7.08 (m, 1H), 7.02 - 6.85 (m, 1H), 3.20 - 3.10 (m, 2H), 2.77 - 2.57 (m, 4H), 2.50 - 2.37 (m, 3H), 1.26 - 1.15 (m, 6H); LCMS [M+H]+ 529.2

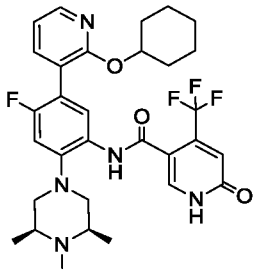
Example 206: N-[5-(5-chloropyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00499] A procedure similar to that of Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol), 3-chloropyridine-5-boronic acid (19.49 mg, 0.124 mmol) to give the silyoxy intermediate which was deprotected using TFA and purified by standard methods to give the title compound in 89% yield. ^{1}H NMR (500 MHz, METHANOL-d^ δ = 8.73 - 8.65 (m, 1H), 8.61 - 8.52 (m, 1H), 8.15 - 8.07 (m, 1H), 8.01 - 7.94 (m, 2H), 7.21 - 7.09 (m, 1H), 6.96 - 6.91 (m, 1H),

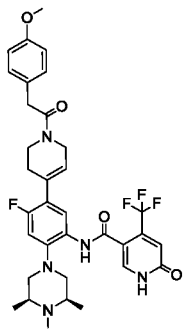
3.20 - 3.08 (m, 2H), 2.71 - 2.62 (m, 4H), 2.47 - 2.40 (m, 3H), 1.20 (br d, *J*=4.9 Hz, 6H); LCMS [M+H]+ 538.2.

Example 207: N-[5-(2<yclohexyloxypyridin-3-yl)-4-fluoro-2-[(3R, 5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridim -3-carboxamide



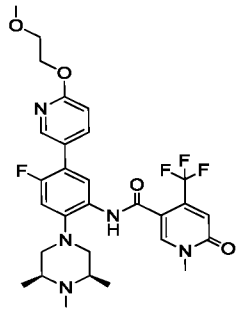
[00500] A procedure similar to that of Example 39 employing N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and 2-cyclohexyloxypyridine-3-boronic acid, pinacol ester (37.6 mg, 0.124 mmol) was used. Deprotection of the N-(5-(2-(cyclohexyloxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide intermediate with TFA and purification by standard procedures gave the title compound in 97% yield for the last step. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.20 - 8.07 (m, 1H), 8.03 - 7.80 (m, 2H), 7.74 - 7.62 (m, 1H), 7.14 - 6.97 (m, 2H), 6.96 - 6.89 (m, 1H), 5.19 - 5.05 (m, 1H), 3.17 - 3.04 (m, 2H), 2.75 - 2.57 (m, 4H), 2.52 - 2.35 (m, 3H), 2.00 - 1.89 (m, 2H), 1.79 - 1.68 (m, 2H), 1.62 - 1.51 (m, 3H), 1.49 . 1.40 (m, 2H), 1.38 - 1.28 (m, 2H), 1.27 - 1.14 (m, 6H); LCMS [M+H]+ 602.5

Example 208: N-[4-fluoro-5-[l-[2-(4-methoxyphenyl)acetyl]-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

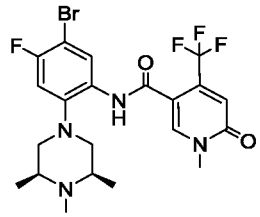


[00501] To N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol obtained from Example 148) and N,N-diisopropylethylamine (0.021 ml, 0.118 mmol) in DCM (3 ml) at RT was added 4-methoxy phenyl acetyl chloride (9.75 µï, 0.065 mmol). The milky reaction mixture became a clear solution. It was stirred at RT. Complete disappearance of the starting material and formation of the desired product was observed after 20 min at rt. The reaction was worked up at this point and purified using standard methods to give the title compound (31.5 mg, 77% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 - 7.77 (m, 1H), 7.66 - 7.55 (m, 1H), 7.15 - 7.01 (m, 2H), 6.88 - 6.75 (m, 4H), 5.96 - 5.75 (m, 1H), 4.19 - 4.09 (m, 2H), 3.72 - 3.59 (m, 7H), 2.97 - 2.85 (m, 2H), 2.54 - 2.39 (m, 5H), 2.30 - 2.23 (m, 4H), 1.09 - 1.03 (m, 6H); LCMS [M+H]+ 656.6.

Example 209: N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



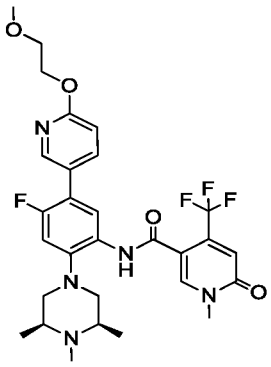
Step 1: Preparation of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00502] To a solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (505 mg, 1 mmol) in DMF (10 mL) was added cesium carbonate (326 mg, 1 mmol). After stirring at rt for 10 min, iodomethane (68 µL, 1.1 mmol) was added. The resulting mixture was stirred at rt for 30 min. then H_20 (50 mL) was

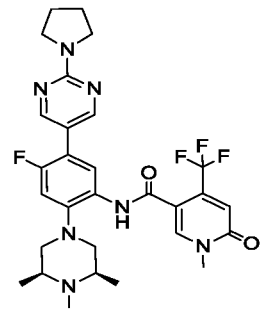
added slowly with stirring and an abundance of white precipitate formed. After stirring at rt for 10 min, it was filtered and washed with H_20 (10 mL), then dried to give the title compound as a light beige solid (417 mg, 78%). LCMS $[M+H]^+$ 519.2.

Step 2: N-(4-fluoro-5-(6-(2-methoxyethoxy)pyridin-3-yl)-2-((3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



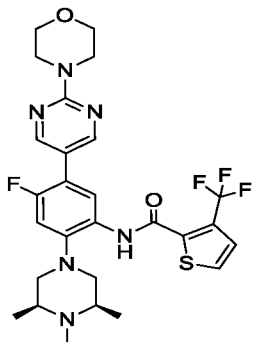
[00503] The title compound (grey solid, 41.2 mg, 67%) was prepared similar to the Suzuki coupling procedure described in Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (56 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (s, IH), 8.47 (d, *J*=8.2 Hz, IH), 8.35 (s, IH), 7.87 (s, IH), 7.78 (br d, *J*=8.7 Hz, IH), 7.02 (d, *J*=10.4 Hz, IH), 6.97 (s, IH), 6.88 (d, *J*=8.7 Hz, IH), 4.57 - 4.49 (m, 2H), 3.81 - 3.74 (m, 2H), 3.64 (s, 3H), 3.46 (s, 3H), 2.81 (br d, *J*=11.0 Hz, 2H), 2.64 (br t, *J*=10.8 Hz, 2H), 2.37 - 2.27 (m, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS $[M+H]^+$ 592.4.

Example 210: N-[4-fluoro-5-(2^yrrolidin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



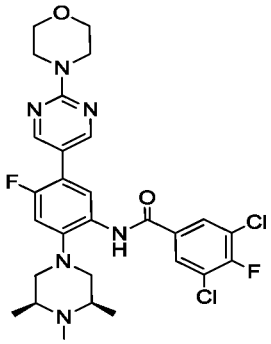
[00504] The title compound (grey solid, 50.6 mg, 84%) was prepared using a procedure similar to Example 29 with N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and 2-(pyrrolidin-l-yl)pyrimidine-5-boronic acid pinacol ester (55 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.72 (s, 1H), 8.54 (s, 2H), 8.45 (d, *J*=8.1 Hz, 1H), 7.88 (s, 1H), 7.01 (d, *J*=10.5 Hz, 1H), 6.97 (s, 1H), 3.68 - 3.60 (m, 7H), 2.80 (br d, *J*=10.9 Hz, 2H), 2.63 (br t, *J*=10.8 Hz, 2H), 2.37 - 2.26 (m, 5H), 2.08 - 1.99 (m, 4H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 588.4.

Example 211: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-(trifluoromethyl)thiophene-2-carboxamide



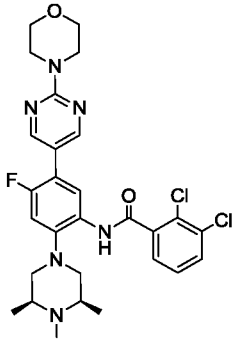
[00505] The title compound (beige solid, 36.1 mg, 62%) was prepared similar to Example 34 using 4-(trifluoromethyl)-l,3-thiazole-5-carboxylic acid (39 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.58 (d, *J*=8.3 Hz, 1H), 8.56 (d, *J*=1.2 Hz, 2H), 7.54 (d, *J*=5.1 Hz, 1H), 7.36 (d, *J*=5.3 Hz, 1H), 7.04 (d, *J*=11.2 Hz, 1H), 3.90 - 3.83 (m, 4H), 3.83 - 3.76 (m, 4H), 2.85 (br d, *J*=10.8 Hz, 2H), 2.65 (t, *J*=10.9 Hz, 2H), 2.46 - 2.37 (m, 2H), 2.34 (s, 3H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 579.3.

Example 212: 3,5-dichloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[00506] The title compound (beige solid, 49.8 mg, 83%) was prepared in a manner similar to that described in Example 34 using 3,5-dichloro-4-fluorobenzoic acid (42 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.25 (s, IH), 8.58 - 8.54 (m, 3H), 7.88 (d, *J*=6.0 Hz, 2H), 7.02 (d, *J*=ll.l Hz, IH), 3.91 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.89 (br d, *J*=11.0 Hz, 2H), 2.71 (t, *J*=10.9 Hz, 2H), 2.47 - 2.40 (m, 2H), 2.38 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^{+}$ 591.3.

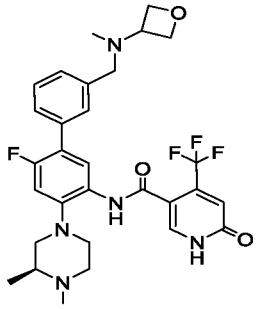
Example 213: 2,3-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJbenzamide



[00507] The title compound (beige solid, 45.5 mg, 77%) was prepared by a procedure similar to that of Example 34 using 2,3-dichlorobenzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.91 (s, IH), 8.63 (d, *J*=8.2 Hz, IH), 8.58 (s, 2H), 7.60 (dd, *J*=8.0, 9.1 Hz, IH), 7.61 (dd, *J*=7.9, 12.2Hz, IH), 7.36 (t, *J*=7.8 Hz, IH), 7.01 (d, *J*=11.2

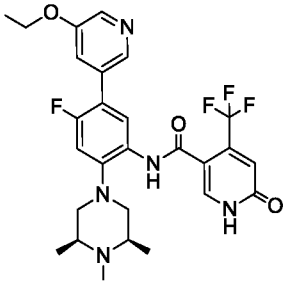
Hz, 1H), 3.91 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.88 (br d, *J*=11.0 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.39 - 2.29 (m, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^+$ 573.3.

Example 214: N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)aminoJmethylJphenylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



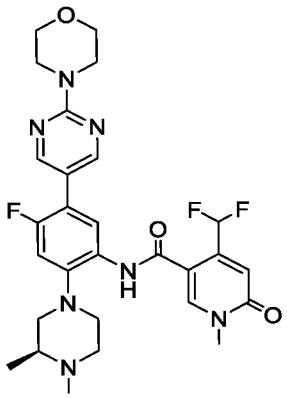
[00508] (S)-N-(4-(3,4-dimethylpiperazin-l -yl)-6-fluoro-3'-formyl-[1,Γ-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (116 mg, 0.225 mmol), (S)-N-(4-(3,4-dimethylpiperazin-l-yl)-6-fluoro-3'-formyl-[l, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (116 mg, 0.225 mmol) and acetic acid, glacial, 99.8% (53.9 mg, 0.898 mmol) were mixed in anhydrous DCE. A cloudy solution was obtained. After 5-10 min, Sodium triacetoxyborohydride (143 mg, 0.674 mmol) was added and the reaction mixture was stirred at RT overnight. LCMS showed complete disappearance of the starting material and formation of the desired product. The reaction mixture was quenched with sat aq NaHCCb solution. The organic phase was separated, the aqueous phase was extracted with DCM, the combined organic phase was washed with brine, then dried over Na_2S04 and concentrated to obtain the crude. The product was purified using silica gel chromatography (4 G column), eluting with DCM containing 0-6 % DCM. The appropriate fractions were combined and concentrated to afford the desired product as a white foam (71 mg, 51% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.25 - 8.19 (m, 1H), 7.95 - 7.87 (m, 1H), 7.86 - 7.79 (m, 1H), 7.44 - 7.41 (m, 1H), 7.40 - 7.37 (m, 1H), 7.37 - 7.32 (m, 1H), 7.29 - 7.24 (m, 1H), 7.07 - 7.01 (m, 1H), 6.86 - 6.81 (m, 1H), 4.56 - 4.51 (m, 2H), 4.50 - 4.45 (m, 2H), 3.70 - 3.58 (m, 1H), 3.47- 3.39 (m, 2H), 3.31 - 3.25 (m, 1H), 3.18 - 3.10 (m, 2H), 3.04 - 2.91 (m, 3H), 2.78 - 2.68 (m, 1H), 2.68 - 2.58 (m, 3H), 2.09 - 1.98 (m, 3H), 1.24 -1.21 (m, 3H); LCMS [M+H]+ 588.

Example 215: N-[5-(5-ethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



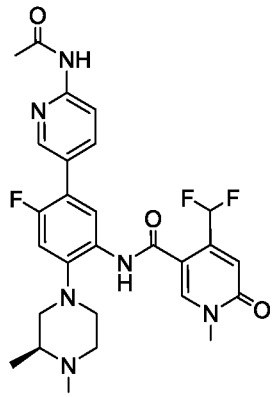
[00509] The procedure was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (30 mg, 0.050 mmol), 3-(Cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (27.3 mg, 0.099 mmol) to give the intermediate N-(5-(5-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide which was deprotected by TFA and purified by standard methods to give the title compound (5.0 mg, Yield = 71% for the last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.22 - 8.17 (m, 1H), 8.16 - 8.08 (m, 1H), 7.93 - 7.88 (m, 1H), 7.87 - 7.80 (m, 1H), 7.50 - 7.44 (m, 1H), 7.10 - 7.00 (m, 1H), 6.86 - 6.79 (m, 1H), 3.90 - 3.83 (m, 2H), 3.16 - 3.08 (m, 2H), 3.01 - 2.81 (m, 2H), 2.73 - 2.65 (m, 2H), 2.63 - 2.43 (m, 3H), 1.23 - 1.18 (m, 7H), 0.59 - 0.52 (m, 2H), 0.33 - 0.27 (m, 2H); LCMS [M+H]+ 574.6.

Example 216: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

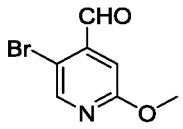


[00510] The title compound was prepared similar to the procedure described above for the preparation of Example 78 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid as the acylating agent. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.40 (s, 1H), 8.45 (s, 2H), 8.23 (s, 1H), 7.67 (d, *J*=8.7 Hz, 1H), 7.02 (d, *J*=12.2 Hz, 1H), 6.80 (s, 1H), 3.71 - 3.66 (m, 4H), 3.63 - 3.59 (m, 4H), 3.46 (s, 3H), 3.01 - 2.91 (m, 2H), 2.78 - 2.66 (m, 2H), 2.35 - 2.27 (m, 2H), 2.20 - 2.09 (m, 4H), 0.90 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 590.3.

Example 217: N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide

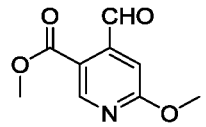


Step 1: 5-bromo-2-methoxyisonicotinaldehyde



[00511] To a solution of DiPA (30.6mL, 212.76mmol, 2eq) in dry THF (100 mL) was added n-BuLi (2.5M in n-hexane, 84.8 mL, 212.76 mmol, 2eq) at -78°C and allowed to warm up to -30°C over 30min. To freshly prepared LDA was added a solution of 5-bromo-2-methoxypyridine Exact Mass: 186.96 (2 X 20 g, 106.38 mmol, leq) in dry THF (400 mL) at -78°C under an argon arm and maintained for 1h at the same temperature before being quenched with DMF (15.7mL, 212.76mmol, 2eq) added dropwise and stirred at the same temperature for 10 mins. TLC analysis indicated formation of polar spots. Then, the reaction mixture was quenched with sat.NH_4Cl (150mL) and extracted with EtOAc (2 X 200 ml) and washed with water and brine. The combined organic layers were dried over Na_2S0_4 and concentrated under reduced pressure to give crude product of 5-bromo-2-methoxypyridine. TLC: 10% EtOAc in pet ether; R_f 0.6

Step 2: methyl 4-formyl-6-methoxynicotinate

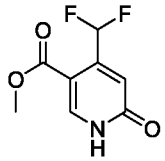


[00512] To a stirred solution of 5-bromo-2-methoxypyridine (2 X 20g, 93.45 mmol, leq) in methanol (200 mL) was added TEA (65.27 ml, 462.27 mmol, 5eq) at RT in a steel bomb degassed with argon for 10 mins, then $Pd_2(dppf)Cl_2DCM$(2.28g, 2.8 mmol, 0.03 eq) was added and the reaction mixture heated to 70°C under 250 Psi (CO gas) for 16 h. TLC analysis indicated formation of polar spots. The reaction mixture was filtered through a celite bed washed with methanol; then the filtrate was evaporated under reduced pressure. The crude compound was purified by silica gel column chromatography (230-400 mesh) using 0-5% EtOAc in pet ether as an eluent to give methyl 4-formyl-6-methoxynicotinate (8.2 g, 43.9%) as an off white solid. TLC system: 20% EtOAc in pet ether; R_f: 0.6.

Step 3: methyl 4-(difluoromethyl)-6-methoxynicotinate

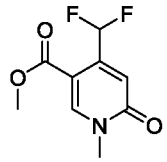
[00513] To a stirred solution of methyl 4-formyl-6-methoxynicotinate (2X8g, 41.0mmol, leq) in DCM (80mL) was added DAST (10.8mL, 81.98mmol, 2eq) at -78°C under argon then slowly warmed to RT and stirred for 16h. TLC analysis indicated formation of less polar spots. The reaction mixture was cooled to 0°C, quenched with satd. aq.$NaHC0_3$ solution, extracted with DCM (2 X 200ml), and washed with water (2 X lOOmL) and brine (2 X lOOmL). The combined organic layers were dried **overNa_2S0_4** and concentrated under reduced pressure to give crude product of methyl 4-(difluoromethyl)-6-methoxynicotinate (8g, crude) as an off white solid. The crude product was used without further purification. TLC: 20% EtOAc in pet ether; R_f: 0.7

Step 4: methyl 4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate



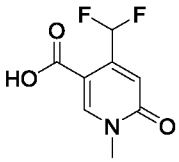
[00514] To a stirred solution of methyl 4-(difluoromethyl)-6-methoxynicotinate (16g, 73.7 mmol, leq) in ACN (160 mL) was added Nal (33.13 g, 22.1 mmol, 2eq) followed by TMS-C1 (28.1 mL, 22.1 mmol, 3 eq) dropwise at rt under argon then slowly warmed to 80°C and stirred for 2h. TLC analysis indicated formation of polar spots. The reaction mixture was cooled to rt and poured into ice water. Isolation of the product gave methyl 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylate (14g, 78.6%) as an off white solid. The crude product was used without further purification. TLC: 70% EtOAc in pet ether; R_f: 0.3

Step 5: methyl 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylate



[00515] To a stirred solution of methyl 4-(difiuoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylate (14 g, 68.96 mmol, leq) in DMF (140 mL) was added Cs_2C0_3 (33.62 g, 103.44 mmol, 1.5eq) followed by CH_3I (4.16 mL, 82.69 mmol, 1.2eq) dropwise at RT under argon then stirred for lh. TLC analysis indicated formation of less polar spots. The reaction mixture was at rt poured into ice water. The solids were collected by suction filtration and dried under vacuum to give methyl 4-(difiuoromethyl)-l -methyl-6-oxo-l ,6-dihydropyridine-3-carboxylate (13g, 87.2%) as an off white solid. The crude product was used without further purification. TLC: 5% EtOAc in pet ether; R_f: 0.6

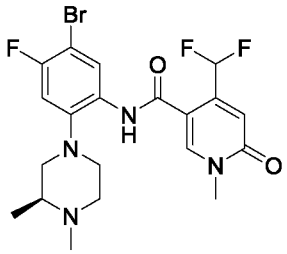
Step 6: 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid



[00516] To a stirred solution of methyl 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylate (13g, 59.9 mmol, leq) in MeOH: THF: H_20 (50mL: 50mL: 30mL) was added LiOH (5.02 g, 119.81 mmol, 2 eq) at RT stirred for 16h. TLC analysis indicated formation of polar spot. The solvent was evaporated under reduced pressure, the reaction mixture was cooled to 0°C, acidified with 2N HC1, extracted with EtOAc (2 X 200mL) and washed with water (2X100mL) and brine

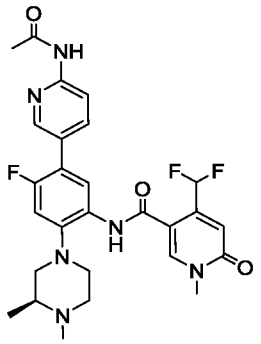
(2X100mL). Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was washed with n-pentane to obtain pure 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (10 g, 82.6%) as an off white solid. LCMS: [M+H]+: 203.95:

Step 7: (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide



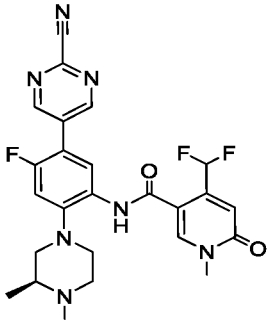
[00517] To a stirred solution of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (8 g, 39.40 mmol, leq) in DMF (80 mL) under argon atm was added DIPEA (21.7mL, 118.2 mmol, 3 eq), HATU (44.9g, 118.2 mmol, 3 eq) and then (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (11.94 g, 39.4 mmol, leq, preparation described in Example 196) at 0°C and then was stirred for 16 h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200mL) and extracted with EtOAc (2 X 500mL). The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% MeOH in EtOAc as an eluent to afford (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l -yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxarnide (5.5g, 50%) as a pale brown solid.; LCMS: [M+H]+ 487.25.

Step 8: N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



[00518] The title compound was prepared through a procedure similar to that described in the final step of Example 100 using 2-acetamidopyridine-5-boronic acid, pinacol ester and (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-moϕ holinopyrirnidin-5-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide to give the title compound which was purified using standard methods. ^{1}H NMR (500 MHz, MeOD) δ 8.47 (s, 1H), 8.30 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.95 (d, *J* = 9.6 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 55.1 Hz, 1H), 7.09 (d, *J* = 12.1 Hz, 1H), 6.82 (s, 1H), 3.65 (s, 3H), 3.14 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.08 (d, *J* = 11.6 Hz, 1H), 2.93 (ddd, *J* = 11.6, 10.0, 2.4 Hz, 2H), 2.52 (ddd, *J* = 14.1, 13.6, 6.3 Hz, 2H), 2.41 - 2.36 (m, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.11 (d, *J* = 6.3 Hz, 3H); LCMS [M+l]+ = 543.30.

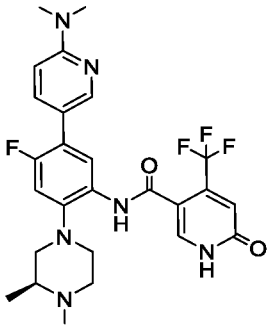
Example 218: N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



[00519] The title compound was prepared using a procedure similar to Example 217 using 2-cyanopyrimidine-5-boronic acid pinacol ester and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide in the final step. ^{1}H NMR (500 MHz, MeOD) δ 9.04 (s, 2H), 8.19 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 55.0 Hz, 1H), 7.07 (d, *J* = 12.6 Hz, 1H), 6.72 (s, 1H), 3.55 (s, 3H), 3.11 (dq, *J* = 11.6, 2.2 Hz, 1H), 3.05 (dt, *J* =

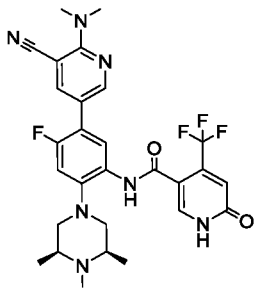
11.9, 2.4 Hz, 1H), 2.86 (t, *J* = 11.6 Hz, 1H), 2.82 (dt, *J* = 11.5, 2.1 Hz, 1H), 2.50 - 2.45 (m, 1H), 2.42 (td, *J* = 11.4, 2.9 Hz, 1H), 2.31 - 2.27 (m, 1H), 2.25 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H); LCMS [M+l]+ = 512.30.

Example 219: N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3 -carboxamide



[00520] The title compound was prepared similar to the sequence described above for the preparation of Example 196 using 6-(dimethylamino)pyridine-3-boronic acid pinacol ester in place of 2-acetamidopyridine-5-boronic acid, pinacol ester. ^{1}H NMR (500 MHz, MeOD) δ 8.25 (s, 1H), 7.96 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.06 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 3.12 (s, 6H), 3.09 (dq, *J* = 11.3, 1.9 Hz, 1H), 3.04 (dt, *J* = 11.5 Hz, 1H), 2.97 - 2.90 (m, 2H), 2.55 (ddd, *J* = 11.4, 10.3, 3.9 Hz, 2H), 2.44 - 2.40 (m, 1H), 2.38 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H); LCMS [M+l]+ = 533.29.

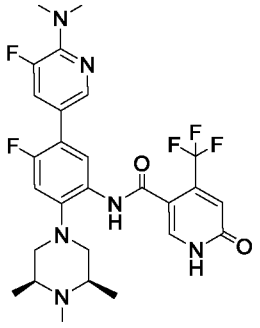
Example 220: N-[5-[5-cyano-6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00521] The procedure was similar to Example 39 using 3-cyano-2-(N,N-dimethylamino)pyridine-5-boronic acid, pinacol ester (0.034 g, 0.125 mmol),N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-

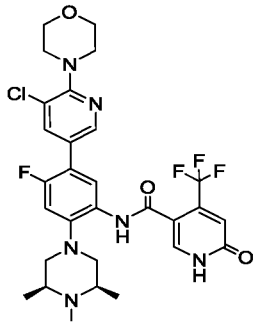
6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.05033 g, 0.083 mmol) to give, after deprotection of the silyloxy coupled product 38.3 mg (77% yield) the title compound. ^{1}H NMR (500 MHz, MeOD) δ 8.49 (s, 1H), 8.04 (d, *J* = 1.8 Hz, 1H), 7.96 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 12.2 Hz, 1H), 6.91 (s, 1H), 3.33 (s, 6H), 3.06 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.57 - 2.51 (m, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l]+ = 572.34.

Example 221: N-[5-[6-(dimethylamino)-5-fluoropyridin-3-yl]-4-fluoro-2-[(3R, 5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



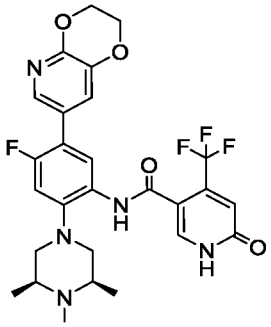
[00522] The title compound was prepared by a procedure similar to that of Example 39 using 2-(N,N-dimethylamino)-3-fluoropyridine-5-boronic acid pinacol ester hydrochloride (0.039 g, 0.129 mmol),N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.05214 g, 0.086 mmol) to give the title compound (14 mg, 29% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.12 (s, 1H), 7.96 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 14.9 Hz, 1H), 7.06 (d, *J* = 12.2 Hz, 1H), 6.91 (s, 1H), 3.13 (d, *J* = 2.0 Hz, 6H), 3.06 (d, *J* = 11.1 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.56 (dt, *J* = 9.8, 6.5 Hz, 2H), 2.38 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.79 (s), -120.46 (s), -131.66 (s); LCMS [M+l]+ = 565.34.

Example 222: N-[5-(5-chloro-6-morpholin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00523] The title compound was prepared similar to the sequence described above for the preparation of Example 39 using 5-chloro-6-mo ϕ holinopyridin-3-ylboronic acid (0.032 g, 0.130 nimol),N-(5¾omo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(†jimethylsilyl)ethoxy)nicotinamide (0.0525 1 g, 0.087 mmol) to give the title compound (14 mg, 26% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.37 (s, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 3.87 - 3.84 (m, 4H), 3.41 - 3.39 (m, 4H), 3.07 (d, *J* = 11.2 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.55 (dd, *J* = 12.6, 6.7 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l]+ = 623.27.

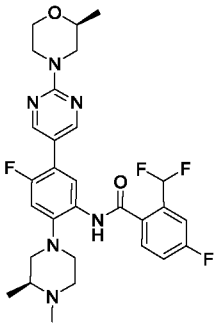
Example 223: N-[5-(2, 3-dihydro-[l ,4]dioxino[2, 3-bJpyridin- 7-yl)-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00524] The procedure used was similar to Example 39 except using 7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2,3-dihydro-[l,4]dioxino[2,3-b]pyridine (0.033 g, 0.125 mmol) and N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(†jifluoromethyl)-6-(2-(†jimethylsilyl)ethoxy)nicotinamide (0.05027 g, 0.083 mmol) to give after deprotection of the silyloxy coupled intermediate the title compound (41 mg, 85% yield). ¾ NMR (500 MHz, MeOD) δ 7.95 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.50 (s,

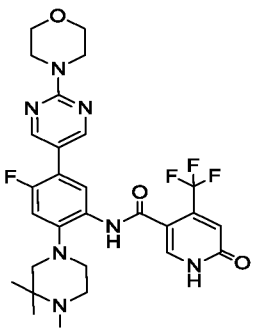
1H), 7.07 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 4.49 (dd, *J* = 5.0, 3.1 Hz, 2H), 4.33 (dd, *J* = 5.0, 3.1 Hz, 2H), 3.07 (d, *J* = 11.2 Hz, 2H), 2.62 (t, *J* = 11.1 Hz, 2H), 2.56 (dt, *J* = 9.6, 6.2 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+H]+ = 562.26.

Example 224: 2-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-((S)-2-methylmorpholino)pyrimidin-5-yl)phenyl)-4-fluorobenzamide

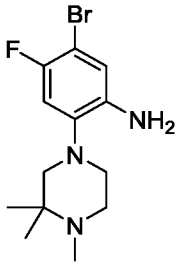


[00525] The title compound (formic acid salt, white solid, 46.9 mg, 41%) was prepared according to a procedure similar to Example 31 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.555 mmol + 0.278 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-2-(difluoromethyl)-4-fluorobenzamide (prepared as described in Example 62) in dioxane (0.185 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (br s, 2H), 8.36 (br dd, *J*=1.7, 2.8 Hz, 1H), 7.96 (br d, *J*=8.1 Hz, 1H), 7.93 - 7.87 (m, 1H), 7.56 (br d, *J*=9.3 Hz, 1H), 7.50 - 7.26 (m, 2H), 7.19 (d, *J*=11.9 Hz, 1H), 4.65 - 4.54 (m, 2H), 3.99 (br d, *J*=11.6 Hz, 1H), 3.68 - 3.58 (m, 2H), 3.48 - 3.38 (m, 1H), 3.31 - 3.25 (m, 2H), 3.22 - 3.04 (m, 4H), 2.94 - 2.83 (m, 1H), 2.82 - 2.71 (m, 4H), 1.37 - 1.30 (m, 3H), 1.25 (d, *J*=6.1 Hz, 3H); LCMS $[M + H]^+$ 573.3

Example 225: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-(3,3,4-trimethylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

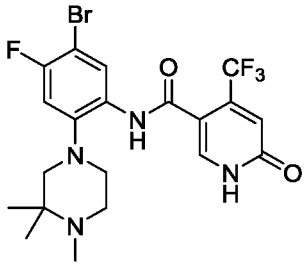


Step 1: Preparation of 5-bromo-4-fluoro-2-(3,3,4-trimethylpiperazin-l-yl)aniline



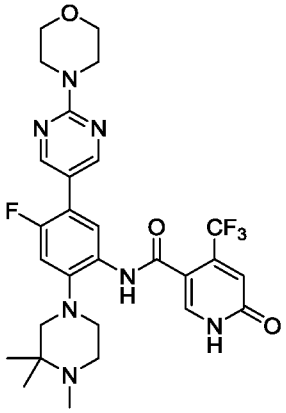
[00526] To a suspension of K2CO 3 (566 mg, 4.09 mmol, 0.525 equiv.) in toluene (20 mL) was added 1,2,2-trimethyl-piperazine (1.00 g, 7.8 mmol), followed by dropwise addition of a solution of 1-bromo-2,4-difluoro-5 -nitrobenzene (0.98 mL, 7.8 mmol) in toluene (3 mL) over 2 min. The resulting mixture was stirred at rt for 30 min, then 45 °C for 1.5 h resulting in an abundance of yellow precipitate. After diluting with H_20 (20 mL) to dissolve the insoluble salts, it was extracted with EtOAc (20 mL x 2). The combined extracts were concentrated and dried under vacuum to give the nitro intermediate as an orange red oil. LCMS $[M + H]^+$ 346.2. To a solution of the above orange oil in MeOH (30 mL) was added a suspension of Raney-Nickel (334 mg, 3.9 mmol) in MeOH (5 mL), followed by hydrazine monohydrate (1.14 mL, 23.4 mmol) dropwise over 2 min. After addition, the reaction mixture was stirred at rt for 30 min. Additional Raney-Nickel (334 mg, 3.9 mmol) in MeOH (5 mL) and hydrazine monohydrate (1.14 mL, 23.4 mmol) were added, followed by THF (15 mL) to make a clear solution. The resulting mixture was heated at 60 °C for 30 min. Additional THF (10 mL) and hydrazine monohydrate (0.38 mL, 7.8 mmol) were added and it was heated at 60 °C for 30 min. After filtration, the filtrate was concentrated to give a dark brown liquid which was purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-10%) to give the title compound as a beige solid (1.796 g, 68%). LCMS $[M + H]^+$ 316.2.

Step 2: Preparation of N-(5-bromo-4-fluoro-2-(3,3,4-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



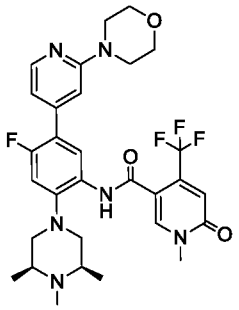
[00527] The title compound (beige solid, 1.303 g, 70%) was prepared by a method similar to that of Example 29 Step 3 using 5-bromo-4-fluoro-2-(3,3,4-trimethylpiperazin-l-yl)aniline. LCMS $[M+H]^+$ 505.2.

Step 3: Preparation of N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(3,3,4-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide

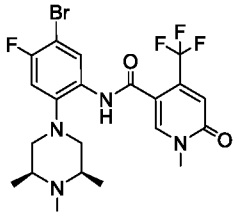


[00528] The title compound (white solid, 36.3 mg, 61%) was prepared using a procedure similar to the final step of Example 31 using N-(5-bromo-4-fluoro-2-(3,3,4-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.09 (s, IH), 7.91 (br d, *J*=8.2 Hz, IH), 7.13 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 3.88 - 3.82 (m, 4H), 3.80 - 3.74 (m, 4H), 3.10 - 2.99 (m, 2H), 2.85 - 2.75 (m, 2H), 2.70 (s, 2H), 2.33 (s, 3H), 1.13 (s, 6H); LCMS $[M+H]^+$ 590.3.

Example 226: N-[4-fluoro-5-(2-morpholin-4-ylpyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

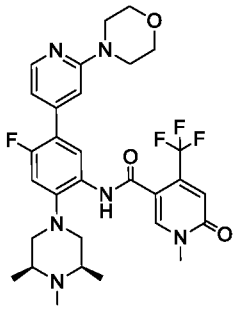


Step 1: N-(5-bromo-4-fluoro-2-((3S,5RJ-3,4,5-trimethylpiperazin-l -yl)phenyl)-l -methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



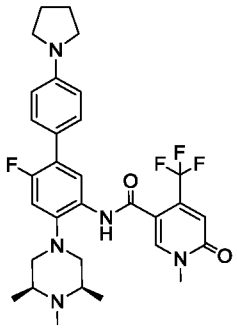
[00529] To a stirred solution of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (2.1g, 9.50mmol, leq, from Example 93) in DMF (30 mL) was added HATU (10.83 g, 28.50 mmol, 3eq) at 0°C under argon atmosphere followed by DIPEA (5.2mL, 28.50mmol, 3eq) and stirred for 15 min at the same temp. Then, 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (2.99g, 9.50mmol, leq) was added at 0°C and allowed to remain at RT over 32h. TLC analysis indicated formation of polar spot. The reaction mixture was diluted with water (300mL) and extracted with DCM (3X100mL). The organic layer was washed with water (2X200mL) and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography (Neutral Alumina) using 0-30% EtOAc in Methanol as an eluent and gave (1.5g, 30.48%) as an off white solid. LCMS: [M+H]+ 221.95.

Step 2: N-[4-fluoro-5-(2-morpholin-4-ylpyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpipemzin-l-yl]phenylJ-l-methyl-6<>xo-4-(trifluoromethyl)pyridme-3-carboxamide



[00530] The title compound (white solid, 21.2 mg, 35%) was prepared according to a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and 2-morpholinopyridine-4-boronic acid, pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.68 (s, 1H), 8.51 (d, *J*=8.1 Hz, 1H), 8.25 (d, *J*=5.1 Hz, 1H), 7.88 (s, 1H), 7.01 (d, *J*=11.4 Hz, 1H), 6.99 - 6.97 (m, 1H), 6.88 (d, *J*=5.1 Hz, 1H), 6.80 (s, 1H), 3.89 - 3.82 (m, 4H), 3.65 (s, 3H), 3.59 - 3.53 (m, 4H), 2.82 (br d, *J*=10.9 Hz, 2H), 2.64 (br t, *J*=10.9 Hz, 2H), 2.37 - 2.27 (m, 5H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^{+}$ 603.4.

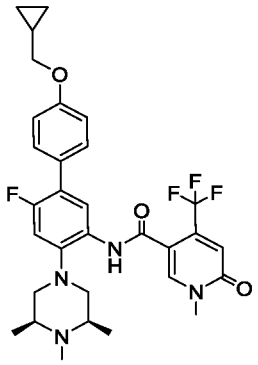
Example 227: N-[4-fluoro-5-(4^yrrolidin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenylJ-l-methyl-6<>xo-4-(trifluoromethyl)pyridme-3-carboxamide



[00531] The title compound (yellow solid, 37.5 mg, 64%) was prepared by a procedure similar to that of Example 29 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and l-[4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine (55 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.72 (s, 1H), 8.48 (d, *J*=8.3 Hz, 1H), 7.86 (s, 1H), 7.48 (br d,

J=7.5 Hz, 2H), 7.01 - 6.94 (m, 2H), 6.62 (d, *J*=8.7 Hz, 2H), 3.64 (s, 3H), 3.34 (br t, *J*=6.4 Hz, 4H), 2.81 (br d, *J*=\ 1.0 Hz, 2H), 2.64 (br t, *J*=10.9 Hz, 2H), 2.36 - 2.27 (m, 5H), 2.07 - 1.99 (m, 4H), 1.13 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 586.3.

Example 228: N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

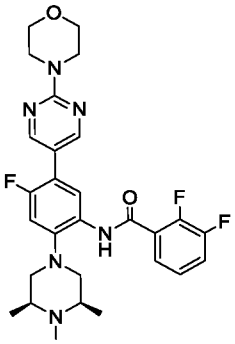


[00532] The title compound (white solid, 37.0 mg, 63%) was prepared in a manner similar to Example 31 using N-(5-bromo-4-fiuoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and 4-(cyclopropylmethoxy)phenylboronic acid (38 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (s, 1H), 8.47 (d, *J*=8.3 Hz, 1H), 7.86 (s, 1H), 7.51 (d, *J*=7.6 Hz, 2H), 7.01 - 6.95 (m, 4H), 3.85 (d, *J*=6.8 Hz, 2H), 3.64 (s, 3H), 2.81 (br d, *J*=10.9 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.35 - 2.28 (m, 5H), 1.35 - 1.25 (m, 1H), 1.13 (d, *J*=6.2 Hz, 6H), 0.70 - 0.63 (m, 2H), 0.40 - 0.35 (m, 2H); LCMS [M + H]$^+$ 587.4.

Example 229: 2,3-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJbenzamide

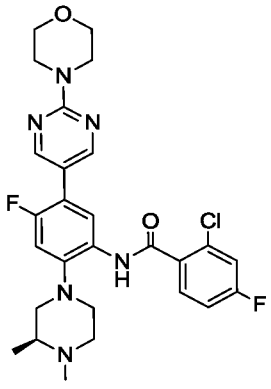
[00533] The title compound (white solid, 37.0 mg, 63%) was prepared through a procedure similar to that of Example 31 using N-(5-bromo-4-fiuoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (51.9 mg, 0.1 mmol) and 4-(cyclopropylmethoxy)phenylboronic acid (38 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (s, 1H), 8.47 (d, *J*=8.3 Hz, 1H), 7.86 (s, 1H), 7.51 (d, *J*=7.6 Hz, 2H), 7.01 - 6.95 (m, 4H), 3.85 (d, *J*=6.8 Hz, 2H), 3.64 (s, 3H), 2.81 (br d,

J=10.9 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.35 - 2.28 (m, 5H), 1.35 - 1.25 (m, 1H), 1.13 (d, *J*=6.2 Hz, 6H), 0.70 - 0.63 (m, 2H), 0.40 - 0.35 (m, 2H); LCMS $[M + H]^+$ 587.4.



[00534] The title compound (light beige solid, 46.8 mg, 84%) was prepared in a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2,3-difluorobenzoyl chloride (19 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.74 (br d, *J*=12.1 Hz, 1H), 8.72 (d, *J*=8.2 Hz, 1H), 8.58 (s, 2H), 7.95 (t, *J*=7.2 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.26 (m, 1H), 7.04 (d, *J*=11.4 Hz, 1H), 3.90 - 3.86 (m, 4H), 3.82 - 3.79 (m, 4H), 2.89 (br d, *J*=10.9 Hz, 2H), 2.67 (t, *J*=10.8 Hz, 2H), 2.55 - 2.46 (m, 2H), 2.38 (s, 3H), 1.16 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 541.3.

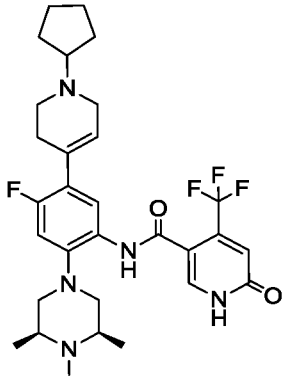
Example 230: 2-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[00535] The title compound (light beige solid, 23.6 mg, 70%) was prepared by a procedure similar to that of Example 78 using (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrirnidin-5-yl)aniline (23 mg, 0.06 mmol) and 2-chloro-4-fluorobenzoylchloride (12 μL, 0.09 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ =

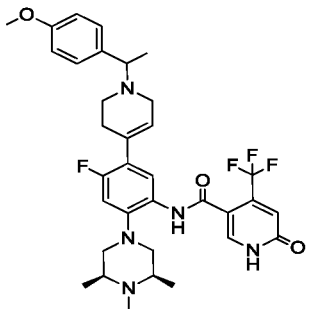
9.20 (s, IH), 8.68 (d, *J*=8.2 Hz, IH), 8.59 (s, 2H), 7.85 (dd, *J*=6.0, 8.7 Hz, IH), 7.25 (dd, *J*=2.4, 8.3 Hz, IH), 7.15 (t, *J*=8.2 Hz, IH), 7.04 (d, *J*=11.2 Hz, IH), 3.91 - 3.86 (m, 4H), 3.82 - 3.78 (m, 4H), 3.01 - 2.85 (m, 4H), 2.60 (t, *J*=10.6 Hz, IH), 2.42 (dt, *J*=3.2, 11.0 Hz, IH), 2.35 (s, 3H), 2.26 (br s, IH), 1.09 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 543.4.

Example 231: N-[5-(l-cyclopentyl-3, 6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^oxamide



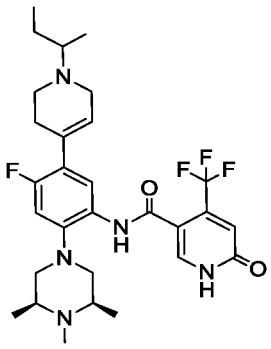
[00536] The procedure used was similar to Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (34 mg, 0.057 mmol) and cyclopentanone (7.59 µï, 0.085 mmol) to give, after isolation of the product combined and concentrated to afford the title compound as a yellow powder (28 mg, 77% yield) of the title compound. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.02 - 7.93 (m, IH), 7.84 - 7.75 (m, IH), 6.98 - 6.92 (m, IH), 6.91 - 6.87 (m, IH), 6.09 - 5.99 (m, IH), 3.43 - 3.38 (m, 2H), 3.07 - 2.99 (m, 2H), 2.97 - 2.90 (m, 2H), 2.89 - 2.81 (m, IH), 2.68 - 2.62 (m, 2H), 2.62 - 2.56 (m, 2H), 2.56 - 2.49 (m, 2H), 2.39 - 2.36 (m, 3H), 2.09 - 2.01 (m, 2H), 1.83 - 1.75 (m, 2H), 1.71 - 1.63 (m, 2H), 1.61 - 1.52 (m, 2H), 1.18 - 1.15 (m, 6H); LCMS [M+H]+ 576.5

Example 232: N-[4-fluoro-5-[l-[l-(4-methoxyphenyl)ethyl]-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00537] The procedure used was similar to that of Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (40 mg, 0.067 mmol), 4'-methoxyacetophenone 99% (15.09 mg, 0.100 mmol) and Titanium(IV) isopropoxide (0.060 ml, 0.201 mmol) which were mixed in anhydrous THF. The reaction mixture was heated at 75°C for 6h. The reaction mixture was then cooled to RT and EtOH (2 ml) and sodium borohydride (10.14 mg, 0.268 mmol) were added in sequence. The mixture was then allowed to stir at room temperature for 16 h. The workup and isolation using standard methods provided the title compound (7 mg, 14% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 - 7.84 (m, 1H), 7.77 - 7.68 (m, 1H), 7.43 - 7.31 (m, 2H), 7.04 - 6.92 (m, 3H), 6.85 - 6.78 (m, 1H), 5.98 - 5.87 (m, 1H), 4.46 - 4.36 (m, 1H), 3.86 - 3.76 (m, 1H), 3.76 - 3.72 (m, 3H), 3.71 - 3.63 (m, 1H), 3.47 - 3.26 (m, 4H), 3.19 - 3.12 (m, 2H), 2.89 - 2.81 (m, 2H), 2.80 - 2.77 (m, 3H), 2.76 - 2.69 (m, 2H), 1.73 - 1.65 (m, 3H), 1.30 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+ 642.6

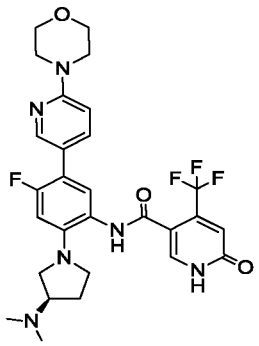
Example 233: N-[5-(l-butan-2-yl-3, 6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



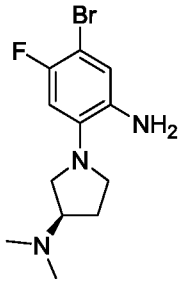
[00538] The procedure was similar to Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-

oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-butanone (7.94 µï, 0.089 mmol) to give the title compound (9 mg, 24 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.83 - 8.30 (m, 2H), 7.93 (br s, 1H), 7.90 - 7.80 (m, 1H), 7.03 (br d, *J*=12.3 Hz, 1H), 6.94 (br s, 1H), 6.09 (br s, 1H), 3.90 (br s, 2H), 3.58 - 3.41 (m, 3H), 3.15 - 3.05 (m, 2H), 2.95 - 2.84 (m, 2H), 2.83 - 2.73 (m, 2H), 2.72 - 2.63 (m, 2H), 2.51 (s, 3H), 2.02 - 1.88 (m, 1H), 1.73 - 1.61 (m, 1H), 1.44 - 1.38 (m, 3H), 1.28 - 1.21 (m, 6H), 1.13 - 1.05 (m, 3H); LCMS [M+H]+ 564.5

Example 234: N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3RJ-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-6<>xo-4-(trifluommethyl)-1H-pyridine-3-carboxamide

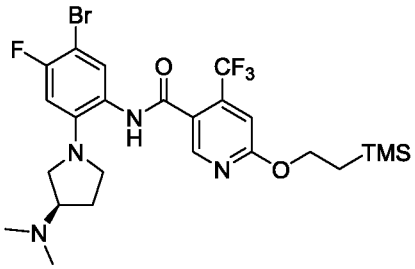


Step 1: (R)-l-(2-amino-4-bromo-5-fluorophenyl)-N,N-dimethylpyrrolidin-3-amine



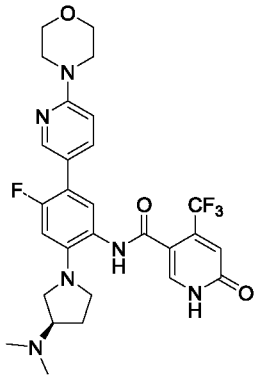
[00539] A mixture of (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3 -amine (0.65 g, 2.0 mmol) and $SnCl_2$ (0.93 g, 4.9 mmol) in EtOH (8 mL) was heated to 75 °C 4 h. After cooling to room temperature the reaction mixture was concentrated onto celite. Purification by flash chromatography [1-20% MeOH/DCM] afforded (R)-l-(2-amino-4-bromo-5-fluorophenyl)-N,N-dimethylpyrrolidin-3 -amine (0.61 g, 95 %). LCMS [M+H]+: 302.3.

Step 2: (R)-N-(5-bromo-2-(3-(dimethylamino)pyrrolidin-l -yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00540] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.30 g, 0.99 mmol) was activated with HATU (0.38 g, 0.99 mmol) and N,N-diisopropylethylamine (0.36 mL, 2.1 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a solution of (R)-l-(2-amino-4-bromo-5-fluorophenyl)-N,N-dimethylpyrrolidin-3-amine (0.250 g, 0.827 mmol) in DMF (3 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction was partitioned between H_20 and DCM. The layers were separated and the aqueous layer was extracted with an additional portion of DCM. The combined organics were washed with water, IN NaOH (Aq.), brine and dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [0-5% MeOH/DCM] afforded (R)-N-(5-bromo-2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.12 g, 24 %). LCMS [M+H]+: 591.2.

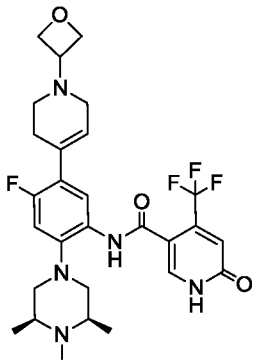
Step 3: (R)-N-(2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluoro-5-(6-morpholinopyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00541] A microwave vial was charged with (R)-N-(5-bromo-2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-

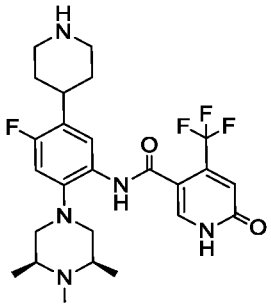
(trimethylsilyl)ethoxy)nicotinamide (0.058 g, 0.098 mmol), 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo rpholine (0.043 g, 0.15 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.007 g, 0.01 mmol) and K_3PO4 (0.042 g, 0.20 mmol). The vial was sealed with a septum cap and evacuated and backfilled with nitrogen. 1,4-Dioxane (1.5 mL) and H_20 (0.15 mL) were added via syringe and the vial was evacuated and backfilled with nitrogen an additional time. The reaction was irradiated to 110 °C for 1.5 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH4OH] afforded the silyl protected biaryl as a clear amber film. The silyl protected product of the Suzuki coupling was dissolved in DCM (2 mL) and treated with trifluoroacetic acid (0.75 mL) at room temperature. After stirring for 1 h at room temperature the volatiles were removed in vacuo and the pure product was isolated by a catch and release protocol using a PoraPak Rxn CX ion exchange cartridge. Lyophilization afforded the title compound (R)-N-(2-(3-(dimethylamino)pyrrolidin-l-yl)-4-fluoro-5-(6-mo rpholinopyridin-3-yl)phenyl)-6-oxo-4- trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.017 g, 30%). ¾ NMR (500MHz, DMSO-d6) δ = 9.71 (s, 1H), 8.18 (s, 1H), 7.89 (br s, 1H), 7.59 (br d, J=9.7 Hz, 1H), 7.21 (br d, J=8.8 Hz, 1H), 6.84 (d, J=8.9 Hz, 1H), 6.71 (s, 1H), 6.58 (d, J=14.2 Hz, 1H), 3.66 - 3.62 (m, 4H), 3.42 - 3.38 (m, 4H), 3.34 - 3.30 (m, 2H), 3.17 (br d, J=8.4 Hz, 1H), 2.08 (s, 6H), 2.03 - 1.96 (m, 1H), 1.63 (quin, J=9.9 Hz, 1H); LCMS [M+H]+: 575.3.

Example 235: N-[4-fluoro-5-[l-(oxetan-3-yl)-3, 6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

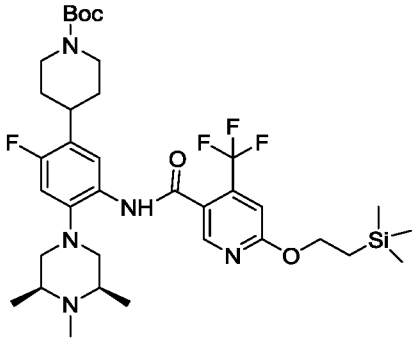


[00542] The procedure used was similar to that of Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (33 mg, 0.055 mmol), and oxetan-3-one (4.18 mg, 0.058 mmol) to give after workup the title compound (31 mg, 95% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.93 (s, 1H), 7.79 (br d, *J*=7.9 Hz, 1H), 6.97 - 6.94 (m, 1H), 6.92 (s, 1H), 6.03 (br s, 1H), 4.78 - 4.67 (m, 4H), 3.70 (t, *J*=6.5 Hz, 1H), 3.16 - 3.08 (m, 2H), 3.04 (br d, *J*=9.8 Hz, 2H), 2.65 - 2.55 (m, 8H), 2.40 (s, 3H), 1.21 - 1.16 (m, 6H); LCMS [M+H]+ 564.6

Example 236: N-[4-fluoro-5-piperidin-4-yl-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



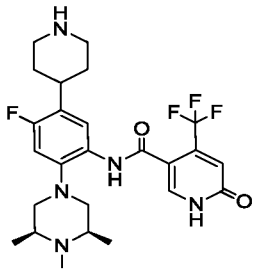
Step 1: tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)piperidine-l-carboxylate



[00543] A solution of tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2 (trimethylsilyl) ethoxy) nicotinamido)-4-((3 S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-5,6-dihydropyridine-l(2H)-carboxylate (310 mg, 0.438 mmol) in MeOH was subjected to hydrogenation using palladium on carbon, 10% catalyst cartridge at RT, under 1 atm. pressure, on an H-cube. The mixture was concentrated to dryness to

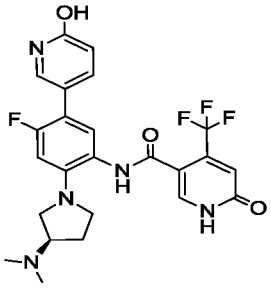
afford a white foam (301 mg, 97 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.47 - 8.35 (m, 1H), 7.77 - 7.66 (m, 1H), 7.07 - 6.99 (m, 1H), 6.89 - 6.78 (m, 1H), 4.51 - 4.42 (m, 2H), 4.18 - 4.07 (m, 2H), 2.97 - 2.90 (m, 1H), 2.89 - 2.85 (m, 2H), 2.84 - 2.67 (m, 2H), 2.52 - 2.42 (m, 2H), 2.40 - 2.31 (m, 2H), 2.26 - 2.20 (m, 3H), 1.77 - 1.66 (m, 2H), 1.62 - 1.51 (m, 2H), 1.40 - 1.37 (m, 9H), 1.11 - 1.07 (m, 2H), 1.05 - 1.02 (m, 6H), 0.05 - 0.04 (m, 9H); LCMS [M+H]+ 710.6.

Step 2: N-(4-fluoro-5-(piperidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



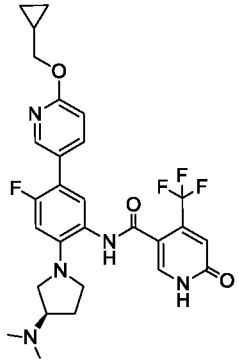
[00544] TFA (2 ml) was added to a solution of tert-butyl 4-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)piperidine-l-carboxylate in DCM (6 ml) at RT and the reaction mixture was stirred at RT for 10 min. The mixture was concentrated to dryness, then the residue was dissolved in MeOH and passed through a cation exchange resin cartridge (Porapak Rxn CX 20 cc). The desired product as a free base was isolated as an off white powder. (210 mg, 94 %). ¾ NMR (500MHz, METHANOL-d4) δ = 8.10 (s, 1H), 7.86 (br d, *J*=7.7 Hz, 1H), 7.00 - 6.94 (m, 1H), 6.78 - 6.72 (m, 1H), 3.44 - 3.39 (m, 2H), 3.21 - 3.11 (m, 1H), 3.09 - 3.01 (m, 2H), 3.01 - 2.95 (m, 2H), 2.60 - 2.54 (m, 2H), 2.53 - 2.47 (m, 2H), 2.39 - 2.34 (m, 3H), 2.04 - 1.98 (m, 2H), 1.96 - 1.86 (m, 2H), 1.15 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 510.5.

Example 237: N-[4-fluoro-5-(5-hydroxypyridin-3-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-6-oxo-4-(rifluoromethyl)-lH-pyridine-3-carboxamide



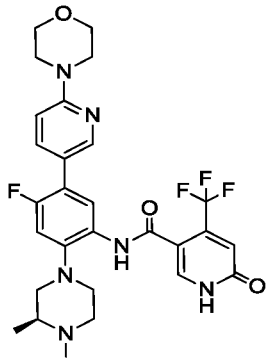
[00545] Examples 237 and 238 were isolated from a single reaction performed using a procedure similar to Example 234 Step 3 using 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine in place of 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo ϕ holine and separating the two products by chromatography. ¾ NMR (500MHz, DMSO-d6) δ = 11.81 - 11.62 (m, IH), 9.66 (br s, IH), 8.00 (br s, IH), 7.61 - 7.55 (m, IH), 7.42 (br s, IH), 7.21 (br d, *J*=8.9 Hz, IH), 6.68 - 6.59 (m, *J*=14.2 Hz, 2H), 6.41 (d, *J*=9.5 Hz, IH), 3.24 - 3.19 (m, IH), 2.14 (s, 6H), 2.09 - 2.03 (m, IH), 1.73 - 1.64 (m, IH), 1.23 (s, IH); LCMS [M+H]+: 506.2

Example 238: N-[5-[6-(cyclopropylmethoxy)pyridin-3-ylJ-4-fluoro-2-[(3R)-3-(dimethylamino)pyrrolidin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



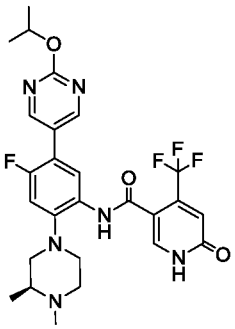
[00546] ¾ NMR (500MHz, DMSO-d6) δ = 12.54 (br s, IH), 9.77 (br s, IH), 8.22 (s, IH), 7.97 (br s, IH), 7.78 (br d, *J*=8.2 Hz, IH), 7.29 (br d, *J*=8.7 Hz, IH), 6.89 (d, *J*=8.6 Hz, IH), 6.74 (br s, IH), 6.66 (d, *J*=14.2 Hz, IH), 4.12 (d, *J*=7.1 Hz, 2H), 3.42 - 3.37 (m, 4H), 3.26 - 3.21 (m, IH), 2.15 (s, 6H), 2.09 - 2.03 (m, IH), 1.74 - 1.64 (m, IH), 1.29 - 1.22 (m, IH), 0.58 - 0.53 (m, 2H), 0.36 - 0.31 (m, 2H); LCMS [M+H]+: 560.3.

Example 239: N-[4-fluoro-5-(5-morpholin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl] -6-oxo-4-(rifluoromethyl)-lH-pyridine-3-carboxamide



[00547] The procedure used was similar that used in the last step of Example 196 using 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-morpholine (0.040 g, 0.138 mmol),(S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.05432 g, 0.092 mmol) to give 18 mg (34% yield) of the title compound. ^{1}H NMR (500 MHz, MeOD) δ 8.31 (s, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 3.83 - 3.79 (m, 4H), 3.55 - 3.52 (m, 4H), 3.11 (d, *J* = 11.7 Hz, 1H), 3.06 (d, *J* = 11.4 Hz, 1H), 2.96 (dd, *J* = 20.2, 10.7 Hz, 2H), 2.60 (dd, *J* = 21.9, 11.5 Hz, 2H), 2.50 (s, 1H), 2.42 (s, 3H), 1.15 (d, *J* = 6.2 Hz, 3H); LCMS [M+l]+ = 575.42.

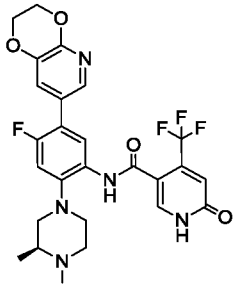
Example 240: N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine -3-carboxamide



[00548] The title compound (18 mg, 38% yield) was prepared similar to the sequence described above for the preparation of Example 196 using (2-isopropoxypyrimidin-5-yl)boronic acid (0.024 g, 0.130 mmol),(S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.05144 g, 0.087 mmol). ^{1}H NMR (500 MHz,

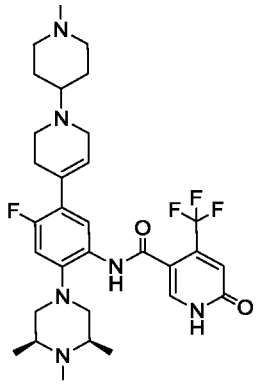
MeOD) δ 8.73 (s, 2H), 7.97 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.14 (d, *J* = 12.0 Hz, 1H), 6.91 (s, 1H), 5.37 (sep, *J* = 6.2 Hz, 1H), 3.11 (dd, *J* = 26.9, 10.8 Hz, 2H), 2.96 (t, *J* = 8.9 Hz, 2H), 2.59 (t, *J* = 10.7 Hz, 2H), 2.47 (s, 1H), 2.40 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); LCMS [M+l]+ = 549.09.

Example 241: N-[5-(2,3-dihydro-[l,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



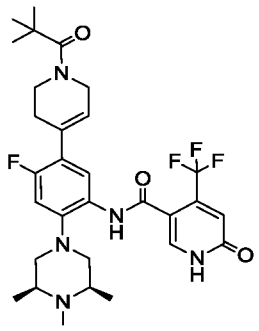
[00549] The title compound (22.5 mg, 45% yield) was prepared similar to the sequence described above for the preparation of Example 196 using 7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2,3-dihydro-[l,4]dioxino[2,3-b]pyridine (0.035 g, 0.132 mmol),(S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.05200 g, 0.088 mmol). ^{1}H NMR (500 MHz, MeOD) δ 7.97 (s, 1H), 7.92 - 7.89 (m, 2H), 7.49 (s, 1H), 7.09 (d, *J* = 12.1 Hz, 1H), 6.91 (s, 1H), 4.49 (dd, *J* = 5.0, 3.1 Hz, 2H), 4.33 (dd, *J* = 4.9, 3.1 Hz, 2H), 3.13 (d, *J* = 11.7 Hz, 1H), 3.08 (d, *J* = 11.5 Hz, 1H), 2.97 (dd, *J* = 19.7, 10.3 Hz, 2H), 2.61 (dd, *J* = 21.5, 11.1 Hz, 2H), 2.51 (s, 1H), 2.42 (s, 3H), 1.15 (d, *J* = 6.2 Hz, 3H); LCMS HSS [M+l]+ = 548.26.

Example 242: N-[4-fluoro-5-[l-(l-methylpiperidin-4-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00550] A procedure similar to that of Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (40 mg, 0.067 mmol), N-methyl-4-piperidone 97% (0.012 ml, 0.100 mmol) gave the title compound (14 mg, 31 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.79 (m, 1H), 7.71 - 7.61 (m, 1H), 6.85 - 6.80 (m, 1H), 6.80 - 6.77 (m, 1H), 5.99 - 5.86 (m, 1H), 3.29 - 3.25 (m, 2H), 3.07 - 3.01 (m, 2H), 2.93 - 2.86 (m, 2H), 2.82 - 2.75 (m, 2H), 2.53 - 2.40 (m, 7H), 2.38 - 2.31 (m, 3H), 2.30 - 2.23 (m, 5H), 1.99 - 1.89 (m, 2H), 1.67 - 1.58 (m, 2H), 1.07 - 1.03 (m, 6H); LCMS [M+H]+ 605.5.

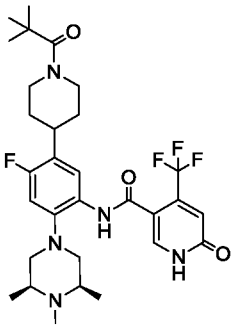
Example 243: N-[5-[1-(2,2-dimethylpropanoyl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00551] To a solution of N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (27 mg, 0.053 mmol) and N,N-diisopropylethylamine (10.66 µï, 0.061 mmol) in DCM (3 ml) at RT was added trimethylacetyl chloride (6.87 µï, 0.056 mmol). After 10 min, the reaction mixture was quenched with water

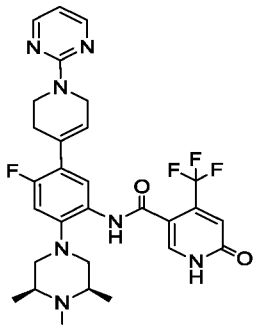
(2 ml), worked up and the crude product purified to provide the title compound (15 mg, 45% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 (s, 1H), 7.78 (br d, *J*=8.2 Hz, 1H), 6.99 - 6.95 (m, 1H), 6.94 - 6.91 (m, 1H), 6.05 (br s, 1H), 4.28 (br s, 2H), 3.88 (t, *J*=5.6 Hz, 2H), 3.04 (br d, *J*=10.3 Hz, 2H), 2.64 - 2.55 (m, 6H), 2.42 - 2.38 (m, 3H), 1.35 - 1.33 (m, 9H), 1.19 - 1.16 (m, 6H); LCMS [M+H]+ 592.6

Example 244: N-[5-[l-(2, 2-dimethylpropanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



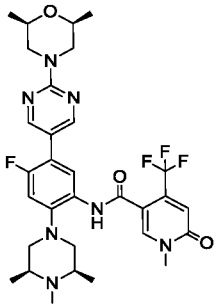
[00552] To a solution of N-(4-fluoro-5-(piperidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and N,N-diisopropylethylamine (9.83 µï, 0.056 mmol) in DCM (3 ml) at RT was added trimethylacetyl chloride (6.34 µï, 0.052 mmol). The mixture became a clear solution. It was stirred at RT. Complete disappearance of the starting material and formation of the desired product was observed after 4 min at rt. The reaction was quenched with water (2 ml) after 10 min. The organic phase was separated, the aqueous phase was extracted with DCM (2 ml), and the combined organic phase was washed with, saturated NaHCCb sola, brine, then dried over Na_2S0_4 and concentrated onto celite. It was then purified by sgc (4 g column), eluting with DCM containing 0-8 % MeOH. The desired fractions were combined and concentrated to afford the title compound as a white powder (26 mg, 85% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.93 (m, 1H), 7.80 - 7.72 (m, 1H), 6.99 - 6.94 (m, 1H), 6.94 - 6.91 (m, 1H), 4.66 - 4.55 (m, 2H), 3.23 - 3.11 (m, 1H), 3.06 - 2.91 (m, 4H), 2.63 - 2.51 (m, 4H), 2.43 - 2.37 (m, 3H), 1.96 - 1.88 (m, 2H), 1.74 - 1.65 (m, 2H), 1.35 - 1.32 (m, 10H),1.18 - 1.15 (m, 6H); LCMS [M+H]+ 594.7.

Example 245: N-[4-fluoro-5-(l-pyrimidin-2-yl-3, 6-dihydro-2H-pyridin-4-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



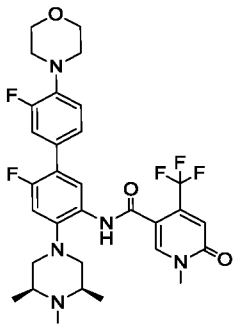
[00553] To a solution of N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-bromopyrimidine 95% (10.34 mg, 0.065 mmol) in ethanol (3 ml) at RT was added N,N-diisopropylethylamine (0.021 ml, 0.118 mmol). The reaction mixture was heated at 80 °C. Complete disappearance of the starting material and formation of the desired product were observed after 4 min. The organic phase was separated, the aqueous phase was extracted with DCM (2 ml), the combined organic phase was washed with saturated NaHCCb soln., brine, then dried over Na_2S0_4 and concentrated onto celite. It was purified by sgc (4 g column), eluting with DCM containing 0-6 % MeOH. The desired fractions were combined and concentrated to afford the title compound as an off white powder (26 mg, 71 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.43 - 8.31 (m, 2H), 7.95 (s, 1H), 7.80 (br d, *J*=8.1 Hz, 1H), 6.98 - 6.94 (m, 1H), 6.92 (s, 1H), 6.63 (t, *J*=4.8 Hz, 1H), 6.13 (br s, 1H), 4.37 (br d, *J*=2.8 Hz, 2H), 4.06 (t, *J*=5.6 Hz, 2H), 3.03 (br d, *J*=10.9 Hz, 2H), 2.62 - 2.52 (m, 6H), 2.38 (s, 3H), 1.17 (d, *J*=6.0 Hz, 6H), 1.00 (d, *J*=6.6 Hz, 1H); LCMS [M+H]+ 586.

Example 246: N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00554] The title compound (pale beige solid, 37.1 mg, 73%) was prepared by a procedure similar to Example 226 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (42 mg, 0.08 mmol) and (2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (38 mg, 0.16 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.73 (s, IH), 8.54 (s, 2H), 8.46 (d, *J*=8.2 Hz, IH), 7.87 (s, IH), 7.02 (d, *J*=10.4 Hz, IH), 6.97 (s, IH), 4.62 (dd, *J*=1.3, 13.0 Hz, 2H), 3.73 - 3.63 (m, 5H), 2.80 (br d, *J*=10.9 Hz, 2H), 2.70 - 2.59 (m, 4H), 2.37 - 2.26 (m, 5H), 1.28 (d, *J*=6.2 Hz, 6H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^{+}$ 632.5.

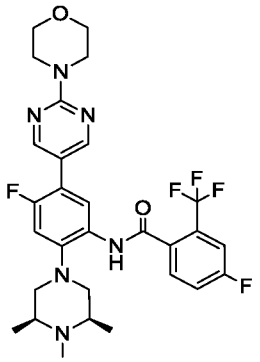
Example 247: N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00555] The title compound (pale beige solid, 35.8 mg, 72%) was prepared by a procedure similar to Example 226 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (42 mg, 0.08 mmol) and 3-fluoro-4-morpholinophenylboronic acid (36 mg, 0.16 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (s, IH), 8.48 (d, *J*=8.3 Hz, IH), 7.87 (s, IH), 7.32 (s, IH), 7.30 (d, *J*=7.7 Hz, IH), 7.02 - 6.96 (m, 3H), 3.93 - 3.87 (m, 4H), 3.65 (s, 3H),

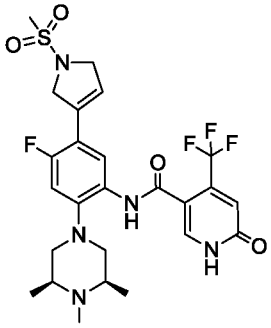
3.18 - 3.11 (m, 4H), 2.82 (br d, *J*=11.0 Hz, 2H), 2.64 (br t, *J*=10.8 Hz, 2H), 2.37 - 2.27 (m, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 620.4.

Example 248: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



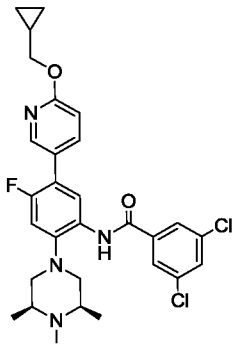
[00556] To a solution of 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) in dioxane (2 mL) was added 4-fluoro-2-(trifluoromethyl)benzoyl chloride (17 μL, 0.11 mmol). The mixture was heated at 110 °C for 30 min, and EtsN (0.028 mL, 0.2 mmol) was added and the resulting mixture was heated at 110 °C for 10 min. Additional dioxane (3 mL) was added and the mixture was heated at 110 °C for 30 min. After quenching with sat. NaHC0 $_3$ (3 mL), the reaction was extracted with DCM (5 mL) and the organic layer was loaded on Biotage samplet and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-10%) to give the title compound as a brown solid (23.9 mg, 39%). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.62 - 8.54 (m, 4H), 7.66 (dd, *J*=5.3, 8.3 Hz, 1H), 7.50 (dd, *J*=2.3, 8.8 Hz, 1H), 7.39 (dt, *J*=2.2, 8.1 Hz, 1H), 7.01 (d, *J*=11.2 Hz, 1H), 3.90 - 3.86 (m, 4H), 3.82 - 3.78 (m, 4H), 2.84 (br d, *J*=ll.l Hz, 2H), 2.72 - 2.56 (m, 2H), 2.38 - 2.20 (m, 5H), 1.12 (br d, *J*=5.6 Hz, 6H); LCMS [M+ H]$^+$ 591.4.

Example 249: N-[4-fluoro-5-(I-methylsulfonyl-2,5-dihydropyrrol-3-yl)-2-[(3R,5S)-3, 4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carb oxamide



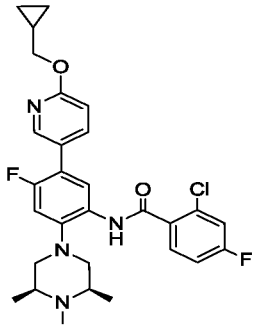
[00557] To a mixture of N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and N,N-diisopropylethylamine (0.018 ml, 0.101 mmol) in DCM (3 ml) at RT, was added methanesulfonyl chloride (3.92 µï, 0.051 mmol). It was stirred at RT. Formation of the desired product along with some di-substituted by-product and starting material was observed even after 20 min at rt. No change between 20 min and 45 min was observed. Therefore, 0.5 eq of methanesulfonyl chloride was added stirring at RT continued. The mixture was quenched with MeOH and concentrated onto celite, then purified by sgc eluting with DCM containing 0-6 % MeOH and 0-0.6 % NH40H. The desired fractions were combined and concentrated to afford the title compound as a white powder (16 mg, 53% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 - 7.81 (m, 1H), 7.73 - 7.62 (m, 1H), 6.94 - 6.85 (m, 1H), 6.83 - 6.76 (m, 1H), 6.27 - 6.19 (m, 1H), 4.50 - 4.40 (m, 2H), 4.30 - 4.19 (m, 2H), 3.00 - 2.90 (m, 2H), 2.87 - 2.79 (m, 3H), 2.54 - 2.38 (m, 4H), 2.30 - 2.22 (m, 3H), 1.10 - 1.02 (m, 6H); LCMS [M+H]+ 572.4.

Example 250: 3,5-dichloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJbenzamide



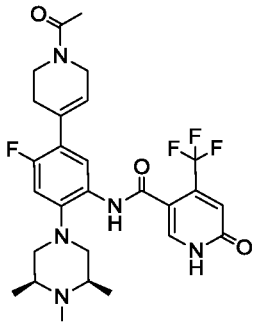
[00558] The title compound (off white solid, 23.0 mg, 40%) was prepared according to a sequence similar to that described hereinabove using 5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (38.4 mg, 0.1 mmol) and 3,5-dichlorobenzoyl chloride (21 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.27 (s, IH), 8.61 (d, *J*=8.2 Hz, IH), 8.37 (s, IH), 7.83 - 7.77 (m, 3H), 7.57 (s, IH), 7.02 (d, *J*=ll.l Hz, IH), 6.85 (d, *J*=8.6 Hz, IH), 4.19 (d, *J*=7.1 Hz, 2H), 2.91 (br d, *J*=ll.l Hz, 2H), 2.73 (t, *J*=10.9 Hz, 2H), 2.52 - 2.42 (m, 2H), 2.39 (s, 3H), 1.37 - 1.28 (m, IH), 1.19 (d, *J*=6.2 Hz, 6H), 0.67 - 0.61 (m, 2H), 0.41 - 0.36 (m, 2H); LCMS $[M + H]^+$ 557.4.

Example 251: 2-chloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-4-fluorobenzamide



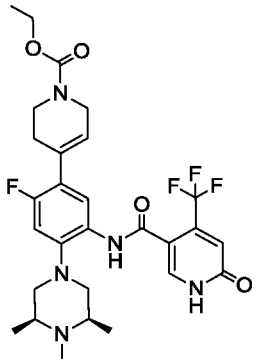
[00559] The title compound (white solid, 44.4 mg, 81%) was prepared in a sequence similar that described hereinabove using 5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (38.4 mg, 0.1 mmol) and 2-chloro-4-fluorobenzoylchloride (20 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, IH), 8.68 (d, *J*=8.3 Hz, IH), 8.37 (s, IH), 7.85 (t, *J*=7.5 Hz, IH), 7.80 (d, *J*=8.4 Hz, IH), 7.24 (dd, *J*=2.4, 8.4 Hz, IH), 7.14 (t, *J*=8.1 Hz, IH), 7.02 (d, *J*=11.2 Hz, IH), 6.85 (d, *J*=8.6 Hz, IH), 4.19 (d, *J*=7.2 Hz, 2H), 2.88 (br d, *J*=11.0 Hz, 2H), 2.65 (t, *J*=10.9 Hz, 2H), 2.42 - 2.31 (m, 5H), 1.37 - 1.28 (m, IH), 1.13 (d, *J*=6.2 Hz, 6H), 0.67 - 0.61 (m, 2H), 0.40 - 0.35 (m, 2H); LCMS $[M + H]^+$ 541.2.

Example 252: N-[5-(l-acetyl-3, 6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3, 4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



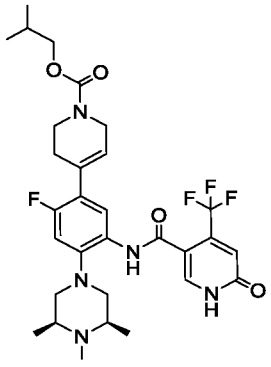
[00560] To a solution of N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and N,N-diisopropylethylamine (0.021 ml, 0.118 mmol) in DCM (3 mL) at RT, was added 4-methoxybenzoyl chloride, 99% (8.55 µï, 0.062 mmol). The reaction mixture was stirred at RT. Complete disappearance of the starting material and formation of the desired product was observed after 4 min. The reaction was quenched with water (2 ml) after 10 min. The organic phase was separated, the aqueous phase was extracted with DCM (2 ml), the combined organic phase was washed with satd. NaHC03 soln., brine, then dried over Na_2S0_4 and concentrated onto celite. It was then purified on Isco column (4 g), eluting with DCM containing 0-8 % MeOH. The desired fractions were combined and concentrated to afford the title compound as a white powder (23 mg, 58 %) ^{19}F NMR (471MHz, METHANOL-d4) δ = -63.83 (s, IF), -117.61 (s, IF); LCMS [M+H]+ 642.5

Example 253: ethyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3,6-dihydro-2H-pyridine-l-carboxylate



[00561] To a solution of N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50 mg, 0.099 mmol) and N,N-diisopropylethylamine (0.034 ml, 0.197 mmol) in dichloromethane (DCM) (3 ml) at RT was added ethyl chloroformate (0.011 ml, 0.118 mmol). The milky reaction mixture became a clear solution. It was stirred at RT. Complete disappearance of the starting material and formation of the desired product was observed after 20 min at RT. The reaction was quenched with water (2 mL), the organic phase was separated, the aqueous phase was extracted with DCM (2 x 2 ml), the combined organic phase was washed with brine, then dried over Na_2S0_4 and concentrated onto celite. It was purified on Isco column (4 g), eluting with DCM containing 0-6 % MeOH to collect the title compound as a white powder (44 mg, 73 *%)*. ^{1}H NMR (500**MHZ**, METHANOLS) δ = 7.94 (s, 1H), 7.77 (br d, ***J***=8.1 Hz, 1H), 6.98 - 6.94 (m, 1H), 6.92 (s, 1H), 6.00 (br s, 1H), 4.21 - 4.16 (m, 2H), 4.16 - 4.07 (m, 2H), 3.68 (br s, 2H), 3.03 (br d, ***J***=10.5 Hz, 2H), 2.63 - 2.50 (m, 6H), 2.39 (s, 3H), 1.33 - 1.30 (m, 3H), 1.20 - 1.15 (m, 6H), 0.94 - 0.94 (m, 1H); LCMS [M+H]+ 580.46

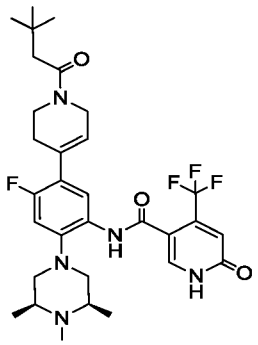
Example 254: 2-methylpropyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3,6-dihydro-2H-pyridine-l-carboxylate



[00562] The procedure used was similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and isobutyl chloroformate (7.73 μï, 0.059 mmol) to give, after workup and purification, the title compound as a white powder (25.5 mg, 67% yield). ^{1}H

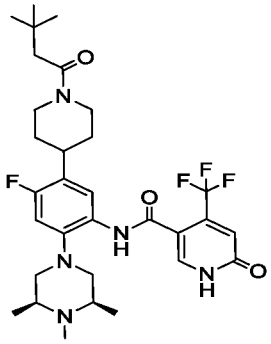
NMR (500MHz, METHANOL-d4) δ = 7.94 - 7.87 (m, 1H), 7.78 - 7.68 (m, 1H), 6.94 - 6.90 (m, 1H), 6.90 - 6.87 (m, 1H), 6.04 - 5.89 (m, 1H), 4.19 - 4.06 (m, 2H), 3.92 - 3.87 (m, 2H), 3.73 - 3.60 (m, 2H), 3.02 - 2.97 (m, 2H), 2.58 - 2.46 (m, 6H), 2.37 - 2.33 (m, 3H), 2.01 - 1.89 (m, 1H), 1.15 - 1.11 (m, 6H), 0.98 - 0.94 (m, 6H), 0.85 - 0.85 (m, 1H); LCMS [M+H]+ 608.45

Example 255: N-[5-[l-(3,3-dimethylbutanoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



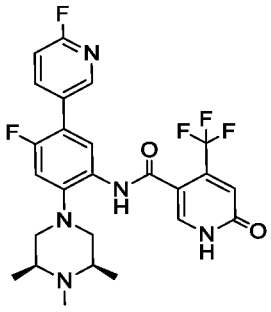
[00563] The procedure used was similar to Example 253 using N-(4-fluoro-5-(l,2,3,64etrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (29.5 mg, 0.058 mmol) and N,N-diisopropylethylamine (0.013 ml, 0.073 mmol) and 3,3-dimethylbutyryl chloride (8.48 µĩ, 0.061 mmol). The workup and purification provided the title compound as a white powder (25 mg, 68% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 - 7.91 (m, 1H), 7.84 - 7.71 (m, 1H), 6.98 - 6.94 (m, 1H), 6.94 - 6.90 (m, 1H), 6.08 - 5.97 (m, 1H), 4.34 - 4.27 (m, 1H), 4.26 - 4.20 (m, 1H), 3.87 - 3.78 (m, 2H), 3.08 - 3.01 (m, 2H), 2.64 - 2.51 (m, 6H), 2.45 - 2.40 (m, 2H), 2.39 - 2.37 (m, 3H), 1.19 - 1.15 (m, 6H), 1.11 - 1.07 (m, 9H); LCMS [M+H]+ 606.5

Example 256: N-[5-[l-(3, 3-dimethylbutanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6-oxo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00564] To a mixture of N-(4-fluoro-5-(piperidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (26.5 mg, 0.052 mmol) and N,N-diisopropylethylamine (0.011 ml, 0.065 mmol) in DCM (3 ml) at RT was added 3,3-dimethylbutyryl chloride (7.59 µï, 0.055 mmol). A workup and purification provided the title compound as a white powder (26 mg, 74% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.00 - 7.90 (m, 1H), 7.81 - 7.70 (m, 1H), 6.99 - 6.94 (m, 1H), 6.94 - 6.90 (m, 1H), 4.82 - 4.73 (m, 1H), 4.28 - 4.19 (m, 1H), 3.29 - 3.21 (m, 1H), 3.17 - 3.09 (m, 1H), 3.02 - 2.94 (m, 2H), 2.77 - 2.69 (m, 1H), 2.63 - 2.51 (m, 4H), 2.49 - 2.44 (m, 1H), 2.40 - 2.37 (m, 3H), 2.36 - 2.29 (m, 1H), 1.95 - 1.86 (m, 2H), 1.78 - 1.70 (m, 1H), 1.69 - 1.62 (m, 1H), 1.18 - 1.14 (m, 6H), 1.08 (s, 9H); LCMS [M+H]+ 608.45

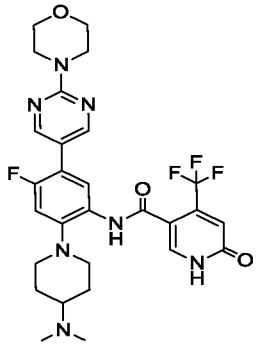
Example 257: N-[4-fluoro-5-(5-fluoropyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00565] The title compound was prepared similar to the procedure described above for the final coupling and deprotection steps in the preparation of Example 31 using 6-fluoropyridine-3-boronic acid pinacol ester. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.81 - 12.30 (m, 1H), 9.59 (s, 1H), 8.36 (s, 1H), 8.16 - 8.06 (m, 1H), 7.92 (s, 1H), 7.78 (d, *J*=8.6 Hz, 1H), 7.32 (dd, *J*=2.7, 8.6 Hz, 1H), 7.08 (d, *J*=12.5 Hz, 1H), 6.81 (s,

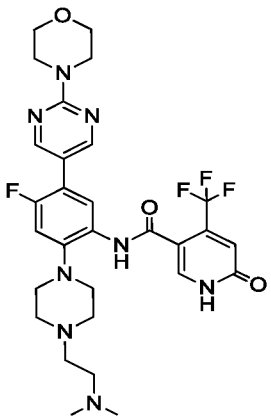
1H), 3.06 (br d, *J*=11.0 Hz, 2H), 2.49 - 2.43 (m, 2H), 2.20 (s, 3H), 1.01 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 522.5.

Example 258: N-[2-[4-(dimethylamino)piperidin-l-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00566] The title compound was prepared similar to the sequence described above for the preparation of Example 234 using 4-(dimethylamino)piperidine in place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.55 (s, 1H), 8.52 (s, 2H), 7.90 (s, 1H), 7.78 (d, *J*=8.4 Hz, 1H), 7.07 (d, *J*=12.3 Hz, 1H), 6.81 (s, 1H), 3.78 - 3.74 (m, 4H), 3.69 - 3.66 (m, 4H), 3.19 (br d, *J*=11.6 Hz, 2H), 2.67 - 2.58 (m, 3H), 2.24 (br s, 6H), 1.87 - 1.76 (m, 2H), 1.58 (br dd, *J*=3.1, 11.7 Hz, 2H); LCMS [M+H]+: 590.5.

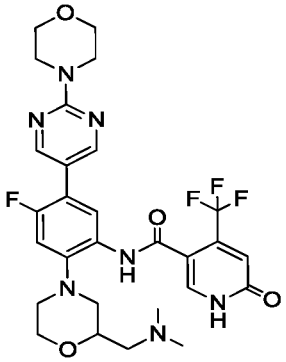
Example 259: N-[2-[4-[2-(dimethylamino)ethylJpiperazin-l-ylJ-4-fluoro-5-(2-morpholm-4-ylpyrimidin-5-yl)phenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbommide



[00567] The title compound was prepared similar to the procedure described above for the preparation of Example 234 using l-(2-dimethylaminoethyl)piperazine in

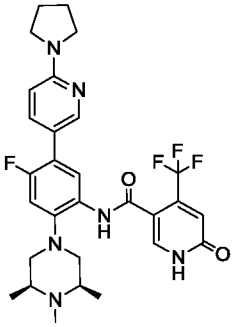
place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 1. 'llNMR (500**MHZ**, DMSO-d6) δ = 9.54 (s, IH), 8.53 (d, *J*=1.0 Hz, 2H), 7.92 (s, IH), 7.75 (d, *J*=8.7 Hz, IH), 7.09 (d, *J*=12.2 Hz, IH), 6.81 (s, IH), 3.78 - 3.73 (m, 4H), 3.70 - 3.65 (m, 4H), 2.90 (br s, 4H), 2.60 - 2.54 (m, 4H), 2.48 - 2.39 (m, 4H), 2.21 (br s, 6H); LCMS [M+H]+: 619.5.

Example 260: N-[2-[2-[(dimethylamino)methyl]morpholin-4-yl]-4-fluoro -5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6<>xo-4-(trifluoromethyl)-lH-pyridim -3-carboxamide



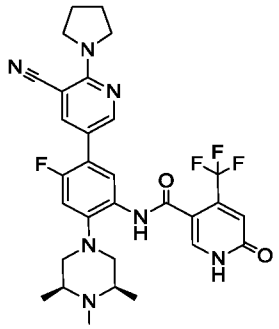
[00568] The title compound was prepared similar to the sequence described above for the preparation of Example 234 using dimethyl-morpηo1iη-2-ylmethy1-3miηe in place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.58 (s, IH), 8.53 (d, *J*=0.9 Hz, 2H), 7.95 (s, IH), 7.77 (d, *J*=8.4 Hz, IH), 7.10 (d, *J*=12.1 Hz, IH), 6.81 (s, IH), 3.85 (br d, *J*=11.4 Hz, IH), 3.77 - 3.74 (m, 4H), 3.73 - 3.70 (m, IH), 3.69 - 3.67 (m, 4H), 3.08 (br d, *J*=11.4 Hz, IH), 2.99 (br d, *J*=11.7 Hz, IH), 2.77 (dt, *J*=2.6, 11.4 Hz, IH), 2.63 (br d, *J*=1.7 Hz, IH), 2.48 (br d, *J*=1.6 Hz, IH), 2.36 (br d, *J*=1.8 Hz, IH), 2.13 (br s, 6H); LCMS [M+H]+: 606.4.

Example 261: N-[4-fluoro-5-(5-pyrrolidin-l -ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



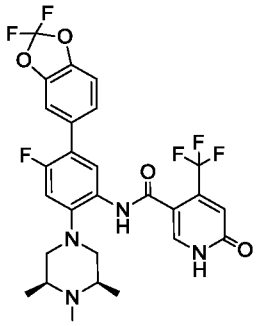
[00569] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 6-(pyrrolidin-l-yl)pyridine-3-boronic acid, pinacol ester (34.0 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) to give the title compound (37 mg, 79%). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.66 - 12.44 (m, 1H), 9.49 (s, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.76 - 7.69 (m, 1H), 7.61 (br d, *J*=8.7 Hz, 1H), 7.00 (br d, *J*=12.5 Hz, 1H), 6.81 (s, 1H), 6.54 (d, *J*=8.8 Hz, 1H), 3.41 (br s, 6H), 3.06 - 2.97 (m, 1H), 2.44 (br d, *J*=9.3 Hz, 1H), 2.36 (br dd, *J*=1.8, 3.5 Hz, 1H), 1.99 - 1.89 (m, 5H), 1.14 (d, *J*=13.2 Hz, 2H), 1.01 (br d, *J*=5.0 Hz, 6H); LCMS [M+H]+: 573.5.

Example 262: N-[5-(5-cyano-6-pyrrolidin-l-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



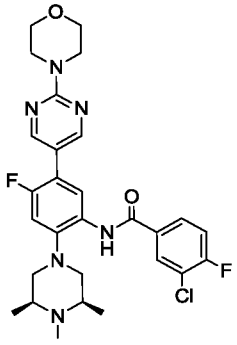
[00570] The title compound was prepared similar to the sequence described for the preparation of Example 100 using 3-cyano-2-pyrrolidinopyridine-5-boronic acid, pinacol ester (37.1 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) to give the title compound (32 mg 64% yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.66 - 12.49 (m, 1H), 9.55 (s, 1H), 8.46 (d, *J*=1.7 Hz, 1H), 8.02 (d, *J*=2.2 Hz, 1H), 7.91 (s, 1H), 7.74 (d, *J*=8.4 Hz, 1H), 7.02 (d, *J*=12.5 Hz, 1H), 6.81 (s, 1H), 3.71 (br t, *J*=6.5 Hz, 5H), 3.02 (br d, *J*=11.2 Hz, 2H), 2.47 - 2.40 (m, 2H), 2.38 - 2.28 (m, 2H), 2.19 (br s, 3H), 1.95 (td, *J*=3.4, 6.3 Hz, 5H), 1.00 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 598.5.

Example 263: N-[5-(2,2-difluoro-l, 3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00571] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2,2-difiuoro-benzo[l,3]dioxole-5-boronic acid (25.01 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) to give the title compound (40.2 mg, 80% yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.77 - 12.43 (m, 1H), 9.55 (s, 1H), 7.91 (s, 1H), 7.75 (d, *J*=8.7 Hz, 1H), 7.59 - 7.46 (m, 2H), 7.31 (d, *J*=8.6 Hz, 1H), 7.04 (d, *J*=12.5 Hz, 1H), 6.80 (s, 1H), 3.04 (br d, *J*=10.9 Hz, 2H), 2.48 - 2.43 (m, 2H), 2.38 - 2.31 (m, 2H), 2.19 (s, 3H), 1.01 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 583.0.

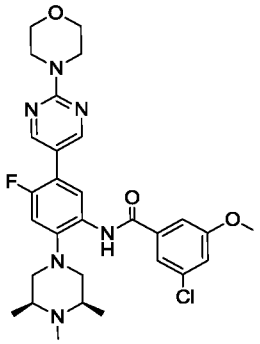
Example 264: 3-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJbenzamide



[00572] The title compound (beige solid, 49.8 mg, 83%) was prepared by a procedure similar to that of Example 34 using 3,5-dichloro-4-fluorobenzoic acid (42 mg, 0.2 mmol) and 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.25 (s, 1H), 8.58 - 8.54 (m, 3H), 7.88 (d, *J*=6.0 Hz, 2H), 7.02 (d, *J*=ll.l Hz, 1H), 3.91 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.89 (br d, *J*=11.0

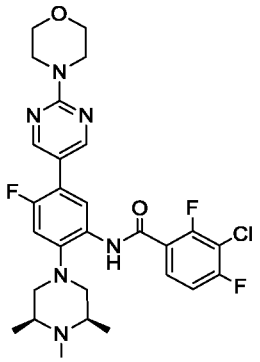
Hz, 2H), 2.71 (t, *J*=10.9 Hz, 2H), 2.47 - 2.40 (m, 2H), 2.38 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 591.3.

Example 265: 3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenyl]'-5-methoxybenzamide



[00573] The title compound (white solid, 42.2 mg, 76%) was prepared by a procedure similar to Example 34 using 3-chloro-5-methoxybenzoic acid (37 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^1H NMR (500MHz, CHLOROFORM-d) δ = 9.24 (s, 1H), 8.62 (d, *J*=8.3 Hz, 1H), 8.57 (s, 2H), 7.42 (s, 1H), 7.39 (s, 1H), 7.10 (t, *J*=2.0 Hz, 1H), 7.01 (d, *J*=11.2 Hz, 1H), 3.90 (s, 3H), 3.89 - 3.86 (m, 4H), 3.82 - 3.78 (m, 4H), 2.91 (br d, *J*=ll.l Hz, 2H), 2.69 (t, *J*=11.0 Hz, 2H), 2.52 - 2.41 (m, 2H), 2.38 (s, 3H), 1.17 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 569.3.

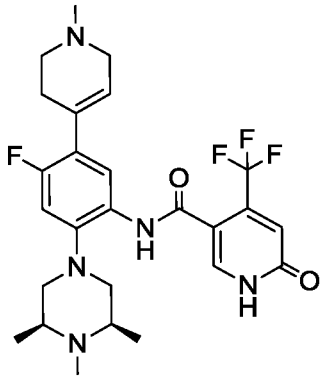
Example 266: 3-chloro-2,4-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[00574] The title compound (off-white solid, 46.6 mg, 79%) was prepared by a procedure similar to that of Example 34 using 3-chloro-2,4-difluorobenzoic acid (39 mg,

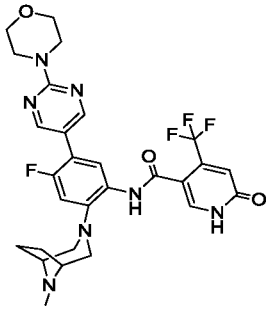
0.2 mmol) and 4-fluoro-5-(2-moϕ holinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.78 (br d, *J*=12.5 Hz, 1H), 8.70 (d, *J*=8.2 Hz, 1H), 8.58 (s, 2H), 8.14 (q, *J*=7.7 Hz, 1H), 7.19 (br t, *J*=8.1 Hz, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 3.87 (br d, *J*=3.8 Hz, 4H), 3.81 (br d, *J*=4.4 Hz, 4H), 2.88 (br d, *J*=ll.l Hz, 2H), 2.68 (br t, *J*=10.8 Hz, 2H), 2.55 - 2.45 (m, 2H), 2.38 (s, 3H), 1.16 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 575.4.

Example 267: N-[4-fluoro-5-(l-methyl-3, 6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



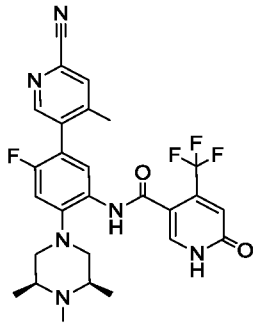
[00575] The procedure followed was similar to Example 148 using N-(4-fluoro-5-(l,2,3,64etrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (30 mg, 0.059 mmol) and paraformaldehyde (3.55 mg, 0.118 mmol) to give, after workup and purification, 3.5 mg (10% yield) of the title compound. ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.90 - 7.85 (m, 1H), 7.72 - 7.64 (m, 1H), 6.86 - 6.79 (m, 1H), 6.78 - 6.72 (m, 1H), 5.93 - 5.88 (m, 1H), 3.11 - 3.06 (m, 2H), 2.93 - 2.87 (m, 2H), 2.68 - 2.61 (m, 2H), 2.52 - 2.49 (m, 2H), 2.48 - 2.43 (m, 2H), 2.42 - 2.37 (m, 2H), 2.34 - 2.30 (m, 3H), 2.26 - 2.23 (m, 3H), 1.04 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 522.46.

Example 268: N-[4-fluoro-2-(8-methyl-3, 8-diazabicyclo[3.2.1]octan-3-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6<>xo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



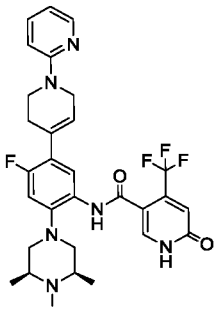
[00576] The title compound was prepared similar to the procedure described above for the preparation of Example 234 using 8-methyl-3,8-diaza-bicyclo[3.2.1]octane dihydrochloride in place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.42 (s, IH), 8.53 (s, 2H), 8.07 (s, IH), 7.66 (br d, *J*=8.4 Hz, IH), 7.07 (d, *J*=12.5 Hz, IH), 6.83 (s, IH), 3.78 - 3.73 (m, 4H), 3.70 - 3.65 (m, 4H), 3.13 (br s, H), 2.96 - 2.81 (m, 4H), 2.22 (s, 3H), 1.95 - 1.82 (m, 2H), 1.75 (br d, *J*=7.1 Hz, 2H); LCMS [M+H]+: 588.4.

Example 269: N-[5-(5<yano-4-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



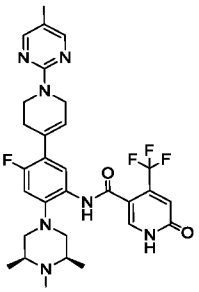
[00577] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 4-methyl-5-(tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile (30.2 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) to give the title compound (41.2 mg, 92% yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.59 (s, IH), 8.55 (s, IH), 8.08 (s, IH), 7.90 (s, IH), 7.65 (br d, *J*=8.1 Hz, IH), 7.11 (d, *J*=11.7 Hz, IH), 6.80 (s, IH), 3.10 (br d, *J*=10.8 Hz, 2H), 2.96 (s, 2H), 2.27 (s, 3H), 2.22 (br s, 3H), 1.14 (d, *J*=13.2 Hz, 4H), 1.02 (br d, *J*=5.9 Hz, 6H); LCMS [M+H]+: 543.2.

Example 270: N-[4-fluoro-5-(I-pyridin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH^yridine-3-carboxamide



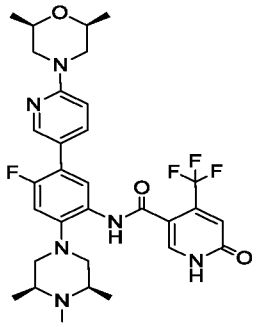
[00578] Copper (I) iodide (1.013 mg, 5.32 μηοϊ) was added to a mixture of 2-chloropyridine 99% (6.50 μϊ, 0.069 mmol), N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (27 mg, 0.053 mmol) and N,N-diisopropylethylamine (0.028 ml, 0.160 mmol) in ethylene glycol (1.5 ml). The mixture was heated in a microwave reactor at 180 °C for lh. The mixture was quenched and worked up in a similar manner to Example 148 to provide the title compound as a yellow powder (8.5 mg, 26 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 (dd, *J*=1.2, 4.9 Hz, 1H), 7.85 - 7.82 (m, 1H), 7.73 - 7.67 (m, 1H), 7.51 - 7.45 (m, 1H), 6.87 - 6.83 (m, 1H), 6.82 - 6.79 (m, 1H), 6.76 - 6.71 (m, 1H), 6.60 - 6.52 (m, 1H), 6.08 - 6.01 (m, 1H), 4.04 - 3.99 (m, 2H), 3.75 - 3.70 (m, 2H), 2.95 - 2.90 (m, 2H), 2.55 - 2.43 (m, 6H), 2.29 - 2.27 (m, 3H), 1.06 (d, *J*=5.9 Hz, 6H); LCMS [M+H]+ 585.5.

Example 271: N-[4-fluoro-5-[l-(5-methylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

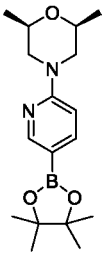


[00579] In a small reaction vessel N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (26 mg, 0.051 mmol) and 2-chloro-5-methylpyrimidine (7.57 mg, 0.059 mmol) in ethanol (3 ml) were combined at ambient temperature, and N,N-diisopropylethylamine (0.018 ml, 0.102 mmol) was added. The mixture was heated for 3 h at 150 °C, and the standard workup and purification provided (12 mg (36% yield) of the title compound. ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.31 - 8.19 (m, 2H), 7.94 (s, 1H), 7.85 - 7.72 (m, 1H), 6.98 - 6.94 (m, 1H), 6.92 (s, 1H), 6.12 (br s, 1H), 4.33 (br d, *J*=2.7 Hz, 2H), 4.01 (t, *J*=5.6 Hz, 2H), 3.04 (br d, *J*=10.5 Hz, 2H), 2.64 - 2.54 (m, 6H), 2.39 (s, 3H), 2.17 (s, 3H), 1.20 - 1.16 (m, 6H); LCMS [M+H]+ 600.4

Example 272: N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-f(3S, 5R)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



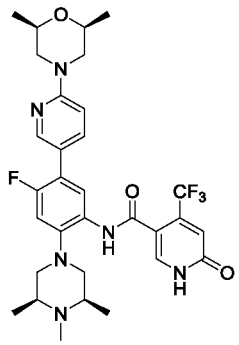
Step 1: (2S, 6RJ-2, 6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine



[00580] To a 20 mL microwave vial charged with 2-chloro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (0.968 g, 4 mmol), cis-2,6-dimethylmorpholine (0.54 mL, 4.4 mmol) and Hunig base (1.39 mL, 8 mmol) was added NMP (2 mL). The resulting solution was heated at 140 °C for 2 h. After

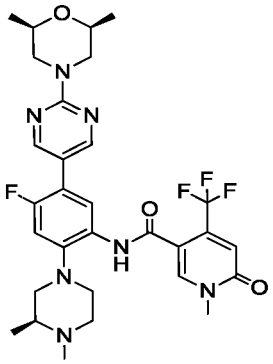
removing Hunig base, the mixture was purified by flash chromatography (gradient: EtOAc/hex 0-100%) to give the title compound as a crystalline beige solid (485 mg, yield 38%). LCMS for boronic acid $[M + H]^+$ 237.2.

Step 2: N-(5-(6-((2S, 6R)-2, 6-dimethylmorpholino)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide

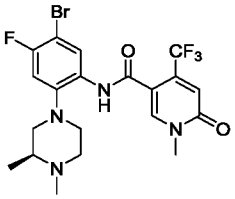


[00581] The title compound (off-white solid, 34.2 mg, 54%) was prepared by a procedure similar to that described in Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and (2S,6R)-2,6-dimethyl-4-(5-(4,4,5, 5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (63 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.31 (s, 1H), 7.97 (s, 1H), 7.92 (br d, *J*=8.3 Hz, 1H), 7.78 (br d, *J*=9.2 Hz, 1H), 7.07 (d, *J*=12.1 Hz, 1H), 6.95 - 6.89 (m, 2H), 4.16 (br d, *J*=11.6 Hz, 2H), 3.74 (ddd, *J*=2.3, 6.3, 10.3 Hz, 2H), 3.07 (br d, *J*=10.4 Hz, 2H), 2.68 - 2.57 (m, 4H), 2.53 (dd, *J*=10.8, 12.6 Hz, 2H), 2.41 (s, 3H), 1.26 (d, *J*=6.2 Hz, 6H), 1.19 (br d, *J*=5.6 Hz, 6H); LCMS $[M + H]^+$ 617.5.

Example 273: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l -yljphenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

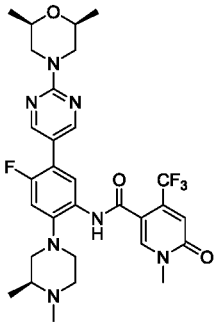


Step 1: (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



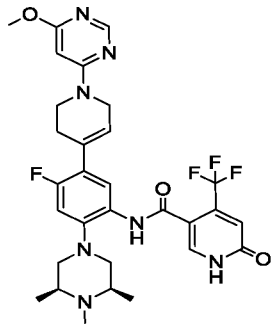
[00582] To a stirred solution of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (5g, 22.62mmol, leq) in DMF (50mL) was added HATU(25.79g, 67.87mmol, 3eq) at 0°C under argon atmosphere followed by DIPEA (11.82mL, 67.87mmol, 3eq) and stirred for 15min at the same temperature. Then, (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (2.99g, 24.88mmol, l.leq) was added at 0°C and the reaction mixture was allowed to remain at RT over 48h. TLC analysis indicated formation of polar spot. The reaction mixture was diluted with water (300mL) and extracted with EtOAc (3X100mL). The organic layer was washed with ice water (2X200mL) and dried over Na_2S04 then concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography (Neutral Alumina) using 0-60% EtOAc in petroleum ether as an eluent to provide (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (4g, 35%) as an off white solid. LCMS $[M + H]^+$ 505.23.

Step 2: N-(4-fluoro-5-(6-(2-methoxyethoxy)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00583] The title compound (white solid, 47.4 mg, 77%) was prepared by a procedure similar to that of Example 31 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-1-yl)-4-fiuorophenyl)- 1-methyl-6-oxo-4-(mfluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and (2-((2S,6R)-2,6-dimethylmo ϕ holino)pyrimidin-5-yl)boronic acid (47 mg, 0.2 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.74 (br s, IH), 8.54 (s, 2H), 8.46 (br d, *J*=7.8 Hz, IH), 7.88 (s, IH), 7.03 (d, *J*=\ 1.1 Hz, IH), 6.97 (s, IH), 4.65 - 4.58 (m, 2H), 3.72 - 3.63 (m, 5H), 3.02 - 2.84 (m, 3H), 2.80 (br d, *J*=10.9 Hz, IH), 2.70 - 2.54 (m, 3H), 2.43 - 2.28 (m, 4H), 2.20 (br s, IH), 1.28 (d, *J*=6.2 Hz, 6H), 1.09 (br d, *J*=6.1 Hz, 3H); LCMS [M+ H]$^+$ 618.4.

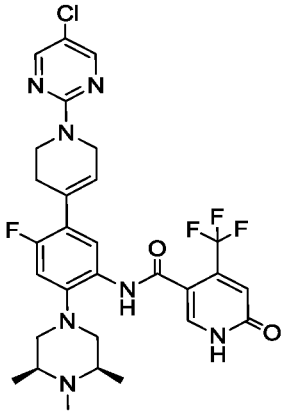
Example 274: N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00584] To a microwave vial charged with N-(4-fluoro-5-(l, 2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25.5 mg, 0.050 mmol) and 4-iodo-6-methoxy pyrimidine (13.64 mg, 0.058 mmol) in ethanol (3 ml) at RT, was added N,N-diisopropylethylamine (0.018 ml, 0.100 mmol) . The mixture was heated at 130 °C for 3 h. The reaction was worked up and the product was purified by sgc to

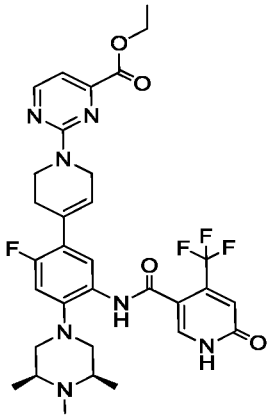
afford the title compound (19 mg, 58 % yield). ¹H NMR (500 MHz, METHANOL-d4) δ = 8.26 - 8.21 (m, 1H), 7.98 - 7.93 (m, 1H), 7.85 - 7.76 (m, 1H), 6.99 - 6.94 (m, 1H), 6.94 - 6.90 (m, 1H), 6.12 (br s, 1H), 6.04 (s, 1H), 4.26 - 4.16 (m, 2H), 4.00 - 3.88 (m, 5H), 3.03 (br d, *J*=11.0 Hz, 2H), 2.65 - 2.52 (m, 6H), 2.38 (s, 3H), 1.19 - 1.15 (m,6H); LCMS [M+H]+ 616.6

Example 275: N-[5-[l-(5-chloropyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



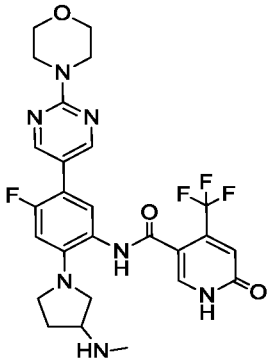
[00585] To a microwave vial charged with N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25.5 mg, 0.050 mmol) and 2,5-dichloropyrimidine (8.61 mg, 0.058 mmol) in ethanol (3 ml) at RT, was added N,N-diisopropylethylamine (0.018 ml, 0.100 mmol) . The mixture was heated at 90 °C for 2 h. 95 % conversion to the desired product was observed after 2 h. Standard workup and purification yielded the title compound (23 mg, 69% yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.25 - 8.18 (m, 2H), 7.87 - 7.79 (m, 1H), 7.73 - 7.62 (m, 1H), 6.87 - 6.82 (m, 1H), 6.81 - 6.78 (m, 1H), 6.04 - 5.96 (m, 1H), 4.30 - 4.22 (m, 2H), 3.97 - 3.90 (m, 2H), 2.96 - 2.89 (m, 2H), 2.52 - 2.40 (m, 6H), 2.28 - 2.25 (m, 3H), 1.07 - 1.03 (m, 6H); LCMS [M+H]+ 620.

Example 276: ethyl 2-[4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridin-l-ylJpyrimidine-4-carboxylate

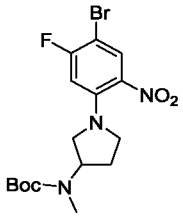


[00586] A small microwave flask was charged with N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25. mg, 0.049 mmol) and methyl 2-chloropyrimidine-4-carboxylate (9.78 mg, 0.057 mmol) in ethanol (3 ml) at RT, followed by N,N-diisopropylethylamine (0.017 ml, 0.099 mmol). The mixture was heated at 90 °C for 72 h. A standard workup and purification yielded the title compound (16 mg, 47 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.61 - 8.57 (m, 1H), 8.06 - 7.95 (m, 1H), 7.87 - 7.77 (m, 1H), 7.22 - 7.14 (m, 1H), 7.09 - 7.01 (m, 1H), 6.99 - 6.90 (m, 1H), 6.21 - 6.11 (m, 1H), 4.49 - 4.40 (m, 4H), 4.17 - 4.10 (m, 2H), 3.24 - 3.10 (m, 4H), 2.86 - 2.78 (m, 2H), 2.78 - 2.70 (m, 3H), 2.66 - 2.59 (m, 2H), 1.45 - 1.40 (m, 3H), 1.36 - 1.32 (m, 6H); LCMS [M+H]+ 658.4.

Example 277: N-[4-fluoro-2-[3-(methylamino)pyrrolidin-l-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

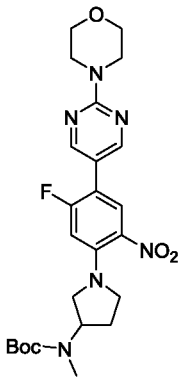


Step 1: tert-butyl (l-(4-bromo-5-fluoro-2-nitrophenyl)pyrrolidin-3-yl) (methyl)carbamate



[00587] A suspension of 3-N-boc-3-(methylamino)pyrrolidine (1.33 g, 6.64 mmol) and K_2CO_3 (0.459 g, 3.32 mmol) in toluene (10 ml) was stirred for 5 min at room temperature. Then a solution of 1-bromo-2,4-difiuoro-5 -nitrobenzene (1.580 g, 6.64 mmol) in toluene (1 ml) was added dropwise from a pipette (2 ml of toluene were used to rinse the vial) and the reaction was stirred at 50 °C for 3 h 30 min. Then the reaction mixture was partitionned into water and DCM and the product was extracted by DCM (3x20mL). The organic phase was dried over $MgSO_4$ and after filtration and solvents removal, the crude material was dry loaded and purified by flash chromatography [0-10% MeOH/DCM] to afford the desired tert-butyl (l-(4-bromo-5-fluoro-2-nitrophenyl)pyrrolidin-3-yl)(methyl)carbamate (2.17 g, 5.19 mmol, 78 % yield) as an orange oil. LCMS [M+H]+ 418.2.

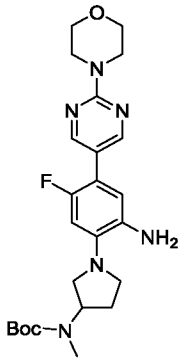
Step 2: tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)pyrrolidin-3-yl) (methyl)carbamate



[00588] A 100 mL RBF was charged with a mixture of tert-butyl (l-(4-bromo-5-fluoro-2-nitrophenyl)pyrrolidin-3-yl)(methyl)carbamate (2.17 g, 5.19 mmol), XPhos (0.049 g, 0.104 mmol), XPhos (0.049 g, 0.104 mmol) and XPhos (0.049 g, 0.104 mmol). Then 1,4-dioxane (50 ml) and sodium carbonate solution (2 M) (2.75 mL) were added via syringe and the vial was flushed with argon. The reaction was stirred at 90 °C overnight. Then the reaction mixture was partitionned into water and DCM and the product was

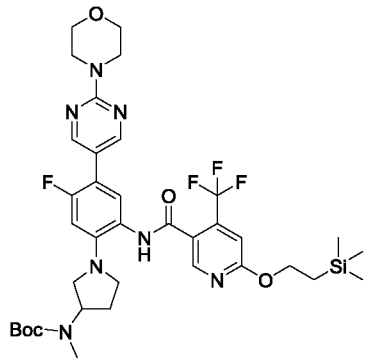
extracted by DCM (3x50mL). The organic phase was dried over MgSC>4 and after filtration and solvents removal, the crude material was dry loaded and purified by Flash chromatography [0-10% MeOH/DCM] to afford the desired tert-butyl (l-(5-fiuoro-4-(2-moϕ holinopyrimidin-5-yl)-2-nitrophenyl)pyrrolidin-3-yl)(methyl)carbamate (1.21 g, 2.415 mmol, 46.6 % yield) as a dark orange oil. LCMS [M+H]+ 503.4.

Step 3: tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate



[00589] A mixture of tert-butyl (l-(5-fluoro-4-(2-mo rpholinopyrimidin-5-yl)-2-nitrophenyl)pyrrolidin-3-yl)(methyl)carbamate (1.8598 g, 3.70 mmol) and tin(II) chloride, 98% (2.105 g, 11.10 mmol) in a mixture of EtOH (10 ml) and MeOH (10 ml) was heated to 90 °C for 3 h. Then the reaction mixture was concentrated onto celite and purified by flash [0.5-10% MeOH/DCM] to afford the tert-butyl (l-(2-amino-5-fluoro-4-(2-moϕ holinopyrirnidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (0.94 g, 1.990 mmol, 53.8 % yield) as a yellow solid. LCMS [M+H]+ 473.2.

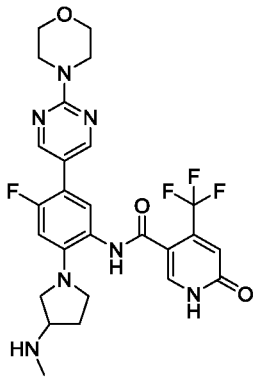
Step 4: tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)pyrrolidin-3-yl)(methyl)carbamate



[00590] Propylphosphonic anhydride solution (0.189 ml, 0.317 mmol) was added dropwise to a mixture of 4-(trifluoromethyl)-6-(2-

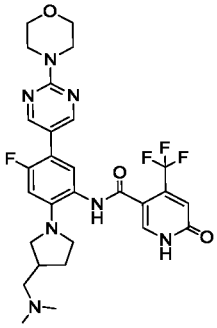
(trimethylsilyl)ethoxy)nicotinic acid (72 mg, 0.234 mmol) and pyridine (5.24 ml, 65.1 mmol) in DCM (2 ml) under N_2 atmosphere at room temperature. After 15 minutes of stirring at 50 °C a solution of tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (100 mg, 0.212 mmol) in 2mL of DCM was added and the reaction mixture was heated at 50 °C overnight. The reaction mixture was then concentrated onto celite and purified by flash chromatography [0-10% MeOH/DCM] to afford the tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)pyrrolidin-3-yl)(methyl)carbamate (161 mg, 0.21 1 mmol, 100 % yield) as an off-white powder. LCMS [M+H]+ 762.5.

Step 5: N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



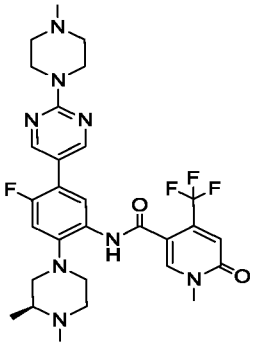
[00591] To a solution of tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)pyrrolidin-3-yl)(methyl)carbamate (161 mg, 0.211 mmol) in DCM (3 ml) was added trifluoroacetic acid (2 ml, 26.1 mmol). The reaction mixture was stirred at 60 °C for 50 minutes. Then the TFA and solvent were removed under vacuum and the crude material was purified by flash chromatography [0-40% DCM/MeOH] to afford the N-(4-fluoro-2-(3-(methylalnino)pyl·rolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-a^hydropyridine-3-carboxarnide (6.4 mg, 0.011 mmol, 5.39 % yield) as a white powder (yield for 2 steps). ¾ NMR (500MHz, DMSO-d6) δ = 9.79 (br s, 1H), 8.49 (s, 2H), 7.98 (br s, 1H), 7.29 (br d, *J*=8.6 Hz, 1H), 6.75 (s, 1H), 6.62 (d, *J*=14.1 Hz, 1H), 3.75 - 3.71 (m, 4H), 3.69 - 3.65 (m, 4H), 3.46 (br dd, *J*=5.6, 9.2 Hz, 1H), 3.41 - 3.38 (m, 1H), 3.18 - 3.13 (m, 1H), 3.10 (br dd, *J*=4.5, 9.7 Hz, 1H), 2.26 (s, 3H), 2.03 - 1.94 (m, 1H), 1.76 - 1.66 (m, 1H), 1.23 (s, 1H); LCMS [M+H]+ 562.3.

Example 278: N-[2-[3-[(dimethylamino)methyl]pyrrolidin-l-yl]-4-fluoro-5-(2-m orpholin-4-ylpyrimidin-5-yl)phenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carboxamide



[00592] The title compound was prepared similar to the procedure described above for the preparation of Example 234 using N,N-dimethyl(3-pyrrolidinyl)methanamine in place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 1. ¾ NMR (500MHz, DMSO-d6) δ = 9.81 (s, 1H), 8.50 (s, 2H), 7.95 (s, 1H), 7.29 (d, *J*=8.8 Hz, 1H), 6.80 (s, 1H), 6.62 (d, *J*=14.1 Hz, 1H), 3.76 - 3.70 (m, 4H), 3.69 - 3.65 (m, 4H), 3.10 (br dd, *J*=7.1, 9.3 Hz, 1H), 2.44 - 2.33 (m, 1H), 2.24 (br s, 2H), 2.16 (br s, 6H), 1.98 (qd, *J*=6.0, 11.8 Hz, 1H), 1.64 - 1.52 (m, 1H); LCMS [M+H]+: 590.4.

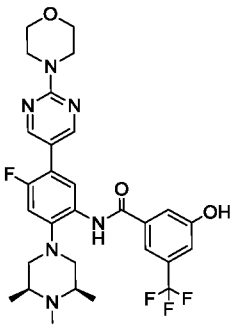
Example 279: N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00593] The title compound (light beige solid, 44.2 mg, 72%) was prepared by a procedure similar to Example 273 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-ihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 2-(4-methylpiperazin-l-yl)pyrimidine-5-boronic acid pinacol ester (61 mg, 0.2 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 8.57 - 8.53 (m, 2H), 8.26 (s, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.11 (br d, *J*=10.9 Hz, 1H), 6.95 (s, 1H), 3.97 - 3.85

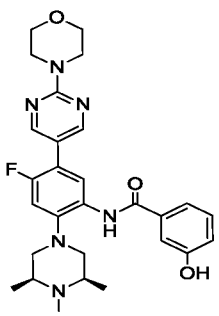
(m, 4H), 3.66 (s, 3H), 3.14 - 3.03 (m, 2H), 3.00 - 2.87 (m, 2H), 2.61 - 2.49 (m, 6H), 2.43 - 2.34 (m, 7H), 1.13 (d, *J*=6.1 Hz, 3H); LCMS $[M+H]^+$ 603.4.

Example 280: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenyl]-3-hydroxy-5-(trifluoromethyl)benzamide



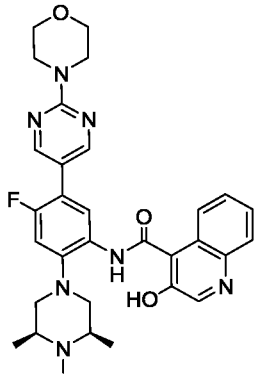
[00594] To a 25 mL RBF was charged with 3-hydroxy-5-(trifluoromethyl)benzoic acid (41 mg, 0.2 mmol) was added thionyl chloride (0.364 mL, 5 mmol). The resulting suspension was heated at 80 °C for 1 h (very insoluble, tumed clear in about 15 min). The solvents were evaporated to give a light yellow oil which was treated with DCM (5 mL), 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and Et_3N (42 µL, 0.3 mmol). The resulting dark brown suspension was stirred at rt for 30 min and purified by flash chromatography and prep-HPLC to give the title compound as a beige solid (formic acid salt, 2.6 mg, 4%). ^1H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.50 (br s, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.29 (s, 1H), 7.14 (d, *J*=11.9 Hz, 1H), 3.88 - 3.83 (m, 4H), 3.80 - 3.76 (m, 4H), 3.17 (br d, *J*=10.6 Hz, 2H), 2.83 - 2.71 (m, 4H), 2.53 (s, 3H), 1.24 (d, *J*=5.9 Hz, 6H); LCMS $[M+H]^+$ 589.4.

Example 281: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3-hydroxybenzamide



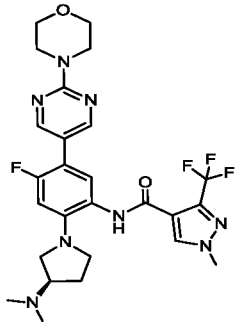
[00595] To a solution of N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3-methoxybenzamide (21.4 mg, 0.04 mmol) in DCM (1 mL) at 0 °C was added boron tribromide solution (1.0 M in methylene chloride, 0.2 mL, 0.2 mmol). The mixture was stirred at rt for 3 h, quenched with H_20 (20 mL), sat. $NaHC0_3$ (15 mL) and extracted with DCM (30 mL x 2). The combined DCM extracts were concentrated and purified by prep-HPLC to give the title compound as off-white solid (6.6 mg, 31%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.07 (d, *J*=8.2 Hz, 1H), 7.44 - 7.36 (m, 3H), 7.16 (d, *J*=11.9 Hz, 1H), 7.06 (br d, *J*=7.7 Hz, 1H), 3.89 - 3.82 (m, 4H), 3.81 - 3.75 (m, 4H), 3.23 (br d, *J*=11.6 Hz, 2H), 3.00 (br s, 2H), 2.88 - 2.74 (m, 2H), 2.65 (s, 3H), 1.28 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 521.4.

Example 282: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-hydroxyquinoline-4-carboxamide



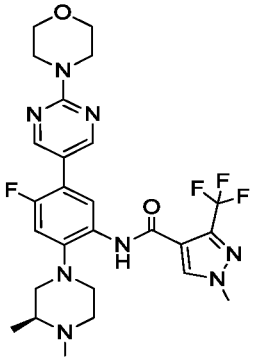
[00596] A mixture of 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (80 mg, 0.2 mmol), 3-hydroxy quinoline-4-carboxylic acid (76 mg, 0.4mmol) and DCC (103 mg, 0.5 mmol) in DCM (6 mL) in a 30 mL vial was sealed and heated d at 45 °C for 18 h. It was loaded directly onto Biotage samplet and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-20%) to give the title compound as a dark yellow solid (85.6 mg, 74%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.21 (br d, *J*=8.7 Hz, 1H), 8.63 (s, 2H), 8.56 (d, *J*=8.4 Hz, 1H), 8.53 (s, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.46 (t, *J*=7.8 Hz, 1H), 7.33 (t, *J*=7.5 Hz, 1H), 7.07 (d, *J*= 12.0 Hz, 1H), 3.89 - 3.83 (m, 4H), 3.81 - 3.76 (m, 4H), 3.44 - 3.35 (m, 2H), 3.31 - 3.25 (m, 2H), 2.79 - 2.68 (m, 5H), 1.28 (d, *J*=6.5 Hz, 6H); LCMS $[M+ H]^+$ 572.5.

Example 283: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-l-methyl-3-(Mfluoromethyl)pyrazole-4-carboxamide



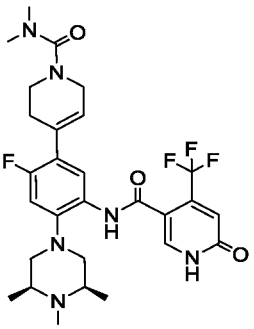
[00597] l-Methyl-3-(trifluoromethyl)-lH-pyrazole-4-carboxylic acid (0.038 g, 0.194 mmol) was activated in DMF (1 ml) with HATU (0.074 g, 0.194 mmol) and N,N-diisopropylethylamine (0.034 ml, 0.194 mmol). The solution of activated acid was then added to a stirring solution of (R)-l-(2-armno-5-fluoro-4-(2-mo rpholinopyrimidin-5-yl)phenyl)-N,N-dimethylpyrrolidin-3-amine (0.050 g, 0.129 mmol) in N,N-dimethylformamide (DMF) (1 ml) at room temperature. The reaction was warmed to 50 °C then heated at 60 °C overnight. Workup and purification using standard methods afforded the title compound (0.071 mmol, 55.0 % yield) as a tan solid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.29 (s, 1H), 8.55 (d, *J*=0.7 Hz, 2H), 8.49 (s, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J*=12.2 Hz, 1H), 4.01 (s, 3H), 3.78 - 3.73 (m, 4H), 3.72 - 3.65 (m, 4H), 3.05 - 2.98 (m, 1H), 2.95 (br d, *J*=10.9 Hz, 1H), 2.88 - 2.79 (m, 1H), 2.78 - 2.72 (m, 1H), 2.66 - 2.63 (m, 1H), 2.45 (br d, *J*=10.5 Hz, 1H), 2.37 (br d, *J*=1.6 Hz, 1H), 2.34 - 2.27 (m, 1H), 2.25 - 2.16 (m, 4H), 0.96 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 563.4.

Example 284: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-l-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide



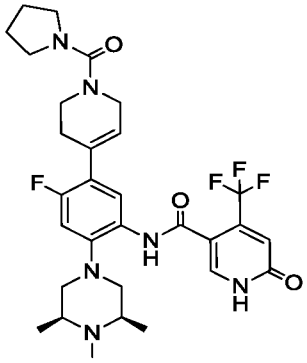
[00598] l-Methyl-3-(trifluoromethyl)-lH-pyrazole-4-carboxylic acid (0.038 g, 0.194 mmol) was activated in DMF (1 mL) with HATU (0.074 g, 0.194 mmol) and N,N-diisopropylethylamine (0.034 ml, 0.194 mmol). The solution of activated acid was then added to a stirring solution of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (0.050 g, 0.129 mmol) in DMF (1 ml) at room temperature. The reaction was warmed to 50 °C and monitored by LCMS [230 pm - start heating]. After heating at 60 °C overnight, workup and purification afforded the title compound (27 mg, 37% yield). ¾I NMR (500MHz, DMSO-d6) δ = 9.72 (s, IH), 8.51 (s, 2H), 8.47 (s, IH), 7.21 (d, *J*=8.8 Hz, IH), 6.67 (d, *J*=13.8 Hz, IH), 3.99 (s, 3H), 3.75 - 3.72 (m, 4H), 3.70 - 3.66 (m, 4H), 3.40 - 3.35 (m, 3H), 3.21 (t, *J*=8.8 Hz, IH), 2.11 (s, 6H), 2.09 - 2.03 (m, IH), 1.68 (quin, *J*=10.0 Hz, IH); LCMS [M+H]+: 563.5.

Example 285: N-[5-[l-(dimethylcarbamoyl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



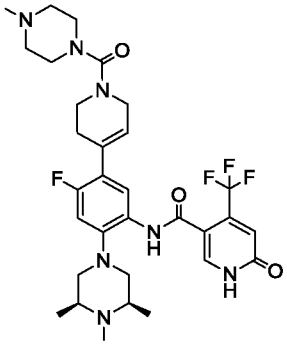
[00599] The procedure used was similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and dimethylcarbamoyl chloride (4.76 μï, 0.052 mmol) to give after workup and purification the title compound (24 mg, 75% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 - 7.90 (m, IH), 7.82 - 7.73 (m, IH), 6.99 - 6.94 (m, IH), 6.93 - 6.90 (m, IH), 6.06 - 5.97 (m, IH), 4.01 - 3.92 (m, 2H), 3.50 - 3.46 (m, 2H), 3.06 - 2.99 (m, 2H), 2.93 - 2.87 (m, 6H), 2.65 - 2.52 (m, 6H), 2.43 - 2.36 (m, 3H), 1.21 - 1.15 (m, 6H); LCMS [M+H]+ 579.3.

Example 286: N-[4-fluoro-5-[1-(pyrrolidine-1 -carbonyl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5SJ-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00600] The procedure was similar to Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 1-pyrrolidinecarbonyl chloride (5.71 µï, 0.052 mmol) to give, after workup and purification, the title compound (19 mg, 61% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.91 (m, 1H), 7.84 - 7.73 (m, 1H), 6.98 - 6.93 (m, 1H), 6.93 - 6.91 (m, 1H), 6.06 - 5.97 (m, 1H), 4.04 - 3.96 (m, 2H), 3.57 - 3.50 (m, 2H), 3.46 - 3.41 (m, 4H), 3.09 - 2.96 (m, 2H), 2.63 - 2.50 (m, 6H), 2.43 - 2.35 (m, 3H), 1.93 - 1.85 (m, 4H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 605.4.

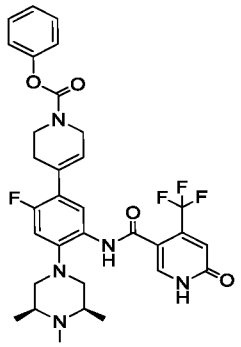
Example 287: N-[4-fluoro-5-[l-(4-methylpiperazine-l-carbonyl)-3, 6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00601] The procedure employed was similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-

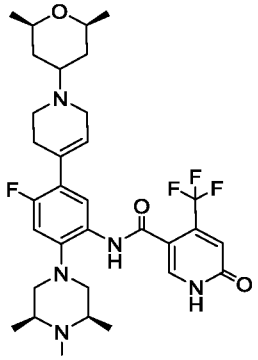
yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 4-methyl-l-piperazinecarbonyl chloride hydrochloride (10.30 mg, 0.052 mmol) to give, after workup and purification, the title compound as a white powder (24 mg, 73% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.90 (m, 1H), 7.83 - 7.72 (m, 1H), 6.99 - 6.93 (m, 1H), 6.93 - 6.91 (m, 1H), 6.04 - 5.97 (m, 1H), 4.03 - 3.97 (m, 2H), 3.54 - 3.49 (m, 2H), 3.38 - 3.35 (m, 4H), 3.06 - 2.99 (m, 2H), 2.64 - 2.53 (m, 6H), 2.53 - 2.47 (m, 4H), 2.41 - 2.37 (m, 3H), 2.37 - 2.33 (m, 3H), 1.17 (d, *J*=5.9 Hz, 6H); LCMS [M+H]+ 634.7.

Example 288: phenyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



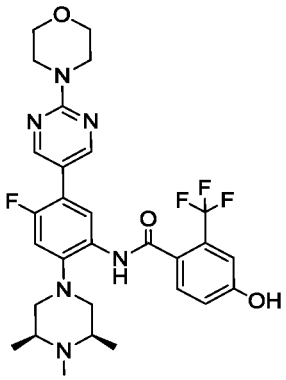
[00602] The procedure was similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and phenyl chloroformate (6.51 μï, 0.052 mmol) to give, after standard workup and purification, the title compound (23 mg, 71 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 7.99 - 7.93 (m, 1H), 7.86 - 7.78 (m, 1H), 7.45 - 7.37 (m, 2H), 7.29 - 7.22 (m, 1H), 7.21 - 7.11 (m, 2H), 7.03 - 6.95 (m, 1H), 6.95 - 6.90 (m, 1H), 6.12 - 6.03 (m, 1H), 4.45 - 4.17 (m, 2H), 3.98 - 3.74 (m, 2H), 3.08 - 3.01 (m, 2H), 2.71 - 2.52 (m, 6H), 2.43 - 2.36 (m, 3H), 1.21 - 1.16 (m, 6H); LCMS [M+H]+ 628.3.

Example 289: N-[4-fluoro-5-[l-[(2R, 6S)-2, 6-dimethyloxan-4-yl]-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00603] The procedure followed was similar to that of Example 148 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and cis-2,6-dimethyloxan-4-one (15.15 mg, 0.118 mmol) to give, after workup and purification, the title compound (16 mg, 40% yield). ^{1}H NMR (500MHz, METHANOLS) δ = 8.02 - 7.94 (m, 1H), 7.91 - 7.82 (m, 1H), 7.15 - 7.04 (m, 1H), 6.99 - 6.91 (m, 1H), 6.15 - 6.03 (m, 1H), 3.98 - 3.87 (m, 2H), 3.66 - 3.46 (m, 4H), 3.27 - 3.16 (m, 4H), 2.88 - 2.88 (m, 1H), 2.92 - 2.81 (m, 3H), 2.80 - 2.66 (m, 4H), 2.22 - 2.11 (m, 2H), 1.42 - 1.33 (m, 8H), 1.30 - 1.19 (m, 6H); LCMS [M+H]+ 620.6

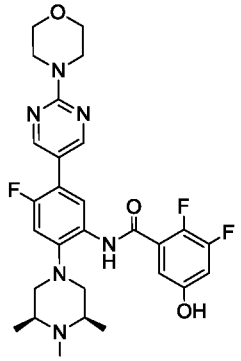
Example 290: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenyl]-4-hydroxy-2-(trifluoromethyl)benzamide



[00604] A mixture of 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (80 mg, 0.2 mmol), 4-hydroxy-2-(trifluoromethyl)benzoic acid (82 mg, 0.4mmol) and DCC (103 mg, 0.5 mmol) in DCM (5 mL) in a 30 mL vial was sealed and heated d at 45 °C for 18 h. It was purified by flash chromatography and prep-HPLC to give the title compound as a

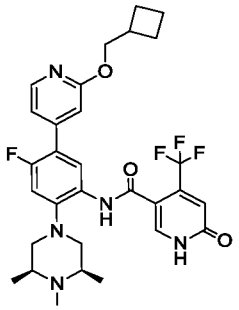
beige solid (TFA salt, 23.9 mg, 17%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.32 (br s, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 7.59 (br d, *J*=8.4 Hz, 1H), 7.23 - 7.18 (m, 2H), 7.14 (br d, *J*=8.3 Hz, 1H), 3.87 - 3.82 (m, 4H), 3.80 - 3.74 (m, 4H), 3.57 - 3.43 (m, 2H), 3.33 - 3.28 (m, 2H), 3.01 (br t, *J*=12.1 Hz, 2H), 2.93 (s, 3H), 1.43 (d, *J*=6.4 Hz, 6H); LCMS [M + H]$^+$ 589.4.

Example 291: 2,3-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-hydroxybenzamide



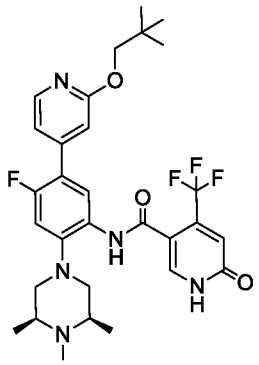
[00605] A mixture of 4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (80 mg, 0.2 mmol), 2,3-difiuoro-5-hydroxybenzoic acid (70 mg, 0.4mmol) and DCC (103 mg, 0.5 mmol) in DCM (5 mL) in a 30 mL vial was sealed and heated at 45 °C ovemight (18 h). It was purified by flash chromatography and prep-HPLC to give the title compound as a light purple solid (TFA salt, 15.7 mg, 12%). ¾ NMR (500MHz, METHANOL-d4) δ = 8.59 (s, 2H), 8.31 (d, *J*=8.3 Hz, 1H), 7.36 (q, *J*=9.5 Hz, 1H), 7.25 (br d, *J*=11.6 Hz, 1H), 6.81 (d, *J*=8.7 Hz, 1H), 3.92 - 3.85 (m, 4H), 3.82 - 3.75 (m, 4H), 3.58 - 3.43 (m, 2H), 3.39 (br d, *J*=12.8 Hz, 2H), 3.02 - 2.90 (m, 5H), 1.45 (d, *J*=6.5 Hz, 6H); LCMS [M+ H]$^+$ 557.3.

Example 292: N-[5-[2-(cyclobutylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[00606] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-(cyclobutylmethoxy)-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (33.7 mg, 0.116 mmol), N-(5-bromo-4-iluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (47 mg, 0.078 mmol) to give the title compound (34.6 mg, 76% yield). ¾ NMR (500MHz, DMSO-d6) δ = 9.59 (s, IH), 8.21 (d, *J*=5.3 Hz, IH), 7.93 (s, IH), 7.82 (d, *J*=8.4 Hz, IH), 7.11 (d, *J*=5.4 Hz, IH), 7.03 (d, *J*=12.8 Hz, IH), 6.88 (s, IH), 6.81 (s, IH), 4.27 (d, *J*=6.8 Hz, 2H), 3.09 (br d, *J*=10.9 Hz, 2H), 2.70 - 2.68 (m, IH), 2.73 (td, *J*=7.4, 14.7 Hz, IH), 2.36 (br s, 2H), 2.20 (br s, 3H), 2.12 - 2.01 (m, 2H), 1.97 - 1.74 (m, 4H), 1.01 (br d, *J*=5.9 Hz, 6H); LCMS [M+H]+: 588.6.

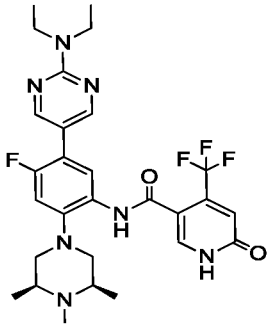
Example 293: N-[5-[2-(2,2-dimethylpropoxy)pyridin-4-yl]-4-fluoro-2-[(3R, 5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00607] The title compound was prepared by a procedure similar to the sequence described for Example 100 using 2-(neopentyloxy)-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (36.1 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.083 mmol) to give the title compound (21.1 mg, 43% yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.59 (s, IH), 8.20 (d, *J*=5.4

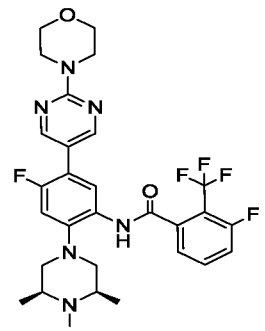
Hz, IH), 7.94 (s, IH), 7.82 (d, *J*=8.4 Hz, IH), 7.11 (br d, *J*=5.4 Hz, IH), 7.04 (d, *J*=12.8 Hz, IH), 6.89 (s, IH), 6.81 (s, IH), 3.99 (s, 2H), 3.09 (br d, *J*=10.9 Hz, 2H), 2.48 (br s, IH), 2.36 (br d, *J*=1.7 Hz, 2H), 2.20 (br s, 3H), 1.01 (br s, 6H), 1.00 (s, 9H); LCMS [M+H]+: 590.6.

Example 294: N-[5-[2-(diethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



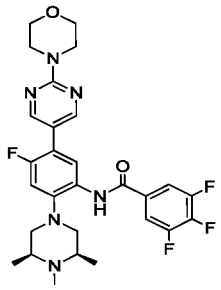
[00608] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-diethylaminopyrirnidine-5-boronic acid, pinacol ester (34.3 mg, 0.124 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(mfluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) to give the title compound (33.5 mg, 71% yield). ¾ NMR (500MHz, DMSO-d6) δ = 9.52 (s, IH), 8.46 (s, 2H), 7.90 (s, IH), 7.73 (d, *J*=8.7 Hz, IH), 7.03 (d, *J*=12.2 Hz, IH), 6.81 (s, IH), 3.62 (q, *J*=7.0 Hz, 4H), 3.01 (br d, *J*=11.0 Hz, 2H), 2.46 (br t, *J*=11.0 Hz, 2H), 2.35 (br d, *J*=6.1 Hz, 2H), 2.19 (s, 3H), 1.14 (t, *J*=7.0 Hz, 6H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 576.6.

Example 295: 3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



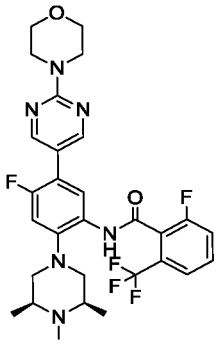
[00609] The title compound (beige solid, 49.3 mg, 82%) was prepared by a procedure similar to that of Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) in DCM (3 mL) and 3-fluoro-2-(trifluoromethyl)benzoyl chloride (23 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.58 (s, 2H), 8.51 (d, *J*=8.2 Hz, 1H), 8.42 (s, 1H), 7.67 (dt, *J*=5.0, 7.9 Hz, 1H), 7.39 - 7.33 (m, 2H), 7.00 (d, *J*=11.2 Hz, 1H), 3.91 - 3.84 (m, 4H), 3.83 - 3.78 (m, 4H), 2.85 (br d, *J*=ll.l Hz, 2H), 2.62 (br t, *J*=10.8 Hz, 2H), 2.32 - 2.18 (m, 5H), 1.12 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 591.5.

Example 296: 3,4,5-trifluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-ylJphenylJbenzamide



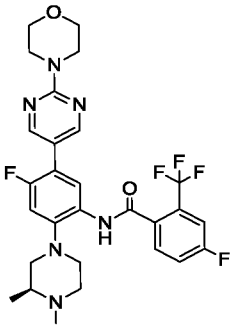
[00610] The title compound (tan solid, 38.3 mg, 67%) was prepared by a procedure similar to that of Example 34 using 3,4,5-trifluorobenzoic acid (35 mg, 0.2 mmol) and 4-fluoro-5-(2-moϕ holinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)aniline (40 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 9.20 (s, 1H), 8.60 - 8.54 (m, 3H), 7.56 (t, *J*=7.0 Hz, 2H), 7.03 (d, *J*=ll.l Hz, 1H), 3.91 - 3.84 (m, 4H), 3.84 - 3.77 (m, 4H), 2.87 (br d, *J*=11.0 Hz, 2H), 2.70 (t, *J*=10.9 Hz, 2H), 2.47 - 2.36 (m, 5H), 1.17 (d, *J*=6.2Hz, 6H); LCMS [M + H]$^+$ 559.5.

Example 297: 2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-(trifluoromethyl)benzamide



[00611] The title compound (off-white solid, 43.0 mg, 72%) was prepared by a procedure similar to Example 34 using 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol) and 2-fluoro-6-(trifiuoromethyl)benzoyl chloride (23 μL, 0.15 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.58 (s, 2H), 8.50 (d, *J*=8.2 Hz, 1H), 8.44 (s, 1H), 7.63 - 7.57 (m, 2H), 7.46 - 7.40 (m, 1H), 6.98 (d, *J*=11.4 Hz, 1H), 3.91 - 3.84 (m, 4H), 3.82 - 3.77 (m, 4H), 2.90 (br d, *J*=ll.l Hz, 2H), 2.61 (br t, *J*=10.8 Hz, 2H), 2.33 - 2.23 (m, 5H), 1.12 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^{+}$ 591.5.

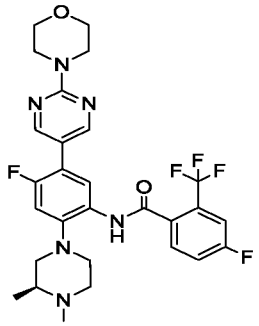
Example 298: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00612] The title compound (formic acid salt, pale beige solid, 34.8 mg, 56%) was prepared by a procedure similar to that of Example 29 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.104 mmol) and 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.36 (br s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.83 (dd, *J*=5.4, 8.4 Hz, 1H), 7.67 (dd, *J*=2.0, 9.0 Hz, 1H), 7.58 (t, *J*=8.3 Hz, 1H), 7.20 (d, *J*=11.9 Hz, 1H), 3.89 - 3.83 (m, 4H), 3.80 - 3.76

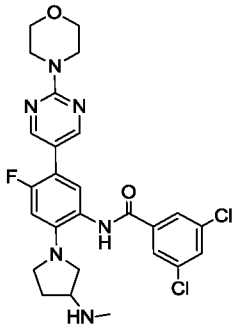
(m, 4H), 3.48 - 3.39 (m, 1H), 3.31 - 3.24 (m, 2H), 3.21 - 3.07 (m, 3H), 2.93 - 2.84 (m, 1H), 2.83 - 2.77 (m, 3H), 1.38 - 1.32 (m, 3H); LCMS $[M + H]^+$ 577.5.

Example 299: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide

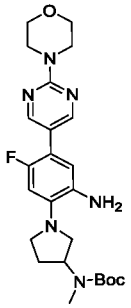


[00613] The title compound (formic acid salt, pale beige solid, 34.8 mg, 56%) was prepared through a procedure similar to Example 31 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.104 mmol) and 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (58 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.36 (br s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.83 (dd, *J*=5.4, 8.4 Hz, 1H), 7.67 (dd, *J*=2.0, 9.0 Hz, 1H), 7.58 (t, *J*=8.3 Hz, 1H), 7.20 (d, *J*=11.9 Hz, 1H), 3.89 - 3.83 (m, 4H), 3.80 - 3.76 (m, 4H), 3.48 - 3.39 (m, 1H), 3.31 - 3.24 (m, 2H), 3.21 - 3.07 (m, 3H), 2.93 - 2.84 (m, 1H), 2.83 - 2.77 (m, 3H), 1.38 - 1.32 (m, 3H); LCMS $[M + H]^+$ 577.5.

Example 300: 3,5-dichloro-N-[4-fluoro-2-[3-(methylamino)pyrrolidin-l-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide

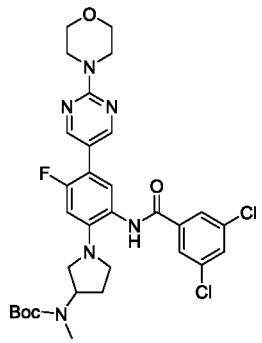


Step 1: tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate



[00614] A mixture of tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)pyrrolidin-3-yl)(methyl)carbamate (1.8598 g, 3.70 mmol, prepared as shown hereinabove in Example 277) and tin(II) chloride, 98% (2.105 g, 11.10 mmol) in a mixture of ethanol (EtOH) (10 ml) and methanol (MeOH) (10 ml) was heated to 90 °C. for 3 hours. Then the reaction mixture was concentrated onto celite and purified by flash chromatography [0-30% MeOH/DCM] to afford the tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (0.94 g, 1.990 mmol, 53.8 % yield) as a yellow powder. LCMS [M+H]+ 473.2.

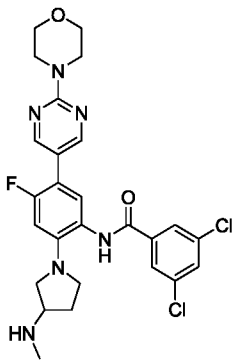
Step 2: tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate



[00615] To a solution of tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (211 mg, 0.446 mmol) and triethylamine (0.187 ml, 1.339 mmol) in DCM (40 ml) was added 3,5-dichlorobenzoyl chloride (94 mg, 0.446 mmol). Then the reaction mixture was stirred at room temperature for 2 hours. Then the crude material was dry loaded and purified by Flash chromatography [0-10% DCM/MeOH] to afford the desired tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-mo rpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (288 mg, 0.424 mmol, 95 % yield) as a yellow solid. ^{1}H

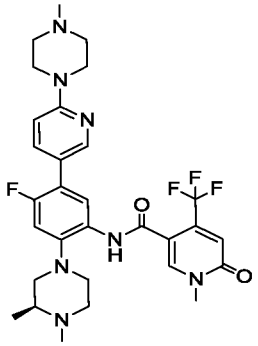
NMR (500 MHz, DMSO-d6) δ = 10.16 (s, IH), 8.52 (s, 2H), 7.95-8.02 (m, 2H), 7.88 (s, IH), 7.34 (d, *J*=8.80 Hz, IH), 6.72 (d, *J*=13.94 Hz, IH), 5.75 (s, IH), 4.55 (br. s., IH), 3.71-3.75 (m, 5H), 3.65-3.68 (m, 4H), 3.35-3.41 (m, 2H), 3.25-3.30 (m, 2H), 2.69 (s, 3H), 1.92-2.07 (m, 2H), 1.35 (s, 9H); LCMS [M+H]+ 645.2.

Step 3: 3,5-dichloro-N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide, 2Trifluoroacetic Acid, 2CF3COOH



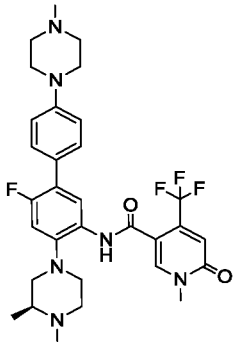
[00616] To a solution of tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (288 mg, 0.446 mmol) in DCM (3 mL) was added trifluoroacetic acid (2 ml, 26.1 mmol). The reaction mixture was stirred at 24 °C for 1 hour. Then the TFA and solvent were removed under vacuum and the crude material was purified by flash chromatography [0-20% DCM/MeOH] to afford the 3,5-dichloro-N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)benzamide (TFA salt), (77.4 mg, 0.095 mmol, 21.31 % yield) as a light brown powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 10.18 (s, IH), 8.73 (br. s., 2H), 8.53 (s, 2H), 7.97-8.04 (m, 2H), 7.89 (s, IH), 7.39 (d, *J*=8.80 Hz, IH), 6.76 (d, *J*=13.82 Hz, IH), 3.78 (d, *J*=5.38 Hz, IH), 3.71-3.75 (m, 4H), 3.65-3.69 (m, 4H), 3.62 (dd, *J*=6.85, 10.76 Hz, IH), 3.43-3.49 (m, 2H), 3.39 (dd, *J*=5.07, 10.70 Hz, 2H), 3.31-3.37 (m, 2H), 3.17 (s, 2H), 2.58 (br. s., 3H), 2.22-2.31 (m, IH), 1.98-2.07 (m, 1H);LCMS [M+H]+ 545.3.

Example 301: N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00617] The title compound (white solid, 36.9 mg, 61%) was prepared by a procedure similar to Example 273 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and 2-(4-methylpiperazin-l-yl)pyridine-5-boronic acid, pinacol ester (61 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.27 (s, IH), 8.17 (d, *J*=5.3 Hz, IH), 7.95 (d, *J*=7.9 Hz, IH), 7.10 (d, *J*=12.1 Hz, IH), 6.99 (s, IH), 6.95 (br s, IH), 6.90 (br d, *J*=4.6 Hz, IH), 3.66 (s, 3H), 3.65 - 3.59 (m, 4H), 3.19 - 3.06 (m, 2H), 3.00 - 2.88 (m, 2H), 2.66 - 2.51 (m, 6H), 2.44 - 2.34 (m, 7H), 1.13 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 602.4.

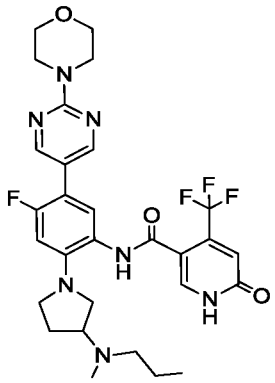
Example 302: N-[4-fluoro-5-[4-(4-methylpiperazin-l-yl)phenyl]-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00618] The title compound (light brown solid, 38.6 mg, 63%) was prepared by a procedure similar to Example 273 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-1-yl)-4-fluorophenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol) and [4-(4-methylpiperazin-l-yl)phenylboronic acid, pinacol ester (60 mg, 0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.25 (br s, IH), 7.93 (br d, *J*=8.2 Hz, IH), 7.47 (br d, *J*=7.8 Hz, 2H), 7.08 - 7.03 (m, 3H),

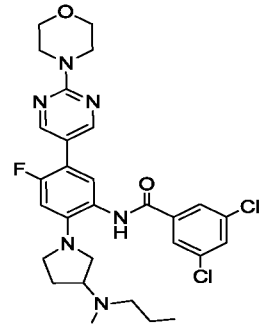
6.95 (s, 1H), 3.66 (s, 3H), 3.31 - 3.26 (m, 4H), 3.12 - 3.01 (m, 2H), 2.98 - 2.89 (m, 2H), 2.69 - 2.62 (m, 4H), 2.59 - 2.49 (m, 2H), 2.43 - 2.35 (m, 7H), 1.13 (d, *J*=6.4 Hz, 3H); LCMS $[M + H]^+$ 601.5.

Example 303: N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-l-yl]-5-(2-mo rpholin-4-ylpyrimidin-5-yl)phenyl]-6<>xo-4-(trifluoromethyl)-lH-pyridine -3-carboxamide

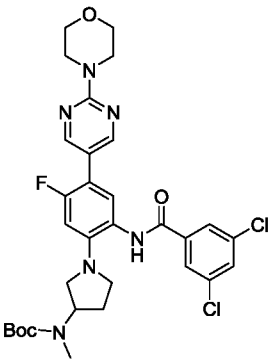


[00619] To a solution of N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (39 mg, 0.069 mmol) and propionaldehyde (17.7 mg, 0.305 mmol) in 1,2-dichloroethane (DCE) (3 ml) was added acetic acid (33 mg, 0.550 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Then sodium triacetoxyborohydride (53.0 mg, 0.250 mmol) was added and the reaction mixture was stirred at room temperature for an additional 20 minutes. Then a saturated solution of NaHCCb (3 mL) was added and the product was extracted using DCM (3x20mL). The organic phase was dried over MgSC>4 and after filtration and solvents removal, the crude material was dry loaded and purified by flash chromatography [0-30% MeOH/DCM] to afford the N-(4-fluoro-2-(3-(methyl(propyl)amino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide ·TFA (42.0 mg, 0.056 mmol, 80 % yield) as an off-white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.80 (s, 1H), 8.50 (s, 2H), 7.98 (s, 1H), 7.31 (d, *J*=8.56 Hz, 1H), 6.77 (s, 1H), 6.66 (d, *J*=14.06 Hz, 1H), 3.71-3.75 (m, 4H), 3.65-3.69 (m, 4H), 3.22-3.28 (m, 4H), 2.85-2.92 (m, 1H), 2.26 (q, *J*=6.77 Hz, 2H), 2.13 (s, 3H), 2.07 (d, *J*=6.72 Hz, 1H), 1.64-1.74 (m, 1H), 1.34-1.43 (m, 2H), 0.79 (t, *J*=7.34 Hz, 3H); LCMS [M+H]+ 604.5.

Example 304: 3,5-dichloro-N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-l-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide

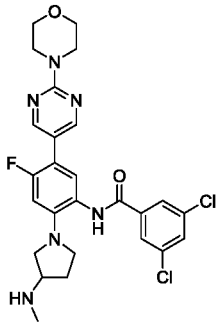


Step 1: tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl) (methyl)carbamate



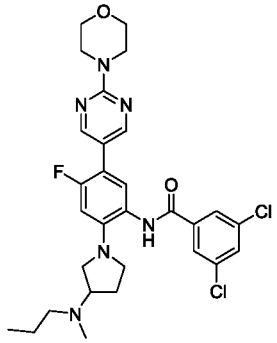
[00620] To a solution of tert-butyl (l-(2-amino-5-fluoro-4-(2-moϕ holinopyrimidin-5-yl)phenyl)pyrroli ώn-3-yl)(methyl)carbamate (211 mg, 0.446 mmol, preparation described in Example 277) and triethylamine (0.187 ml, 1.339 mmol) in DCM (40 ml) was added 3,5-dichlorobenzoyl chloride (94 mg, 0.446 mmol). Then the reaction mixture was stirred at room temperature for 2 hours. Then the crude material was dry loaded and purified by Flash chromatography [0-10% DCM/MeOH] to afford the desired tert-butyl (1-(2-(3,5-dicWorobenzamido)-5-fluoro-4-(2-mo ϕ holinopyrilnidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (288 mg, 0.424 mmol, 95 % yield) as a yellow solid. ¾ NMR (500MHz, DMSO-d6) δ = 10.16 (s, 1H), 8.52 (s, 2H), 7.95-8.02 (m, 2H), 7.88 (s, 1H), 7.34 (d, *J*=8.80 Hz, 1H), 6.72 (d, *J*=13.94 Hz, 1H), 5.75 (s, 1H), 4.55 (br. s., 1H), 3.71-3.75 (m, 5H), 3.65-3.68 (m, 4H), 3.35-3.41 (m, 2H), 3.25-3.30 (m, 2H), 2.69 (s, 3H), 1.92-2.07 (m, 2H), 1.35 (s, 9H); LCMS [M+H]+ 645.2.

Step 2: 3,5-dichloro-N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide ·TFA salt



[00621] To a solution of tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-moϕ holinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (288 mg, 0.446 mmol) in dichloromethane (DCM) (3 ml) was added trifluoroacetic acid (2 ml, 26.1 mmol). The reaction mixture was stirred at 24 °C for 1 hour. Then the TFA and solvent were removed under vacuum and the crude material was purified by Flash chromatography [0-20% DCM/MeOH] to afford the 3,5-dichloro-N-(4-fluoro-2-(3-(methylalmno)pyl·rolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)benzamide·2TFA, (77.4 mg, 0.095 mmol, 21.31 % yield) as a light brown powder. ¾ NMR (500MHz, DMSO-d6) δ = 10.18 (s, 1H), 8.73 (br. s., 2H), 8.53 (s, 2H), 7.97-8.04 (m, 2H), 7.89 (s, 1H), 7.39 (d, *J*=8.80 Hz, 1H), 6.76 (d, *J*=13.82 Hz, 1H), 3.78 (d, *J*=5.38 Hz, 1H), 3.71-3.75 (m, 4H), 3.65-3.69 (m, 4H), 3.62 (dd, *J*=6.85, 10.76 Hz, 1H), 3.43-3.49 (m, 2H), 3.39 (dd, *J*=5.07, 10.70 Hz, 2H), 3.31-3.37 (m, 2H), 3.17 (s, 2H), 2.58 (br. s., 3H), 2.22-2.31 (m, 1H), 1.98-2.07 (m, 1H); LCMS [M+H]+ 545.3.

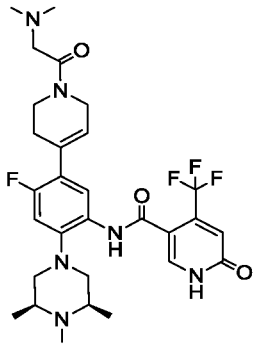
Step 3: 3,5-dichloro-N-(4-fluoro-2-(3-(methyl(propyl)amino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)benzamide



[00622] To a solution of 3,5-ichloro-N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)benzalnide (35 mg, 0.064 mmol) and propionaldehyde (3.73 mg, 0.064 mmol) in 1,2-dichloroethane (DCE) (3 ml) was added acetic acid (23 mg, 0.383 mmol) and the reaction mixture was stirred at room temperature

for 15 minutes. Then sodium triacetoxyborohydride (50 mg, 0.236 mmol) was added and the reaction mixture was stirred at room temperature for an hour. Then a saturated solution of NaHC03 (3 mL) was added and the product was extracted using DCM (3x20mL). The organic phase was dried over MgSC)4 and after filtration and solvents removal, the crude material was dry loaded and purified by Flash chromatography [0-10% MeOH/DCM] to afford the 3,5-dichloro-N-(4-fluoro-2-(3-(methyl(propyl)alnino)pyrrolidin-l-yl)-5-(2-mo ϕ holinopyrirnidin-5-yl)phenyl)benzamide (25.0 mg, 0.040 mmol, 63.0 % yield) as a slightly yellow powder. ¾ NMR (500MHz, DMSO-d6) δ = 10.17 (s, 1H), 8.51 (s, 2H), 7.99 (s, 1H), 7.98 (s, 1H), 7.85-7.92 (m, 1H), 7.30 (d, *J*=8.80 Hz, 1H), 6.66 (d, *J*=14.06 Hz, 1H), 3.70-3.79 (m, 5H), 3.65-3.70 (m, 5H), 3.35-3.44 (m, 2H), 3.18-3.29 (m, 2H), 2.86 (br. s., 1H), 2.13-2.25 (m, 2H), 2.05-2.13 (m, 4H), 1.91 (s, 1H), 1.60-1.72 (m, 1H), 1.26-1.50 (m, 3H), 0.73-0.93 (m, 1H), 0.70 (t, *J*=7.27 Hz, 3H); LCMS [M+H]+ 587.4.

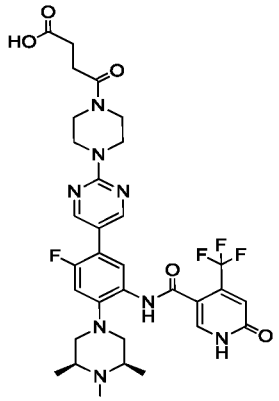
Example 305: N-[5-[l-[2-(dimethylamino)acetyl]-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00623] The procedure followed was similar to Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-(dimethylamino)acetyl chloride hydrochloride (12.09 mg, 0.065 mmol) to give the title compound (21.5 mg, 55% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 - 7.93 (m, 1H), 7.84 - 7.75 (m, 1H), 7.01 - 6.94 (m, 1H), 6.91 (s, 1H), 6.09 - 5.98 (m, 1H), 4.31 - 4.18 (m, 2H), 3.84 - 3.72 (m, 2H), 3.50 - 3.45

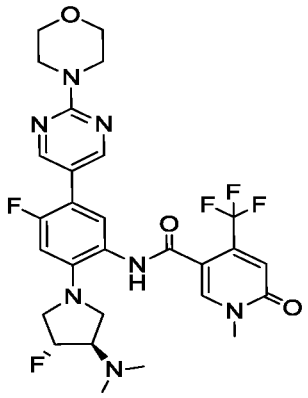
(m, 2H), 3.07 - 2.98 (m, 2H), 2.65 - 2.50 (m, 6H), 2.49 - 2.41 (m, 6H), 2.40 - 2.36 (m, 3H), 1.18 - 1.14 (m, 6H); LCMS [M+H]+ 593.

Example 306: 4-[4-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]pyrimidin-2-yl]piper azin-l-yl]-4-oxobutanoic acid

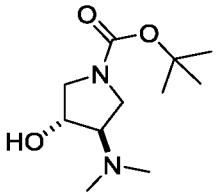


[00624] N-(4-fluoro-5-(2-(piperazin-l-yl)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (15.32 mg, 0.026 mmol) and succinic anhydride (5.21 mg, 0.052 mmol) were dissolved in N,N-diisopropylethylamine (4.53 μL, 0.026 mmol) and tetrahydrofuran (THF) (521 μL). The suspension was stirred overnight, and the residue was purified using a cation exchange column eluting with MeOH:NH_4OH. ^1H NMR (500 MHz, MeOD) δ 8.55 (s, 2H), 7.97 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 12.0 Hz, 1H), 6.91 (s, 1H), 3.97 - 3.93 (m, 2H), 3.89 - 3.85 (m, 2H), 3.67 (d, *J* = 9.7 Hz, 4H), 3.09 (d, *J* = 8.9 Hz, 2H), 2.70 (dt, *J* = 10.4, 7.1 Hz, 6H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 1.20 (d, *J* = 5.5 Hz, 6H); LCMS HSS $[M+l]^+$ = 689.40.

Example 307: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4RJ-3-(dimethylamino)-4-fluoropyrrolidin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

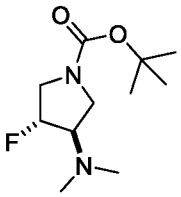


Step 1: trans-tert-butyl-3-(dimethylamino)-4-hydroxypyrrolidine-l-carboxylate



[00625] A solution of tert-butyl 6-oxa-3-azabicyclo[3. 1.0]hexane-3-carboxylate (0.42 mL, 2.7 mmol) and dimethylamine (2.0 M THF, 6.0 mL, 12 mmol) in a sealed vial was heated at 90 °C for 40 h in an aluminum reaction block. After cooling to room temperature the reaction mixture was concentrated onto celite and purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded *trans*-tert-butyl-3-(dimethylamino)-4-hydroxypyrrolidine-l-carboxylate (1.6 g, 64 %). ^1H NMR (500MHz, DMSO-d6) δ = 5.08 (d, *J*=4.9 Hz, 1H), 4.10 (br s, 1H), 3.49 - 3.37 (m, 3H), 3.18 - 3.10 (m, 1H), 3.05 - 2.97 (m, 1H), 2.18 (s, 6H), 1.39 (s, 9H).

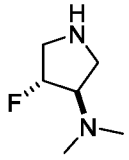
Step 2: trans-tert-butyl-3-(dimethylamino)-4-fluoropyrrolidine-l-carboxylate



[00626] (Diethylamino)sulfur trifluoride (0.40 mL, 3.0 mmol) was added dropwise to a stirring solution of frafts-tert-butyl-3-(dimethylamino)-4-hydroxypyrrolidine-l-carboxylate (0.50 g, 2.2 mmol) in DCM (10 mL) at -78 °C. The reaction was allowed to warm to room temperature overnight. The reaction mixture was concentrated onto celite and purification by flash chromatography [0 -

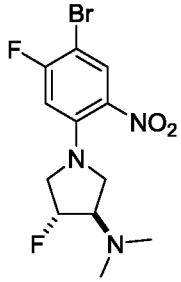
3% DCM/MeOH + 0.5% NH_4OH] afforded irara-tert-butyl-3-(dimethylamino)-4-fluoropyrrolidine-l-carboxylate (0.39 g, 78 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 5.27 - 5.12 (m, 1H), 3.67 - 3.55 (m, 1H), 3.48 (dd, *J*=6.8, 11.5 Hz, 1H), 3.42 - 3.35 (m, 1H), 3.27 (br s, 1H), 2.90 (br s, 1H), 2.19 (s, 6H), 1.41 (s, 9H).

Step 3: Trms-4-fluoro-N,N-dimethylpyrrolidin-3-amine



[00627] Trifluoroacetic acid (1.3 mL, 17 mmol) was added to a solution of *tra«s*4ert-butyl-3-(dimethylamino)-4-fluoropyrrolidine-l-carboxylate (0.39 g, 1.7 mmol) in DCM (3 mL) at room temperature. After stirring for 3 h the volatiles were removed under a stream of air and the pure product was isolated by a catch and release protocol using an SCX-2 silica cartridge. 7a «*s*-4-fluoro-N,N-dimethylpyrrolidin-3 -amine (0. 12 g, 54%). ^{1}H NMR (500MHz, DMSO-d6) δ = 5.08 - 4.90 (m, 1H), 3.09 (dd, *J*=7.1, 10.8 Hz, 1H), 3.02 - 2.80 (m, 2H), 2.59 (dt, *J*=2.0, 7.5 Hz, 1H), 2.45 (dd, *J*=8.0, 10.8 Hz, 1H), 2.17 (s, 6H).

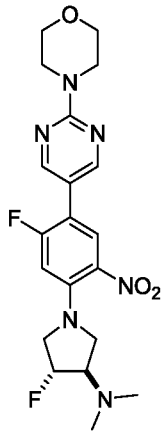
Step 4: Trans-l-(4-bromo-5-fluoro-2-nitrophenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine



[00628] A solution of l-bromo-2,4-difluoro-5-nitrobenzene (0.225 g, 0.945 mmol) in PhMe (1 mL) was slowly added to a rapidly stirring mixture of *trans*-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.13 g, 0.95 mmol) and K2CO $_3$ (0.065 g, 0.47 mmol) in PhMe (2 mL) at room temperature. After stirring for 15 minutes the reaction was warmed to 45 °C for 5 h. The reaction was cooled to room temperature and partitioned between $\mathbf{H_20}$ (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with an additional portion of EtOAc. The combined organic extracts

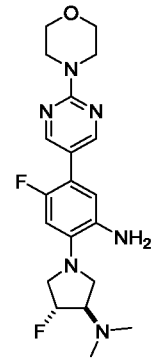
were concentrated onto celite and purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded /rara-l-(4-bromo-5-fluoro-2-nitrophenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.25 g, 76 %). LCMS [M+H]+: 350.3.

Step 5: trans-4-fluoro-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



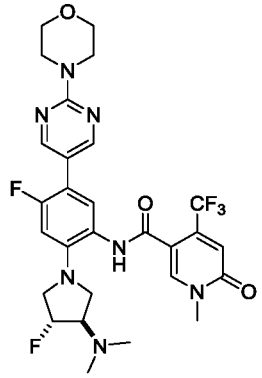
[00629] A 30 mL vial was charged with a mixture of *trans*-\-(4-bromo-5-fluoro-2-nitrophenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.13 g, 0.36 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (0.12 g, 0.39 mmol), XPhos Pd G2 (6 mg, 7 μηιοϊ) and XPhos (4 mg, 7 μηιοϊ). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and aqueous sodium carbonate (2 M, 0.6 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 90 °C in an aluminum block for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded the product (0.16 g, 95 %). LCMS [M+H]+: 435.4.

Step 6: trms-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine



[00630] A mixture of *trans*-4-fluoro-1-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.17 g, 0.38 mmol) and $SnCl_2$ (0.22 g, 1.2 mmol) in EtOH (6 mL) was heated to 75 °C for 5 h. After cooling to room temperature the reaction was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded *trans*-1-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.13 g, 83 %). LCMS [M+H]+: 405.4.

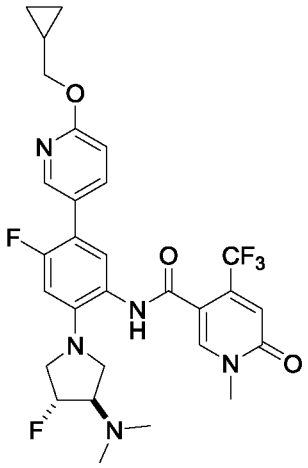
Step 7: trans-N-(2-(3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide



[00631] 1-Methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylic acid (0.050 g, 0.22 mmol) was activated with HATU (0.085 g, 0.22 mmol) and N,N-diisopropylethylamine (0.04 mL, 0.22 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a solution of *trans*-1-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.060 g, 0.15 mmol) in DMF (1 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH].

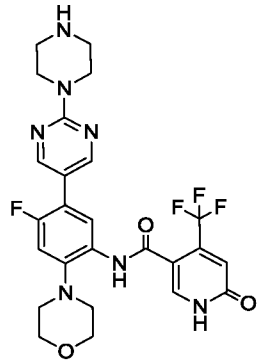
Further purification by a catch and release protocol using an SCX-2 silica cartridge afforded the title compound *trans*-N-(2-(3-(dimethylamino)-4-fluoropyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.055 g, 61 %). LCMS [M+H]+: 608.5.

Example 308: trans-N-(5-(6-(cyclopropylmethoxy)pyridin-3-yl)-2-(3-(dimethylamino)-4-fluoropyrrolidin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-!, 6-dihydropyridine-3-carboxamide

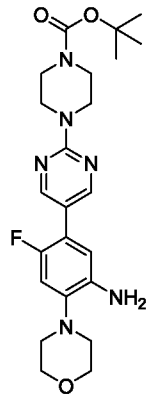


[00632] The title compound (76 mg, 53% yield) was prepared from (3R,4S)-l-(2-amino-4-(6-(cyclopropylmethoxy)pyridin-3-yl)-5-fluorophenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (50 mg, 0.129 mmol) and 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (42.7 mg, 0.193 mmol) according to methods similar to Example 34. ¾ NMR (500 MHz, DMSO-d6) δ = 9.85 (s, IH), 8.37 (s, IH), 8.24 (s, IH), 7.80 (br d, *J*=7.7 Hz, IH), 7.38 (d, *J*=8.6 Hz, IH), 6.93 (d, *J*=8.9 Hz, IH), 6.89 - 6.82 (m, 2H), 5.31 - 5.14 (m, IH), 4.14 (d, *J*=7.1 Hz, 2H), 3.63 - 3.58 (m, 2H), 3.54 (s, 3H), 3.16 (br dd, *J*=6.6, 10.0 Hz, IH), 2.98 - 2.89 (m, IH), 2.22 (s, 6H), 0.59 - 0.54 (m, 2H), 0.34 (q, *J*=4.8 Hz, 2H); LCMS [M+H]+: 592.5.

Example 309: N-[4-fluoro-2-morpholin-4-yl-5-(2-piperazin-l -ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

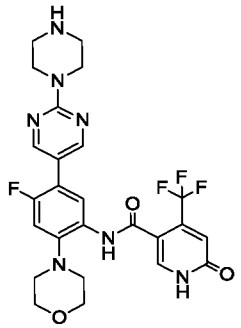


Step 1: tert-butyl 4-(5-(5-amino-2-fluoro-4-morpholinophenyl)pyrimidin-2-yl)piperazine-l-carboxylate



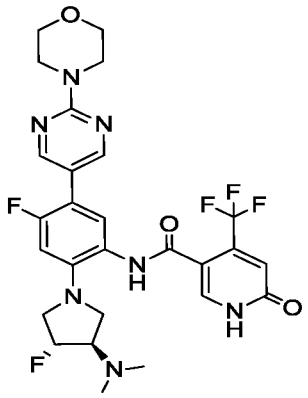
[00633] To a 5 mL microwave vial charged with 5-bromo-4-fluoro-2-(morpholin-4-yl)aniline (190 mg, 0.691 mmol), 2-(4-boc-piperazino)pyrimidine-5-boronic acid pinacol ester (323 mg, 0.829 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (48.9 mg, 0.069 mmol) and potassium phosphate tribasic (0.440 g, 2.072 mmol) was added 1,4-dioxane (12 mL) / water (1.3 mL) (9 : 1 mixture) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 110 °C. The solvent was evaporated and 15 mL of CH2CI2 were added. The suspension was sonicated and extracted from water (15 mL). The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2). The compound was freeze dried for 2 days to afford the title reagent. ^{1}H NMR (500 MHz, MeOD) δ 8.49 (d, J = 1.0 Hz, 2H), 6.87 (d, J = 12.1 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 3.85 (dd, J = 10.0, 7.1 Hz, 8H), 3.52 (s, 4H), 2.94 - 2.90 (m, 4H), 1.49 (s, 9H); LCMS [M+l] $^+$ = 459.40.

Step 2: N-(4-fluoro-2-morpholino-5-(2-(piperazin-l-yl)pyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



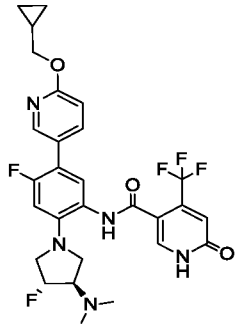
[00634] In a 5 mL microwave vial to a suspension of 6-hydroxy-4-(trifluoromethyl)nicotinic acid (145 mg, 0.698 mmol) in pyridine, anhydrous (847 µï, 10.47 mmol) was added slowly diethyl chlorophosphate (103 µï, 0.715 mmol at RT in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 hours. The suspension turned into a solution and then into a suspension again. To this, tert-butyl 4-(5-(5-amino-2-fluoro-4-mo rpholinophenyl)pyrirnidin-2-yl)piperazine-l-carboxylate (80 mg, 0.174 mmol) was added and the reaction was heated at 70 °C for 3 h. After completion, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous $Na_2SC>4$. The solvent was evaporated in vacuo yielding the crude product. The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the silyloxy intermediate. The product was dissolved in 2 mL of dichloromethane and trifluoroacetic acid (398 mg, 3.49 mmol) was added. The purple solution was stirred for 1 hour and the solvent was evaporated. The residue was purified using a cation exchange column eluting with MeOH:NH_4OH and freeze dried for 2 days to afford the title compound. ^1H NMR (500 MHz, MeOD) δ 8.55 (d, *J* = 0.9 Hz, 2H), 8.00 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 12.1 Hz, 1H), 6.88 (s, 1H), 3.92 - 3.88 (m, 4H), 3.85 - 3.81 (m, 4H), 2.96 (dd, *J* = 9.8, 5.2 Hz, 8H); LCMS $[M+l]^+$ = 548.41.

Example 310: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-l-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



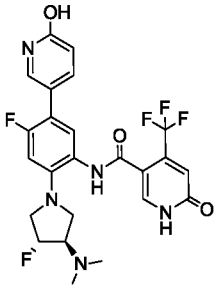
[00635] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.068 g, 0.22 mmol) was activated with HATU (0.085 g, 0.22 mmol) and N,N-diisopropylethylamine (0.04 mL, 0.22 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a solution of trans- l-(2-amino-5 -fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-N,N-dimethylpyrrolidin-3-amine (0.060 g, 0.15 mmol, from Example 307) in DMF (1 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with trifluoroacetic acid (2 mL) at room temperature. After stirring for 3 h the volatiles were removed under a stream of air and the residue was concentrated onto celite. Reverse phase chromatography [5-95% MeCN/H_2**0** + 10 mM NH_4HCO_3] followed by lyophilization afforded trans-N-(2-(3-(dimethylamino)-4-fluoropyrrolidin-l-yl)-4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.040 g, 45 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.81 (br s, 1H), 8.52 (s, 2H), 8.01 (br s, 1H), 7.40 (d, *J*=8.8 Hz, 1H), 6.82 (d, *J*=13.6 Hz, 1H), 6.75 (br s, 1H), 5.30 - 5.14 (m, 1H), 3.76 - 3.73 (m, 4H), 3.70 - 3.67 (m, 4H), 3.62 - 3.53 (m, 4H), 3.19 - 3.14 (m, 1H), 2.97 - 2.88 (m, 1H), 2.22 (s, 6H); LCMS [M+H]+: 594.5.

Example 311: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R, 4RJ-3-(dimethylamino)-4-fluoropyrrolidin-l-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



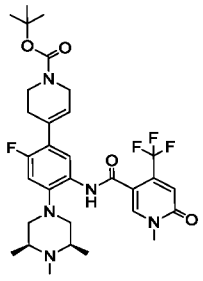
[00636] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.060 g, 0.19 mmol) was activated with HATU (0.073 g, 0.19 mmol) and N,N-diisopropylethylamine (0.04 niL, 0.19 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a solution of trans-l-(2-amino-4-(6-(cyclopropylmethoxy)pyridin-3-yl)-5-fluorophenyl)-4-fluoro-N,N-dimethylpyrrolidin-3 -amine (0.050 g, 0.13 mmol) in DMF (1 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with trifluoroacetic acid (2 mL) at room temperature. After stirring for 3 h the volatiles were removed under a stream of air and the residue was concentrated onto celite. Reverse phase chromatography [5-95% MeCN/H_2**0** + 10 mM NH_4HCO_3] afforded 18 mg (27% yield) of the title compound. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.81 (br s, IH), 8.24 (s, IH), 8.01 (br s, IH), 7.81 (br d, *J*=9.5 Hz, IH), 7.40 (br d, *J*=8.7 Hz, IH), 6.92 (d, *J*=8.7 Hz, IH), 6.82 (d, *J*=13.7 Hz, IH), 6.75 (br s, IH), 5.30 - 5.15 (m, IH), 4.13 (d, *J*=7.1 Hz, 2H), 3.63 - 3.53 (m, 4H), 3.17 (dd, *J*=6.3, 10.2 Hz, IH), 2.97 - 2.87 (m, IH), 2.22 (s, 6H), 1.30 - 1.23 (m, IH), 0.59 - 0.53 (m, 2H), 0.36 - 0.32 (m, 2H); LCMS [M+H]+: 578.5.

Example 312: N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R, 4R)-3-(dimethylamino)-4-fluoropyrrolidin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carbom mide



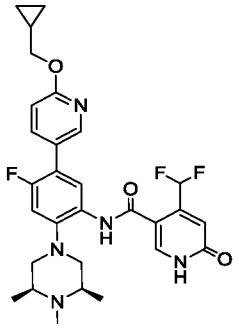
[00637] The reverse phase chromatography from Example 311 afforded 17 mg (23% yield) of the title compound. ^{1}H NMR (500MHz, DMSO-d6) δ = 11.92 - 11.65 (m, IH), 9.77 (br s, IH), 8.01 (br s, IH), 7.61 (br d, *J*=9.0 Hz, IH), 7.46 (br s, IH), 7.34 (d, *J*=8.8 Hz, IH), 6.85 - 6.71 (m, 2H), 6.44 (d, *J*=9.5 Hz, IH), 5.33 - 5.10 (m, IH), 3.61 - 3.53 (m, 5H), 3.13 (dd, *J*=6.7, 10.0 Hz, IH), 2.97 - 2.85 (m, IH), 2.21 (s, 6H); LCMS [M+H]+: 524.3.

Example 313: tert-butyl 4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl] amino] -4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -3,6-dihydro-2H-pyridine-l-carboxylate



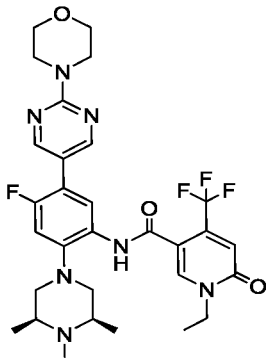
[00638] Iodomethane (1. 178 μï, 0.019 mmol) was added to a solution of tert-butyl 4-(2-fluoro-5-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate (10 mg, 0.016 mmol) and cesium carbonate (5.36 mg, 0.016 mmol) in DMF (1. ml) at RT to give the title compound (8 mg, 74% yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.15 - 8.07 (m, IH), 7.71 - 7.63 (m, IH), 6.90 - 6.82 (m, 2H), 5.95 - 5.83 (m, IH), 4.02 - 3.94 (m, 2H), 3.58 - 3.49 (m, 5H), 2.94 - 2.88 (m, 2H), 2.52 - 2.38 (m, 6H), 2.28 - 2.24 (m, 3H), 1.42 - 1.39 (m, 9H), 1.06 - 1.03 (m, 6H); LCMS [M+H]+ 622.5.

Example 314: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide



[00639] The title compound (19 mg, 46% yield) was obtained from 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylic acid (59.0 mg, 0.312 mmol) and 5-(6-(cyclopropylmethoxy)pyridin-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (30 mg, 0.078 mmol). ¹H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 8.01 (s, 1H), 7.86 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 55.1 Hz, 1H), 7.05 (d, *J* = 12.1 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.81 (s, 1H), 4.15 (d, *J* = 7.1 Hz, 2H), 3.07 (d, *J* = 11.3 Hz, 2H), 2.60 (t, *J* = 11.1 Hz, 2H), 2.55 - 2.47 (m, 2H), 2.36 (s, 3H), 1.34 - 1.25 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 6H), 0.64 - 0.58 (m, 2H), 0.36 (q, *J* = 4.7 Hz, 2H); LCMS [M+l]+ = 556.5.

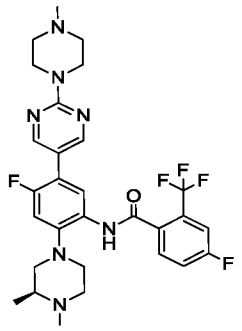
Example 315: l-ethyl-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidm-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)pyridme-3-carbomm ide



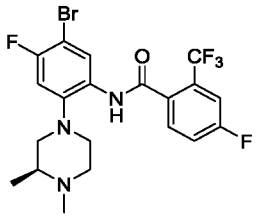
[00640] Cesium carbonate (25.5 mg, 0.078 mmol) was added to a solution of N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihy dropyridine-3 -carboxamide (46.06 mg, 0.078 mmol) and iodoethane (7.19 µï, 0.090 mmol) in DMF (1562 µï) at RT. The reaction mixture was stirred at RT overnight. The solvent was evaporated in vacuo yielding the crude product then purification was performed by flash column

chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the desired compound. ^1H NMR (500 MHz, MeOD) δ 8.55 (s, 2H), 8.23 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 12.1 Hz, 1H), 6.93 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.85 - 3.82 (m, 4H), 3.78 - 3.75 (m, 4H), 3.06 (d, *J* = 11.4 Hz, 2H), 2.61 (t, *J* = 11.2 Hz, 2H), 2.54 - 2.47 (m, 2H), 2.34 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 6H); LCMS HSS $[M+l]^+$ = 618.61.

Example 316: 4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide

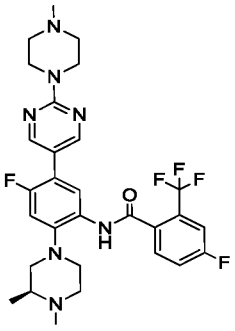


Step 1: (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide



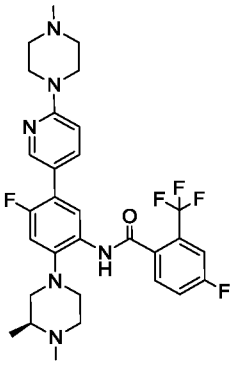
[00641] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.61 mL, 4 mmol) in DCM (15 mL) at rt was added Et_3N (1.12 mL, 8 mmol). After addition, the resulting mixture was stirred at rt for 5 min and a solution of (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (604 mg, 2 mmol) in DCM (10 mL) was added. The resulting dark orange solution was stirred at rt for 2 h. After quenching with sat. $NaHC0_3$ (15 mL) and stirring for 2 min at rt, it was extracted with DCM (20 mL x 2). The combined extracts were combined, and concentrated to give a light beige solid. Purification by flash chromatography (gradient: EtOAc/hex 0-100%) gave the title compound as a light yellow solid (822 mg, 82%). LCMS $[M + H]^+$ 492.4.

Step 2: Preparation of (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-(4-methylpiperazin-l-yl)pyrimidin-5-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide



[00642] The title compound (beige solid, 15.9 mg, 26%) was prepared according to a procedure similar to the last step of Example 31 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (53 mg, 0.1 mmol) and 2-(4-methylpiperazin-l-yl)pyrimidine-5-boronic acid pinacol ester (61 mg, 0.2 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.61 - 8.54 (m, 4H), 7.67 (dd, *J*=5.3, 8.4 Hz, IH), 7.50 (dd, *J*=2.4, 8.7 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.02 (d, *J*=11.2 Hz, IH), 3.97 - 3.87 (m, 4H), 2.97 - 2.81 (m, 4H), 2.56 (t, *J*=10.5 Hz, IH), 2.50 (t, *J*=5.1 Hz, 4H), 2.36 (s, 3H), 2.32 - 2.25 (m, 4H), 2.12 (br s, IH), 1.05 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 590.3.

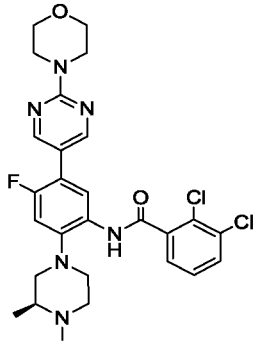
Example 317: 4-fluoro-N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00643] The title compound (beige solid, 6.6 mg, 11%) was prepared through a method similar to Example 31 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (53 mg, 0.1 mmol) and 2-(4-methylpiperazin-l-yl)pyridine-5-boronic acid, pinacol ester (61 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.62 (d, *J*=7.9 Hz, IH), 8.56 (s, IH), 8.24

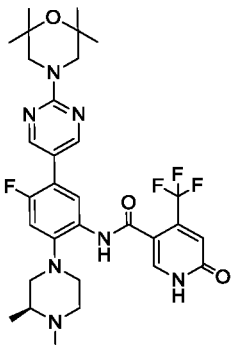
(d, *J*=5.1 Hz, IH), 7.67 (dd, *J*=5.3, 8.4 Hz, IH), 7.51 (dd, *J*=2.3, 8.8 Hz, IH), 7.39 (t, *J*=8.0 Hz, IH), 7.01 (d, *J*=11.2 Hz, IH), 6.88 - 6.83 (m, 2H), 3.67 - 3.59 (m, 4H), 2.99 - 2.82 (m, 4H), 2.61 - 2.52 (m, 5H), 2.36 (s, 3H), 2.32 - 2.26 (m, 4H), 2.13 (br s, IH), 1.06 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 589.5.

Example 318: 2,3-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJbenzamide



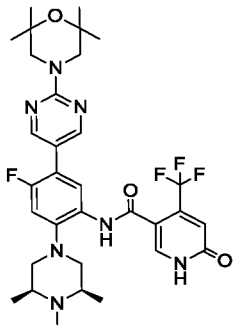
[00644] The title compound (beige solid, 45.5 mg, 77%) was prepared through a method similar to Example 78 using 2,3-dichlorobenzoic acid (38 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.91 (s, IH), 8.63 (d, *J*=8.2 Hz, IH), 8.58 (s, 2H), 7.60 (dd, *J*=8.0, 9.1 Hz, IH), 7.61 (dd, *J*=7.9, 12.2Hz, IH), 7.36 (t, *J*=7.8 Hz, IH), 7.01 (d, *J*=11.2 Hz, IH), 3.91 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.88 (br d, *J*=11.0 Hz, 2H), 2.64 (t, *J*=10.9 Hz, 2H), 2.39 - 2.29 (m, 5H), 1.13 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 573.3.

Example 319: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l -yl]-5-[2-(2,2,6,6-tetramethylmorpholin-4-yl)pyrimidin-5-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



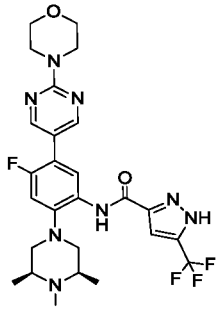
[00645] To a mixture of 2-chloropyrimidine-5-boronic acid (31.7 mg, 0.2 mmol) and 2,2,6,6-tetramethylmo rpholine (30.1 mg, 0.21 mmol) in EtOH (1 mL) was added triethylamine (0.042 mL, 0.3 mmol). The resulting suspension was stirred at 70 °C for 1 h. Solvents were removed to give the crude (2-(2,2,6,6-tetramethylmorpholino)pyrimidin-5-yl)boronic acid intermediate as colorless crystals. LCMS $[M + H]^+$ 266.3. The title compound (white solid, 40.7 mg, 64%) was prepared through methods similar to those described in Example 40 using the above boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (br s, 1H), 8.54 (s, 2H), 8.47 (br d, *J*=8.1 Hz, 1H), 7.87 (s, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 7.01 (s, 1H), 3.72 (s, 4H), 3.02 - 2.87 (m, 3H), 2.83 (br d, *J*=10.8 Hz, 1H), 2.60 (br t, *J*=10.3 Hz, 1H), 2.35 (br s, 4H), 2.22 (br s, 1H), 1.29 (s, 12H), 1.10 (br d, *J*=5.9 Hz, 3H); LCMS $[M + H]^+$ 632.5.

Example 320: N-[4-fluoro-2-[(3R, 5SJ-3,4,5-trimethylpiperazin-l -yl]-5-[2-(2,2,6,6-tetramethylmorpholin-4-yl)pyrimidin-5-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



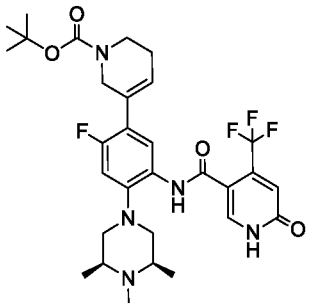
[00646] The title compound (white solid, 32.3 mg, 49%) was prepared by methods similar to those described in Example 31 using crude (2-(2,2,6,6-tetramethylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (br s, 1H), 8.54 (s, 2H), 8.45 (d, *J*=8.1 Hz, 1H), 7.87 (s, 1H), 7.05 - 6.97 (m, 2H), 3.72 (s, 4H), 2.82 (br d, *J*=10.8 Hz, 2H), 2.66 (br t, *J*=10.8 Hz, 2H), 2.40 - 2.26 (m, 5H), 1.29 (s, 12H), 1.14 (br d, *J*=6.0 Hz, 6H); LCMS $[M + H]^+$ 646.5.

Example 321: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)-lH-pyrazole-3-carboxamide



[00647] The title compound (white solid, 48.8 mg, 86%) was prepared by methods similar to Example 34 using 5-(trifluoromethyl)-lH-pyrazole-3-carboxylic acid (27 mg, 0.15 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.37 (s, 1H), 8.61 (d, *J*=1.0 Hz, 2H), 8.58 (d, *J*=8.2 Hz, 1H), 7.05 (d, *J*=11.2 Hz, 1H), 7.01 (s, 1H), 3 .93 - 3.87 (m, 4H), 3.84 - 3.80 (m, 4H), 2.91 (br d, *J*=11.0 Hz, 2H), 2.74 (t, *J*=10.9 Hz, 2H), 2.55 - 2.46 (m, 2H), 2.42 (s, 3H), 1.18 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 563.5.

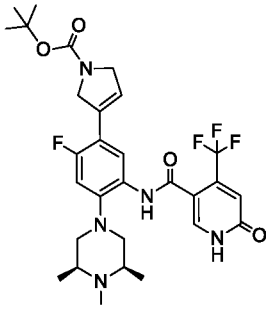
Example 322: tert-butyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



[00648] The procedure followed was similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (400 mg, 0.661 mmol) and l-boc-5,6-dihydro-2H-pyridine-3-boronic acid, pinacol ester (306 mg, 0.991 mmol) to give, after deprotection of the silyloxy intermediate tert-butyl 5-(2-fluoro-5-(6-oxo-4-

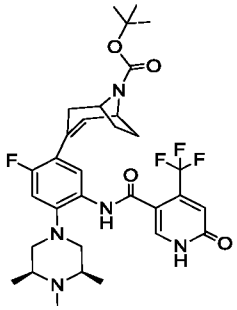
(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate and purification, the title compound.(33 mg, 73% yield). ^{1}H NMR (500MHz, METHANOLS) δ = 7.86 - 7.80 (m, 1H), 7.69 - 7.60 (m, 1H), 6.89 - 6.82 (m, 1H), 6.82 - 6.77 (m, 1H), 6.02 - 5.95 (m, 1H), 4.15 - 4.06 (m, 2H), 3.54 - 3.42 (m, 2H), 2.95 - 2.89 (m, 2H), 2.54 - 2.40 (m, 4H), 2.28 - 2.25 (m, 3H), 2.24 - 2.19 (m, 2H), 1.40 - 1.37 (m, 9H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 608.4

Example 323: tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl] amino] -4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -2,5-dihydropyrrole-l-carboxylate



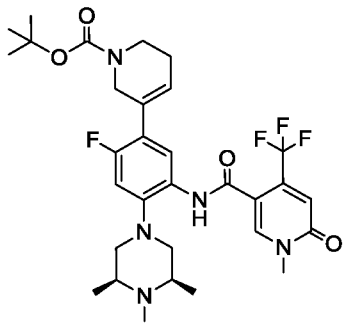
[00649] A procedure similar to that used in Example 100 with N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (400 mg, 0.661 mmol) and tert-butyl 3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-l-carboxylate (292 mg, 0.991 mmol) gave the silyloxypyridyl intermediate that was deprotected and purified to give the title compound (42.5 mg, 94% yield on last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.90 - 7.84 (m, 1H), 7.74 - 7.61 (m, 1H), 6.96 - 6.88 (m, 1H), 6.85 - 6.79 (m, 1H), 6.28 - 6.19 (m, 1H), 4.44 - 4.35 (m, 2H), 4.24 - 4.15 (m, 2H), 3.04 - 2.96 (m, 2H), 2.66 - 2.52 (m, 4H), 2.40 - 2.31 (m, 3H), 1.44 - 1.39 (m, 9H), 1.13 - 1.09 (m, 6H); LCMS [M+H]+ 594.6.

Example 324: tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl] amino] -4-[(3R,5S)-3, 4,5-trimethylpiperazin-l -yljphenyl] -8-azabicyclo[3. 2. 1]oct-2-ene-8-carboxylate



[00650] A similar sequence to that of Example 100 starting from N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (400 mg, 0.661 mmol), 8-Boc-8-azabicyclo[3.2.1]oct-3-ene-3-boronic acid pinacol ester (332 mg, 0.991 mmol) gave, after deprotection of the silyloxy intermediate and purification using standard methods, the title compound (33 mg, 73 % yield for last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.81 (m, 1H), 7.66 - 7.56 (m, 1H), 6.87 - 6.79 (m, 2H), 6.25 - 6.18 (m, 1H), 4.40 - 4.27 (m, 2H), 3.04 - 2.95 (m, 1H), 2.95 - 2.88 (m, 2H), 2.53 - 2.43 (m, 4H), 2.31 - 2.27 (m, 3H), 2.19 - 2.10 (m, 2H), 1.99 - 1.89 (m, 2H), 1.78 - 1.69 (m, 1H), 1.41 - 1.36 (m, 9H), 1.08 - 1.04 (m, 6H); LCMS [M+H]+ 594.6.

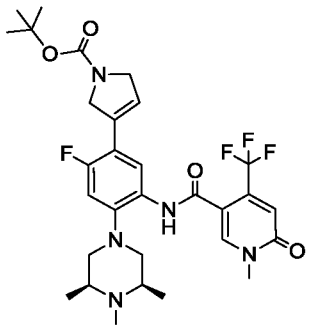
Example 325: tert-butyl 5-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3,6-dihydro-2H-pyridine-l-carboxylate



[00651] Iodomethane (2.83 µï, 0.045 mmol) was added to a solution of tert-butyl 5-(2-fluoro-5-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-3,6-dihydropyridine-l(2H)-carboxylate (24 mg, 0.039 mmol) and cesium carbonate (12.87 mg, 0.039 mmol) in DMF (1. ml) at RT. The mixture was stirred at RT. After 15 min, the mixture was

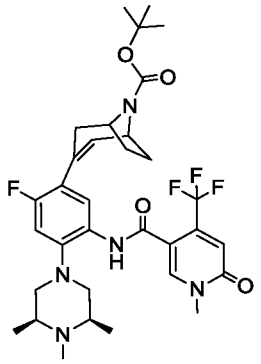
quenched, worked up and purified using standard methods to give the title compound (15.5 mg, 60 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.14 - 8.06 (m, 1H), 7.70 - 7.61 (m, 1H), 6.89 - 6.81 (m, 2H), 6.04 - 5.94 (m, 1H), 4.14 - 4.08 (m, 2H),3.56 - 3.53 (m, 3H), 3.51 - 3.43 (m, 2H), 2.94 - 2.88 (m, 2H), 2.51 - 2.44 (m, 2H), 2.43 - 2.35 (m, 2H), 2.24 - 2.19 (m, 5H), 1.40 - 1.37 (m, 9H), 1.04 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+ 622.5.

Example 326: tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-2,5-dihydropyrrole- 1-carboxylate



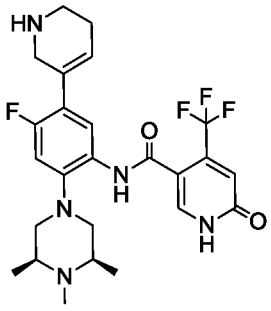
[00652] A similar procedure To Example 325 using iodomethane (3.86 μï, 0.062 mmol), tert-butyl 3-(2-fluoro-5-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-2,5-dihydro-lH-pyrrole- 1-carboxylate (32 mg, 0.054 mmol) and cesium carbonate (17.56 mg, 0.054 mmol) gave the title compound (23.5 mg, 68 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.18 - 8.09 (m, 1H), 7.76 - 7.60 (m, 1H), 6.94 - 6.87 (m, 1H), 6.85 - 6.80 (m, 1H), 6.28 - 6.18 (m, 1H), 4.43 - 4.35 (m, 2H), 4.23 - 4.14 (m, 2H), 3.58 - 3.52 (m, 3H), 2.98 - 2.89 (m, 2H), 2.52 - 2.44 (m, 2H), 2.43 - 2.35 (m, 2H), 2.26 - 2.21 (m, 3H), 1.41 (d, *J*=5.4 Hz, 9H), 1.05 - 1.01 (m, 6H); LCMS [M+H]+ 608.4.

Example 327: tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate



[00653] A similar procedure to Example 325 using iodomethane (2.82 µĭ, 0.045 mmol), tert-butyl 3-(2-fluoro-5-(6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamido)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (25 mg, 0.039 mmol) and cesium carbonate (12.85 mg, 0.039 mmol) gave the title compound (17 mg, 58 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.13 - 8.08 (m, 1H), 7.64 - 7.56 (m, 1H), 6.85 - 6.78 (m, 2H), 6.23 - 6.17 (m, 1H), 4.37 - 4.26 (m, 2H), 3.55 - 3.52 (m, 3H), 3.01 - 2.94 (m, 1H), 2.91 - 2.86 (m, 2H), 2.49 - 2.42 (m, 2H), 2.40 - 2.34 (m, 2H), 2.24 - 2.21 (m, 3H), 2.18 - 2.08 (m, 2H), 1.97- 1.89 (m, 2H), 1.77 - 1.67 (m, 1H), 1.40 - 1.36 (m, 9H), 1.04 - 1.01 (m, 6H); LCMS [M+H]+ 648.5.

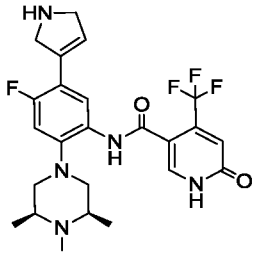
Example 328: N-[4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yl]-5-(l ,2,3,6-tetrahydropyridin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00654] A procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (400 mg, 0.661 mmol) and l-boc-5,6-dihydro-2H-pyridine-3-boronic acid, pinacol ester (306 mg, 0.991 mmol) gave, after deprotection of the silyloxy intermediate, (33 mg, 73 % yield) of the title compound. ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.80 (m, 1H), 7.69 - 7.60 (m, 1H), 6.89 - 6.82

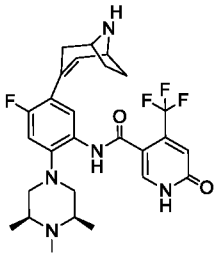
(m, 1H), 6.82 - 6.77 (m, 1H), 6.02 - 5.95 (m, 1H), 4.15 - 4.06 (m, 2H), 3.54 - 3.42 (m, 2H), 2.95 - 2.89 (m, 2H), 2.54 - 2.40 (m, 4H), 2.28 - 2.25 (m, 3H), 2.24 - 2.19 (m, 2H), 1.40 - 1.37 (m, 9H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 608.4

Example 329: N-[5-(2, 5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



[00655] A procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (400 mg, 0.661 mmol) and tert-butyl 3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-l-carboxylate (292 mg, 0.991 mmol) gave, after deprotection of the N-Boc silyloxy pyridine intermediate, the title compound (255 mg, 95 % yield on last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.09 - 8.02 (m, 1H), 7.91 - 7.79 (m, 1H), 7.07 - 6.97 (m, 1H), 6.86 - 6.77 (m, 1H), 6.45 - 6.36 (m, 1H), 4.29 - 4.21 (m, 2H), 4.09 - 4.01 (m, 2H), 3.10 - 3.01 (m, 2H), 2.65 - 2.56 (m, 2H), 2.55 - 2.48 (m, 2H), 2.38 - 2.34 (m, 3H), 1.18 - 1.13 (m, 6H); ^{19}F NMR (471MHz, METHANOL-d4) δ = -63.45 (s, IF), -115.19 (s, IF).

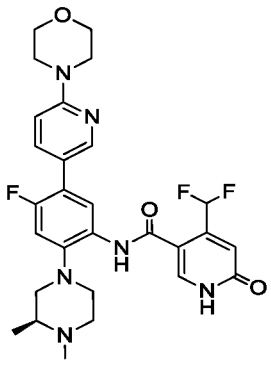
Example 330: N-[5-(8-azabicyclo[3. 2.1]oct-2-en-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00656] The procedure followed was similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (400 mg, 0.661 mmol) and 8-Boc-8-

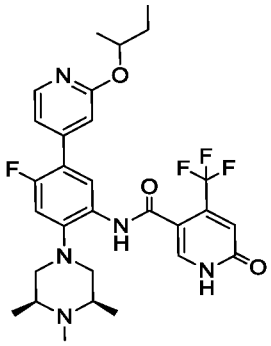
azabicyclo[3.2.1]oct-3-ene-3-boronic acid pinacol ester (332 mg, 0.991 mmol) to give, after deprotection of the silyloxy coupled intermediate, the title compound as an off white powder. (33 mg, 73 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.12 - 8.07 (m, IH), 7.86 - 7.75 (m, IH), 7.00 - 6.93 (m, IH), 6.78 - 6.72 (m, IH), 6.39 - 6.30 (m, IH), 4.19 - 4.07 (m, 2H), 3.15 - 3.06 (m, IH), 3.05 - 2.99 (m, 2H), 2.61 - 2.54 (m, 2H), 2.53 - 2.47 (m, 3H), 2.38 - 2.35 (m, 3H), 2.32 - 2.23 (m, 2H), 2.16 - 2.05 (m, IH), 2.00 - 1.94 (m, IH), 1.17 - 1.14 (m, 6H); LCMS [M+H]+ 534.6

Example 331: 4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



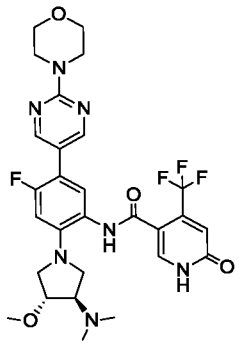
[00657] In a 10 ml microwave vial to a suspension of 4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxylic acid (78 mg, 0.415 mmol) in pyridine, anhydrous (504 µï, 6.23 mmol) was added slowly diethyl chlorophosphate (61.5 µï, 0.425 mmol) at rt in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. The suspension turned into a solution and then into a suspension again. The suspension turned yellow white. To this, (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-morpholinopyridin-3-yl)aniline (40 mg, 0.104 mmol) was added and the reaction was heated at 70 °C for 16 h to give, after workup and purification (58 mg, 93% yield) of the title compound. ^{1}H NMR (500 MHz, MeOD) δ 8.21 (s, IH), 7.94 (s, IH), 7.75 (d, *J* = 8.3 Hz, IH), 7.68 (d, *J* = 9.1 Hz, IH), 7.20 (t, *J* = 55.1 Hz, IH), 6.97 (d, *J* = 12.1 Hz, IH), 6.79 (d, *J* = 8.9 Hz, IH), 6.68 (s, IH), 3.72 - 3.69 (m, 4H), 3.45 - 3.41 (m, 4H), 3.04 (d, *J* = ll.l Hz, IH), 2.98 (d, *J* = 8.9 Hz, IH), 2.91 - 2.86 (m, IH), 2.79 (s, IH), 2.52 (s, 2H), 2.37 (s, 3H), 1.07 (s, 3H); LCMS [M+l]+ = 557.52.

Example 332: N-[5-(2-butan-2-yloxypyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[00658] The title compound was prepared similar to the sequence described above for the preparation of Example 100 using 2-(sec-butoxy)-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (34.3 mg, 0.124 mmol) andN-(5-bromo-4-fiuoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(†jimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) to give the title compound (31.5 mg, 66% yield). ¾ NMR (500MHz, DMSO-d6) δ = 9.58 (s, IH), 8.20 (d, ***J***=5.3 Hz, IH), 7.93 (s, IH), 7.82 (d, ***J***=8.4 Hz, IH), 7.07 (d, ***J***=5.3 Hz, IH), 7.03 (d, ***J***=12.8 Hz, IH), 6.83 (s, IH), 6.81 (s, IH), 5.13 (q, ***J***=6.2 Hz, IH), 3.09 (br d, ***J***=**l** l.l Hz, 2H), 2.49 - 2.45 (m, IH), 2.36 (br s, 2H), 2.20 (s, 3H), 1.77 - 1.56 (m, 2H), 1.27 (d, ***J***=6.1 Hz, 3H), 1.01 (br d, ***J***=6.0 Hz, 6H), 0.92 (t, ***J***=7.4 Hz, 3H); LCMS [M+H]+: 576.6.

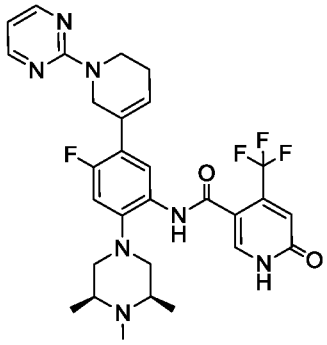
Example 333: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4RJ-3-(dimethylamino)-4-methoxypyrrolidin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00659] The title compound was prepared in a manner similar to the sequence described above for the preparation of Example 307. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.81 (s, IH), 8.51 (s, 2H), 7.96 (s, IH), 7.36 (br d, ***J***=8.7 Hz, IH), 6.80 (s, IH), 6.75 (d, ***J***=13.8 Hz, IH), 3.87 (br d, ***J***=5.4 Hz, IH), 3.77 - 3.71 (m, 4H), 3.69 - 3.65

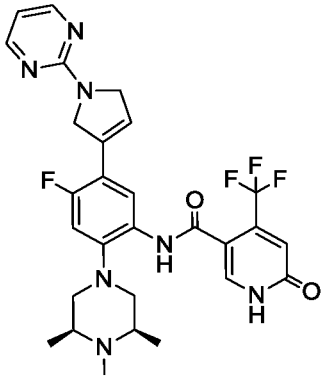
(m, 4H), 3.52 - 3.42 (m, 2H), 3.25 (s, 3H), 3.19 (br dd, *J=5.9,* 10.1 Hz, 1H), 2.75 (br d, *J* =4.8 Hz, 1H), 2.19 (s, 6H); LCMS [M+H]+: 606.5.

Example 334: N-[4-fluoro-5-(l-pyrimidin-2-yl-3, 6-dihydro-2H-pyridin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



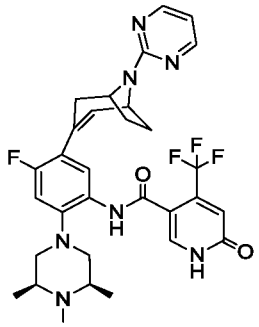
[00660] To N-(4-Fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (35 mg, 0.069 mmol) and 2-bromopyrimidine 95% (12.06 mg, 0.076 mmol) in ethanol (3 ml) at RT was added N,N-diisopropylethylamine (0.024 ml, 0.138 mmol). The mixture was heated at 85-90 °C for 7 h. Workup and purification gave the title compound (38 mg, 88 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.40 - 8.31 (m, 2H), 8.00 - 7.92 (m, 1H), 7.86 - 7.74 (m, 1H), 7.04 - 6.96 (m, 1H), 6.94 - 6.89 (m, 1H), 6.66 - 6.59 (m, 1H), 6.21 - 6.12 (m, 1H), 4.59 - 4.51 (m, 2H), 4.05 - 3.98 (m, 2H), 3.09 - 3.01 (m, 2H), 2.65 - 2.52 (m, 4H), 2.45 - 2.37 (m, 5H), 1.20 - 1.16 (m, 6H); LCMS [M+H]+ 586.7

Example 335: N-[4-fluoro-5-(I-pyrimidin-2-yl-2, 5-dihydropyrrol-3-yl)-2-[(3R, 5S)-3, 4, 5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[00661] A procedure similar to Example 334 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (35 mg, 0.071 mmol) and 2-bromopyrimidine 95% (12.40 mg, 0.078 mmol) gave, after purification and workup, the title compound (5.5 mg,12 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.31 - 8.25 (m, 2H), 7.90 - 7.83 (m, 1H), 7.82 - 7.75 (m, 1H), 6.96 - 6.90 (m, 1H), 6.85 - 6.81 (m, 1H), 6.61 - 6.54 (m, 1H), 6.43 - 6.36 (m, 1H), 4.67 - 4.60 (m, 2H), 4.50 - 4.41 (m, 3H), 3.00 - 2.94 (m, 2H), 2.55 - 2.44 (m, 4H), 2.30 - 2.27 (m, 3H), 1.09 - 1.05 (m, 6H); LCMS [M+H]+ 572.6.

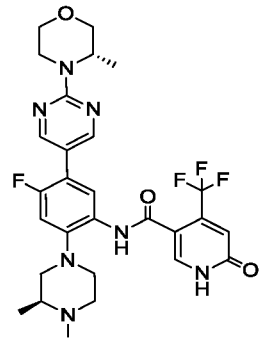
Example 336: N-[4-fluoro-5-(8-pyrimidin-2-yl-8-azabicyclo[3. 2.1]oct-2-en-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00662] A procedure similar to Example 334 using N-(5-(8-azabicyclo[3.2. l]oct-2-en-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (35 mg, 0.066 mmol) and 2-bromopyrimidine 95% (11.5 mg, 0.072 mmol) gave the title compound (31 mg, 74 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.40 - 8.34 (m, 2H), 7.96 - 7.91 (m,

1H), 7.68 - 7.59 (m, 1H), 6.93 - 6.87 (m, 2H), 6.69 - 6.64 (m, 1H), 6.47 - 6.42 (m, 1H), 5.00 - 4.95 (m, 1H), 4.91 - 4.89 (m, 1H), 3.18 - 3.10 (m, 1H), 3.02 - 2.96 (m, 2H), 2.60 - 2.49 (m, 4H), 2.40 - 2.33 (m, 4H), 2.31 - 2.24 (m, 1H), 2.20 - 2.11 (m, 2H), 2.02 - 1.93 (m, 1H), 1.14 (d, J=6.0 Hz, 6H); LCMS [M+H]+ 612.7.

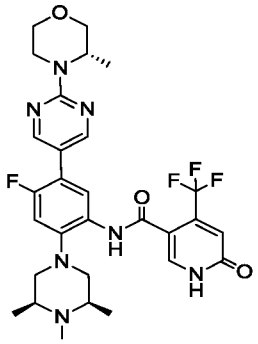
Example 337: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l -yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifl uoromethyl)-1H-pyridine-3-carboxamide



[00663] To a mixture of 2-chloropyrimidine-5-boronic acid (31.7 mg, 0.2 mmol) and (S)-3-methylmorpholine (0.042 mL, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.042 mL, 0.3 mmol). The resulting mixture was stirred at 70 °C for 80 min. Solvents were removed to give a light yellow oil. (S)-3-methylmorpholine (0.042 mL, 0.21 mmol) was added to the above oil, followed by triethylamine (0.042 mL, 0.3 mmol) and EtOH (2 mL). The resulting mixture was heated at 70 °C overnight for 18 h. Solvents were removed to give the crude (S)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid as a yellow oil. LCMS $[M + H]^+$ 224.2. The title compound (off-white solid, 24.5 mg, 41%) was prepared by a procedure similar to Example 40 using the boronic acid and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (br s, 1H), 8.56 (br s, 2H), 8.51 - 8.38 (m, 1H), 7.89 (s, 1H), 7.04 (br d, *J*=11.0 Hz, 1H), 7.00 (br d, *J*=9.4 Hz, 1H), 4.81 - 4.71 (m, 1H), 4.40 (br d, *J*=13.3 Hz, 1H), 4.01 (br d, *J*=11.0 Hz, 1H), 3.84 - 3.77 (m, 1H), 3.77 - 3.70 (m, 1H), 3.58 (br t, *J*=10.8 Hz, 1H), 3.38 - 3.26 (m, 1H), 3.04 - 2.86 (m, 3H), 2.83 (br d,

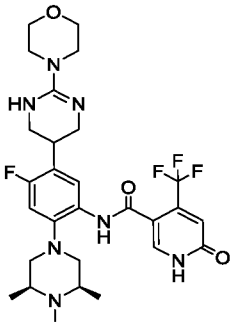
J=9.5 Hz, IH), 2.61 (br s, IH), 2.50 - 2.13 (m, 5H), 1.38 - 1.30 (m, 3H), 1.16 - 1.06 (m, 3H); LCMS [M + H]$^+$ 590.6.

Example 338: N-[4-fluoro-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-f(3S, 5R)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



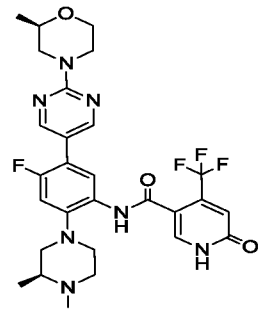
[00664] The title compound (light beige solid, 14.4 mg, 23%) was prepared in a manner similar to Example 31 using crude (S)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ¾H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (br s, IH), 8.57 (s, 2H), 8.47 (br d, *J*=8.1 Hz, IH), 7.86 (br s, IH), 7.06 - 6.98 (m, 2H), 4.81 - 4.75 (m, IH), 4.42 (br d, *J*=13.4 Hz, IH), 4.03 (dd, *J*=3.4, 11.2 Hz, IH), 3.82 (d, *J*=11.4 Hz, IH), 3.75 (dd, *J*=2.7, 11.4 Hz, IH), 3.60 (dt, *J*=2.9, 11.8 Hz, IH), 3.34 (dt, *J*=3.8, 13.0 Hz, IH), 2.83 (br d, *J*=10.4 Hz, 2H), 2.75 - 2.61 (m, 2H), 2.41 - 2.27 (m, 5H), 1.36 (d, *J*=6.7 Hz, 3H), 1.16 (br d, *J*=5.6 Hz, 6H); LCMS [M + H]$^+$ 604.5.

Example 339: N-[4-fluoro-5-(2-morpholin-4-yl-l, 4,5, 6-tetrahydropyrimidin-5-yl)-2-[(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00665] A solution of N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,54rimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (75 mg, 0.127 mmol) and sodium borohydride (289 mg, 7.63 mmol) in MeOH (5 ml) and water (0.5 ml) was agitated at 70 °C for 2.5 days. It was then quenched with sat. aq. NH_4C1 followed by MeOH. A standard workup and purification provided N-(4-fluoro-5-(2-mo rpholino-l,4,5,6-tetrahydropyrirnidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide ·HCl, as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ 12.92 - 12.48 (m, 1H), 9.68 - 9.40 (m, 1H), 8.74 - 8.51 (m, 2H), 8.15 (s, 1H), 7.91 (br s, 1H), 7.74 - 7.48 (m,lH), 7.02 (br d, *J*=11.9 Hz, 1H), 6.82 (s, 1H), 3.74 - 3.61 (m, 5H), 3.60 - 3.51 (m, 3H), 3.44 - 3.39 (m, 8H), 3.10 - 2.91 (m, 3H), 2.35 - 2.25 (m, 2H), 1.14 - 0.98 (m, 6H); LCMS (MH^+) = 594.7.

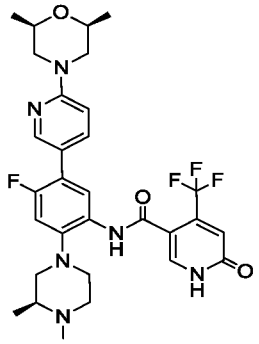
Example 340: N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l-ylJ-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-5-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide



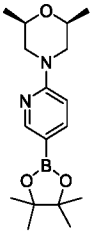
[00666] To a mixture of 2-chloropyrimidine-5-boronic acid (32 mg, 0.2 mmol) and (R)-2-methyl-morpholine, hydrochloride (29 mg, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at

70 °C for 1.5 h. Solvents were removed to give the crude (R)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid as a pale yellow solid. LCMS [M + H]$^+$ 224.2. The title compound (pale beige solid, 34.2 mg, 55%) was prepared through a procedure similar to the last step of Example 273 using this boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (br s, 1H), 8.55 (s, 2H), 8.45 (br d, *J*=5.6 Hz, 1H), 7.89 (s, 1H), 7.04 (d, *J*=11.2 Hz, 1H), 7.01 - 6.99 (m, 1H), 4.64 - 4.53 (m, 2H), 4.01 (br d, *J*=11.2 Hz, 1H), 3.67 - 3.58 (m, 2H), 3.15 - 3.05 (m, 1H), 3.01 - 2.86 (m, 3H), 2.85 - 2.70 (m, 2H), 2.60 (br t, *J*=10.3 Hz, 1H), 2.42 - 2.29 (m, 4H), 2.29 - 2.15 (m, 1H), 1.30 - 1.25 (m, 3H), 1.10 (br d, *J*=6.0 Hz, 3H); LCMS [M + H]$^+$ 590.6.

Example 341: N-[4-fluoro-5-[6-[(2R, 6SJ-2, 6-dimethylmorpholin-4-ylJpyridin-3-ylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



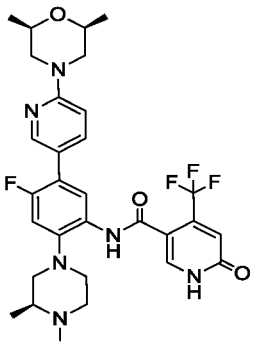
Step 1: (2S, 6RJ-2, 6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine



[00667] To a 20 mL microwave vial charged with 2-chloro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (0.968 g, 4 mmol), cis-2,6-dimethylmorpholine (0.54 mL, 4.4 mmol) and Hunig base (1.39 mL, 8 mmol) was added NMP (2 mL). The resulting solution was heated at 140 °C for 2 h. After

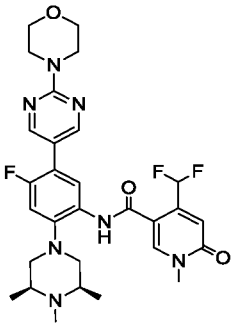
removing the amine base, the mixture was loaded onto Biotage samplet and purified by flash chromatography (gradient: EtOAc/hex 0-100%) to give the title compound as a crystalline beige solid (485 mg, 38%). LCMS $[M + H]^+$ 237.2.

Step 2: N-(4-fluoro-5-(2-((S)-3-methylmorpholino)pyrimidin-5-yl)-2-((3S, 5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



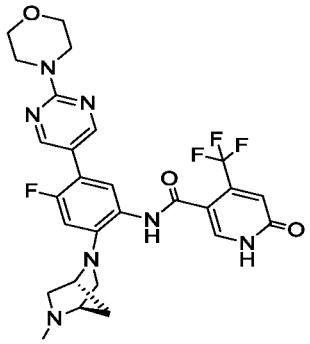
[00668] The title compound (light brown solid, 27.0 mg, 44%) was prepared by a procedure similar to that of the last step of Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49 mg, 0.1 mmol) and (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (63 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.72 (br s, 1H), 8.51 - 8.42 (m, 2H), 7.93 - 7.84 (m, 1H), 7.74 (br d, *J*=8.3 Hz, 1H), 7.08 - 6.97 (m, 2H), 6.71 (br d, *J*=8.7 Hz, 1H), 4.13 (br d, *J*=12.5 Hz, 2H), 3.85 - 3.69 (m, 2H), 3.05 - 2.88 (m, 3H), 2.84 (br d, *J*=10.6 Hz, 1H), 2.68 - 2.54 (m, 3H), 2.50 - 2.31 (m, 4H), 2.30 - 2.14 (m, 1H), 1.31 (dd, *J*=1.9, 6.1 Hz, 6H), 1.11 (br d, *J*=5.7 Hz, 3H); LCMS $[M + H]^+$ 603.6.

Example 342: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidm-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyrM ne-3-carboxamide



[00669] 4-(Difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (0.023 g, 0.11 mmol) was activated with HATU (0.043 g, 0.11 mmol) and N,N-diisopropylethylamine (0.02 niL, 0.11 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.030 g, 0.075 mmol) DMF (0.5 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The product containing fractions were combined and re-concentrated onto celite. Reverse phase chromatography [5-95% MeCN/H_2**0]** afforded 4-(difluoromethyl)-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (0.012 g, 27%). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (s, IH), 8.52 (s, 2H), 8.34 (s, IH), 7.67 (d, *J*=8.6 Hz, IH), 7.50 - 7.18 (m, IH), 7.05 (d, *J*=12.3 Hz, IH), 6.64 (s, IH), 3.76 - 3.74 (m, 4H), 3.69 - 3.66 (m, 4H), 3.52 (s, 3H), 3.03 (br d, *J*=10.8 Hz, 3H), 2.37 - 2.30 (m, 3H), 2.18 (s, 3H), 1.00 (d, *J=6.1* Hz, 6H); LCMS [M+H]+: 586.6.

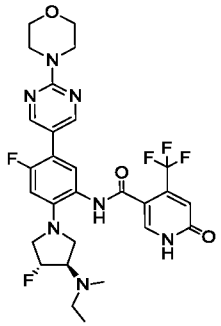
Example 343: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(lR, 4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00670] The title compound was prepared similar to the sequence described above for the preparation of Example 234 using (lR,4R)-2-methyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide in place of (R)-N-ethyl-N-methylpyrrolidin-3 -amine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.71 (s, IH), 8.50 (s, 2H), 7.96 (s, IH), 7.31 (d, *J*=8.8 Hz, IH), 6.79 (s, IH), 6.68 (d, *J*=13.9 Hz,

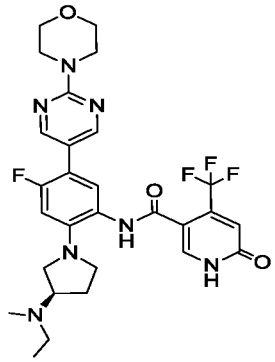
IH), 4.23 (s, IH), 3.75 - 3.71 (m, 4H), 3.70 - 3.65 (m, 4H), 3.44 (br d, *J*=7.9 Hz, IH), 3.23 (br d, *J*=9.3 Hz, IH), 2.79 - 2.73 (m, IH), 2.72 - 2.66 (m, IH), 2.25 (s, 3H), 1.82 (br d, *J*=9.0 Hz, IH), 1.65 (br d, *J*=9.0 Hz, IH); LCMS [M+H]+: 574.4.

Example 344: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4RJ-3-[ethyl(methyl)amino]-4-fluoropyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

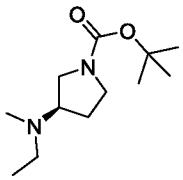


[00671] The title compound was prepared similar to the procedure described above for the preparation of Example 307 using N-ethylmethylamine in place of dimethylamine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.78 (br d, *J*=2.8 Hz, IH), 8.53 (s, 2H), 8.01 (br s, IH), 7.41 (d, *J*=8.8 Hz, IH), 6.82 (d, *J*=13.6 Hz, IH), 6.77 - 6.68 (m, IH), 5.32 - 5.13 (m, IH), 3.77 - 3.73 (m, 4H), 3.70 - 3.67 (m, 4H), 3.63 - 3.56 (m, 2H), 3.55 - 3.52 (m, IH), 3.30 (s, 3H), 3.19 - 3.13 (m, 2H), 2.56 - 2.54 (m, 2H), 2.20 (s, 3H), 0.98 (t, *J*=7.1 Hz, 3H); LCMS [M+H]+: 608.4.

Example 345: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[ethyl(methyl)amino]pyrrolidin-l -yl]phenyl]-6-oxo-4-(ᵀrifluoromethyl)-lH-pyridine-3-carboxamide

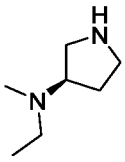


Step 1: tert-butyl (R)-3-(ethyl(methyl)amino)pyrrolidine-l-carboxylate



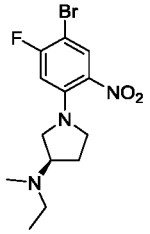
[00672] A mixture of (S)-l-Boc-3-methanesulfonyloxy-pyrrolidine (0.50 g, 1.9 mmol), N-ethylmethyl amine (0.40 mL, 4.7 mmol) and N,N-diisopropylethylamine (0.82 mL, 4.7 mmol) was heated to 70 °C in a sealed tube for 40 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0-5% MeOH/DCM + 0.5% NH_4OH] to afford tert-butyl (R)-3-(ethyl(methyl)amino)pyrrolidine-l-carboxylate (0.20 g, 47 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 3.51 - 3.43 (m, 1H), 3.39 - 3.36 (m, 1H), 3.22 - 3.09 (m, 1H), 2.97 - 2.79 (m, 2H), 2.47 - 2.33 (m, 2H), 2.12 (s, 3H), 1.98 (br dd, *J*=6.4, 10.8 Hz, 1H), 1.72 - 1.56 (m, 1H), 1.39 (s, 9H), 0.96 (t, *J*=7.1 Hz, 3H).

Step 2: (R)-N-ethyl-N-methylpyrrolidin-3-amine



[00673] A solution of tert-butyl (R)-3-(ethyl(methyl)amino)pyrrolidine-l-carboxylate (0.20 g, 0.89 mmol) in DCM (4 mL) was treated with TFA (1.4 mL, 18 mmol) at room temperature. After stirring for 2 h the volatiles were removed under a stream of air and the product was isolated by a catch and release protocol using a SCX2 silica cartridge to afford (R)-N-ethyl-N-methylpyrrolidin-3-amine (0.12 g, 100%). ^{1}H NMR (500MHz, DMSO-d6) δ = 2.91 (dd, *J*=7.1, 10.4 Hz, 1H), 2.85 - 2.66 (m, 3H), 2.46 (dd, *J*=7.6, 10.4 Hz, 1H), 2.43 - 2.29 (m, 2H), 2.09 (s, 3H), 1.77 (dtd, *J*=5.0, 7.4, 12.2 Hz, 1H), 1.45 (qd, *J*=8.0, 12.1 Hz, 1H), 0.96 (t, *J*=7.2 Hz, 3H).

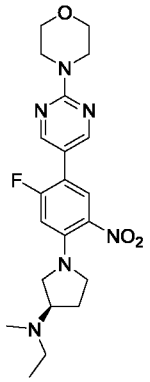
Step 3: (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-ethyl-N-methylpyrrolidin-3-amine



[00674] A solution of 1-bromo-2,4-difluoro-5 -nitrobenzene (0.22 g, 0.95 mmol) in PhMe (1 mL) was slowly added to a rapidly stirring mixture of (R)-N-

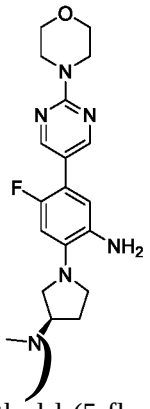
ethyl-N-methylpyrrolidin-3-amine (0.12 g, 0.95 mmol) and K_2C0_3 (0.065 g, 0.47 mmol) in PhMe (2 mL) at 45 °C. After 4 h the heat was turned off and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-ethyl-N-methylpyrrolidin-3-amine (0.22 g, 66 %). LCMS [M+H]+: 346.3.

Step 4: (R)-N-ethyl-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N-methylpyrrolidin-5'-amine



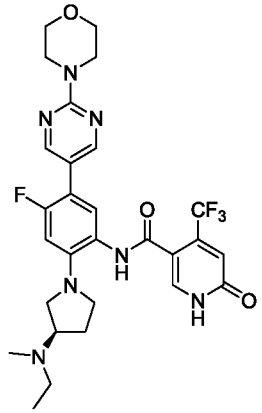
[00675] A reaction vial was charged with a mixture of (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-ethyl-N-methylpyrrolidin-3-amine (0.11 g, 0.32 mmol), 2-(4-moφholino)pyrimidine-5-boronic acid pinacol ester (0.10 g, 0.35 mmol), XPhos Pd G2 (5.0 mg, 6.4 μmoï) and XPhos (3.0 mg, 6.4 μmoï). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and 2 M aqueous sodium carbonate (0.6 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 90 °C in an aluminum block overnight. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford (R)-N-ethyl-1-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N-methylpyrrolidin-3-amine (0.11 g, 78 %). LCMS [M+H]+: 431.4.

Step 5: (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-ethyl-N-methylpyrrolidin-3-amine



[00676] A mixture of (R)-N-ethyl-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-N-methylpyrrolidin-3-amine (0.10 g, 0.25 mmol), $SnCl_2$ (0.24 g, 1.2 mmol) and EtOH (5 mL) was heated to 75 °C for 1 h. The heat was turned off and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 1% NH_4OH] afforded (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-ethyl-N-methylpyrrolidin-3-amine (0.084 g, 84 %). LCMS [M+H]+: 401.3.

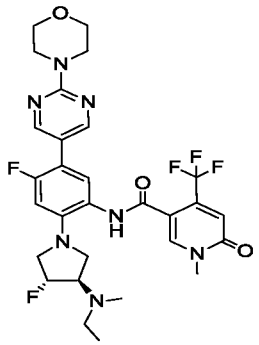
Step 6: (R)-N-(2-(3-(ethyl(methyl)amino)pyrrolidin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00677] 4-(Trifluoromethyl) -6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.046 g, 0.15 mmol) was activated with HATU (0.057 g, 0.15 mmol) and N,N-diisopropylethylamine (0.03 mL, 0.15 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrirnidin-5-yl)phenyl)-N-ethyl-N-methylpyrrolidin-3-amine (0.040 g,

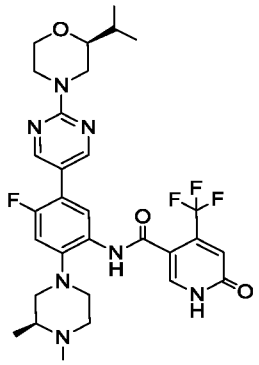
0.10 mmol) in DMF (1 niL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with TFA (1 mL) at room temperature. After stirring for 2 h the volatiles were removed under a stream of air and the title compound was isolated by a catch and release protocol using a SCX2 silica cartridge to afford (R)-N-(2-(3-(ethyl(methyl)amino)pyrrolidin- l-yl)-4-fl uoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.042 g, 71 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.80 (s, 1H), 8.51 (s, 2H), 7.96 (s, 1H), 7.32 (br d, ***J***=8.6 Hz, 1H), 6.80 (s, 1H), 6.67 (d, ***J***=13.9 Hz, 1H), 3.76 - 3.72 (m, 4H), 3.70 - 3.66 (m, 4H), 3.38 (br d, ***J***=8.9 Hz, 4H), 3.27 - 3.22 (m, 1H), 2.90 (br t, ***J***=7.9 Hz, 1H), 2.42 (td, ***J***=6.4, 13.0 Hz, 2H), 2.14 (s, 3H), 2.12 - 2.06 (m, 1H), 1.75 - 1.65 (m, 1H), 0.99 - 0.94 (m, 6H); LCMS [M+H]+: 590.5.

Example 346: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4RJ-3-[ethyl(methyl)amino] -4-fluoropyrrolidin-l -yljphenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



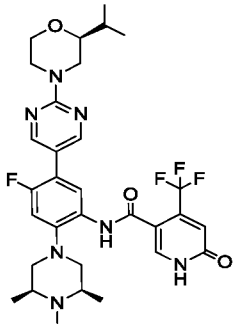
[00678] The title compound was prepared similar to the procedure described above for the preparation of Example 344 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 7. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.84 (s, 1H), 8.52 (s, 2H), 8.36 (s, 1H), 7.39 (d, ***J***=8.6 Hz, 1H), 6.89 - 6.82 (m, 2H), 5.32 - 5.12 (m, 1H), 3.77 - 3.74 (m, 4H), 3.69 - 3.67 (m, 4H), 3.64 - 3.59 (m, 2H), 3.58 - 3.51 (m, 6H), 3.19 - 3.11 (m, 2H), 2.20 (s, 3H), 0.98 (t, ***J***=7.0 Hz, 3H); LCMS [M+H]+: 622.6.

Example 347: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-propan-2-ylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoro methyl)-1H-pyridine-3-carboxamide



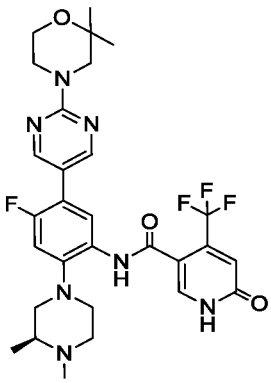
[00679] To a mixture of 2-chloropyrimidine-5 -boronic acid (32 mg, 0.2 mmol) and (S)-2-isopropylmorpholine (27 mg, 0.21 mmol) in EtOH (2 mL) was added triethylanune (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C for 1.5 h. Solvents were removed to give the crude (S)-(2-(2-isopropylmo rpholino)pyrimidin-5-yl)boronic acid as a pale yellow solid. LCMS [M + H]$^+$ 252.3. The title compound (pale beige solid, 34.2 mg, 55%) was prepared by a method similar to the last step of Example 31 using this boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.72 (br s, 1H), 8.57 (s, 2H), 8.47 (br d, *J*=8.1 Hz, 1H), 7.88 (br s, 1H), 7.06 (d, *J*=ll.l Hz, 1H), 7.02 (br s, 1H), 4.69 (br d, *J*=13.1 Hz, 1H), 4.57 (br d, *J*=13.3 Hz, 1H), 4.05 (dd, *J*=2.6, 11.4 Hz, 1H), 3.64 (dt, *J*=2.6, 11.6 Hz, 1H), 3.22 - 3.07 (m, 2H), 3.03 - 2.80 (m, 5H), 2.61 (br t, *J*=10.4 Hz, 1H), 2.44 - 2.30 (m, 4H), 2.23 (br s, 1H), 1.83 (qd, *J*=6.8, 13.5 Hz, 1H), 1.12 (br d, *J*=6.0 Hz, 3H), 1.06 (d, *J*=6.7 Hz, 3H), 1.04 (d, *J*=6.8 Hz, 3H); LCMS [M+ H]$^+$ 618.6.

Example 348: N-[4-fluoro-5-[2-[(2R)-2-propan-2-ylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00680] The title compound (beige solid, 30.8 mg, 49%) was prepared by a procedure similar to the last step of Example 31 using crude (S)-(2-(2-isopropylmorpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.69 (br s, 1H), 8.56 (s, 2H), 8.45 (br d, *J*=7.9 Hz, 1H), 7.86 (s, 1H), 7.06 - 6.97 (m, 2H), 4.67 (br d, *J*=13.0 Hz, 1H), 4.56 (br d, *J*=13.2 Hz, 1H), 4.03 (dd, *J*=2.5, 11.4 Hz, 1H), 3.62 (dt, *J*=2.6, 11.6 Hz, 1H), 3.22 - 3.04 (m, 2H), 2.89 - 2.76 (m, 3H), 2.73 - 2.58 (m, 2H), 2.41 - 2.25 (m, 5H), 1.81 (qd, *J*=6.8, 13.5 Hz, 1H), 1.14 (br d, *J*=5.7 Hz, 6H), 1.04 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H); LCMS $[M + H]^+$ 632.6.

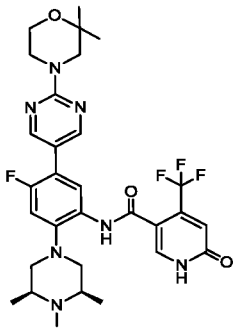
Example 349: N-[5-[2-(2, 2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00681] To a mixture of 2-chloropyrimidine-5-boronic acid (32 mg, 0.2 mmol) and 2,2-dimethylmorpholine (24 mg, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C for 1.5 h. Solvents were removed to give the crude (2-(2,2-

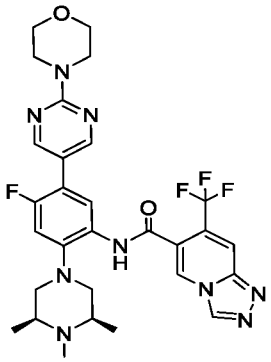
dimethylmorpholino)pyrimidin-5-yl)boronic acid as a pale yellow solid. LCMS [M + H]$^+$ 238.2. The title compound (beige solid, 36.6 mg, 60%) was prepared by a procedure similar to the last step of Example 31 using this boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.70 (s, 1H), 8.54 (s, 2H), 8.45 (br d, *J*=8.1 Hz, 1H), 7.88 (s, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 7.00 (br s, 1H), 3.89 - 3.80 (m, 4H), 3.71 (s, 2H), 3.02 - 2.87 (m, 3H), 2.82 (br d, *J*=10.9 Hz, 1H), 2.86 - 2.77 (m, 1H), 2.60 (br t, *J*=10.4 Hz, 1H), 2.42 - 2.30 (m, 4H), 2.23 (br s, 1H), 1.28 (s, 6H), 1.10 (br d, *J*=6.1 Hz, 3H); LCMS [M+ H]$^+$ 604.5.

Example 350: N-[5-[2-(2, 2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



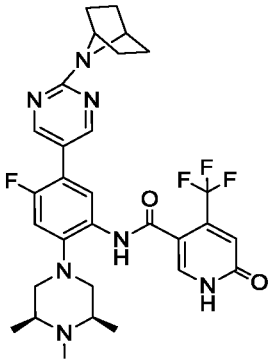
[00682] The title compound (beige solid, 36.6 mg, 58%) was prepared by a procedure similar to that of described in the last step of Example 31 using crude (2-(2,2-dimethylmorpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (br s, 1H), 8.55 (s, 2H), 8.46 (br d, *J*=8.1 Hz, 1H), 7.90 - 7.85 (m, 1H), 7.07 - 7.00 (m, 2H), 3.90 - 3.82 (m, 4H), 3.72 (s, 2H), 2.83 (br d, *J*=10.9 Hz, 2H), 2.67 (br t, *J*=10.8 Hz, 2H), 2.41 - 2.27 (m, 5H), 1.30 (s, 6H), 1.15 (br d, *J*=6.1 Hz, 6H); LCMS [M + H]$^+$ 618.6.

Example 351: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-7-(trifluoromethyl)-[l, 2,4]triazolo[4, 3-a]pyridine-6-carboxamide



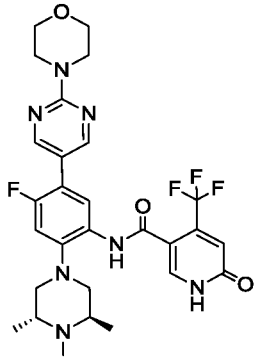
[00683] The title compound (yellow solid, 49.7 mg, 77%) was prepared by a procedure similar to that of Example 331 using 7-(trifluoromethyl)-[l,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (46 mg, 0.2 mmol) and 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (40 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 13.44 (br d, *J*=13.4 Hz, IH), 8.60 (d, *J*=13.7 Hz, IH), 8.54 (s, 2H), 8.36 (s, IH), 7.32 (s, IH), 7.25 (d, *J*=7.1 Hz, IH), 7.12 (d, *J*=ll.l Hz, IH), 3.96 - 3.89 (m, 4H), 3.85 - 3.79 (m, 4H), 2.99 (br d, *J*=10.8 Hz, 2H), 2.82 (br s, 2H), 2.78 - 2.64 (m, 2H), 2.43 (br s, 3H), 1.17 (br d, *J*=5.9 Hz, 6H); LCMS [M+ H]$^{+}$ 614.6.

Example 352: N-[5-[2-(7-azabicyclo[2.2. 1]heptan-7-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

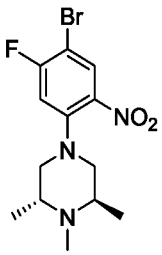


[00684] To a mixture of 2-chloropyrimidine-5-boronic acid (32 mg, 0.2 mmol) and 7-azabicyclo[2.2.1]heptane hydrochloride (28 mg, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C 4 h. Solvents were removed to give the crude (2-(7-azabicyclo[2.2.1]heptan-7-yl)pyrimidin-5-yl)boronic acid as a light yellow solid. LCMS $[M + H]^+$ 220.3. The title compound (beige solid, 6.5 mg, 11%) was prepared by a procedure similar to that of Example 100 using the boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^1H NMR (500MHz, CHLOROFORM-d) δ = 8.69 (br s, 1H), 8.54 (s, 2H), 8.43 (br d, *J*=6.8 Hz, 1H), 7.86 (br s, 1H), 7.05 - 6.94 (m, 2H), 4.74 (br s, 2H), 2.88 - 2.76 (m, 2H), 2.65 (br s, 2H), 2.40 - 2.26 (m, 4H), 1.91 - 1.79 (m, 5H), 1.53 (br d, *J*=7.1 Hz, 4H), 1.14 (br s, 6H); LCMS $[M + H]^+$ 600.6.

Example 353: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



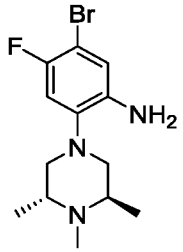
Step 1: (2R,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine



[00685] To a stirred solution of (2R,6R)-l,2,6-trimethylpiperazine (4g, 32.9 mmol, 1.3 eq) in ethanol (20 mL) was added TEA (5.23 mL, 37.5 mmol, 1.5 eq) at RT under argon atmosphere. After 30 min, 1-bromo-2,4-difiuoro-5 -nitrobenzene

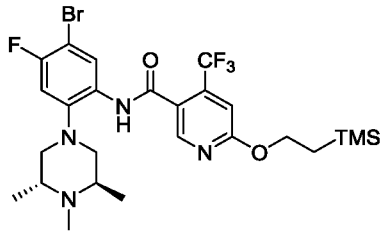
(preparation shown in Example 196 Step 4) was added (6 g, 25.0 mmol, 1 eq) at RT. Then the reaction mixture was heated to 85°C for 16h. TLC analysis indicated formation of polar spot. The reaction mixture was concentrated under reduced pressure gave crude product. The crude product was purified by column chromatography (silica gel 230-400 mesh) using 1-1.5% methanol in DCM as an eluent afforded (2R,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l ,2,6-trimethylpiperazine (2.8 g, 32.2% yield) as yellow liquid. LCMS: [M+H]+ 345.85.

Step 2: 5-bromo-4-fluoro-2-((3R, 5R)-3, 4,5-trimethylpiperazin-l-yl)aniline



[00686] To a stirred solution of (2R,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-1,2,6-trimethylpiperazine (0.82 g, 8.0 mmol, leq) in ethanol: water (90mL: 5mL), was added NH_4Cl (1.29 g, 24.2 mmol, 3 eq) and Fe powder (1.35 g, 24.2 mmol, 3 eq) at RT and the resulting reaction mixture was heated at 80°C for 16 h. The reaction was monitored by TLC, which indicated formation of polar spot. Then, the reaction mixture was cooled to RT and filtered through a celite bed; celite bed was washed with EtOAc (200mL), and the filtrates were concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using DCM as an eluent to give 5-bromo-4-fluoro-2-((3R,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (750 mg, 30% yield) as brown liquid. LCMS: [M+H]+ 316.1.

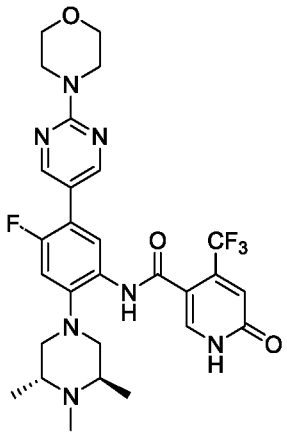
Step 3: N-(5-bromo-4-fluoro-2-((3R, 5R)-3, 4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00687] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.22 g, 0.71 mmol) and propylphosphonic anhydride solution (0.7 mL, 2.4 mmol) were added

to a suspension of 5-bromo-4-fluoro-2-((3R,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (0.15 g, 0.47 mmol) in THF (4 niL). A solution of 4-methylmorpholine (0.10 niL, 0.95 mmol) in THF (1 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with an additional portion of EtOAc. The combined organics were washed with water, aqueous 1 N NaOH, and a saturated brine solution. After drying over magnesium sulfate, the inorganics were removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford N-(5-bromo-4-fluoro-2-((3R,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.12 g, 41 %). LCMS [M+H]+: 605.3.

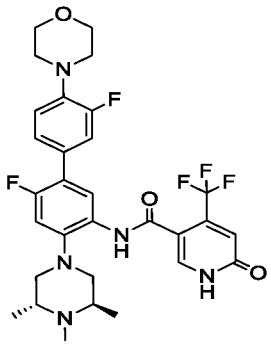
Step 4: N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3R,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6<>xo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00688] A reaction vial was charged with **2**-(**4**-morpholino)pyrimidine-**5**-boronic acid pinacol ester (0.017 g, 0.057 mmol), XPhos Pd G2 (0.00075 g, 0.96 μmol) and XPhos (0.00046 g, 0.96 μmol). The vial was sealed with a septum and evacuated and backfilled with nitrogen. A solution of N-(5-bromo-4-fluoro-2-((3R,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxyNicotinamide (0.029 g, 0.048 mmol) in 1,4-dioxane (0.8 mL) was added via syringe, followed by aqueous sodium carbonate (0.084 mL, 2 M) and the vial was evacuated and backfilled an additional time. The reaction was heated to 80 °C for 18 h. The reaction mixture was partitioned between DCM and water and the layers were separated. The aqueous layer was extracted with an additional portion of DCM

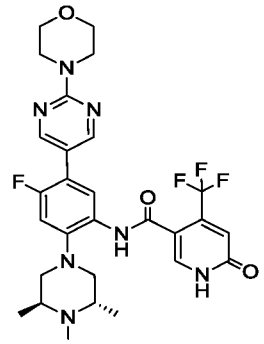
and the combined organics were dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated to dryness and the residue was purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford the silyl protected intermediate which was dissolved in DCM (2 mL) and treated with TFA (0.2 mL) at room temperature. After stirring for 1 h the volatiles were removed in vacuo and the title compound was isolated using a catch and release protocol with a PoraPak Rxn CX ion exchange column to afford the title compound N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3R,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.014 g, 51%). ^1H NMR (500MHz, DMSO-d6) δ = 9.30 (s, 1H), 8.53 (s, 2H), 8.03 (s, 1H), 7.74 (d, *J*=8.6 Hz, 1H), 7.07 (d, *J*=12.3 Hz, 1H), 6.80 (s, 1H), 3.79 - 3.72 (m, 4H), 3.70 - 3.65 (m, 4H), 2.90 (br d, *J*=9.3 Hz, 2H), 2.84 - 2.77 (m, 2H), 2.64 (br dd, *J*=6.2, 10.8 Hz, 2H), 2.20 (s, 3H), 0.97 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+: 590.6.

Example 354: N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R,5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide

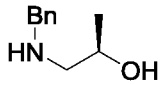


[00689] The title compound was prepared similar to the procedure described above for the preparation of Example 353 using 3-fluoro-4-morpholinophenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 3. ^1H NMR (500MHz, DMSO-d6) δ = 9.29 (s, 1H), 8.03 (s, 1H), 7.75 (br d, *J*=8.7 Hz, 1H), 7.33 - 7.23 (m, 2H), 7.19 - 7.11 (m, 1H), 7.03 (d, *J*=12.7 Hz, 1H), 6.81 (s, 1H), 3.80 - 3.73 (m, 4H), 3.11 - 3.02 (m, 4H), 2.95 - 2.88 (m, 2H), 2.84 - 2.78 (m, 2H), 2.64 (br dd, *J*=6.1, 10.8 Hz, 2H), 2.21 (s, 3H), 0.97 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+: 606.6.

Example 355: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R 5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide

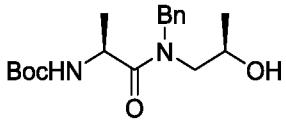


Step 1: (R)-l -(benzylamino)propan-2-ol



[00690] To a solution of (R)-l-aminopropan-2-ol (50 g, 792.8 mmol, leq) in THF (1680 mL) was added benzaldehyde (84 g, 799.9 mmol, 1.2 eq), $MgS0_4$ (41 g) under argon atmosphere. The reaction mixture was stirred at room temperature for 4h. The reaction was filtered and concentrated to obtain the crude intermediate, which was diluted with ethanol, $NaBH_4$ (8.4 g, 220.0 mmol, 0.33 eq) was added portion wise at 10°C and stirred for 2h at RT. Then, $NaBH_4$ (8.4 g, 220.0 mmol, 0.33 eq) was added portion wise at 10°C and stirred for 72 h at RT. The reaction was monitored by TLC, and TLC analysis indicated formation of nonpolar spot. The reaction mixture was concentrated under reduced pressure to give crude product. The crude product was diluted with ethyl acetate then extracted with 2N aq. HC1 (3X100mL). The Aq. layer was neutralized (pH 7) with sat. NaHCCb solution, extracted with DCM (4 X lOOmL) followed by washing with brine solution (100 mL), drying over Na_2S0_4 and concentrating under reduced pressure to provide crude (R)-l-(benzylamino)propan-2-ol (1lOg, 100 % yield) as a colourless liquid. TLC: 5% MeOH: DCM ; R_f: 0.4

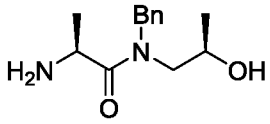
Step 2: tert-butyl ((S)-l^enzyl((R)-2-hydroxypropyl)amino)-l-oxopropan-2-yl)carbamate



[00691] To a stirred solution of (tert-butoxycarbonyl)-L-alanine (45 g, 272.7 mmol, leq) in DCM (800mL) was added CDI (44g, 272.7 mmol, leq) at 10°C under argon atmosphere. The reaction mixture was stirred for 2 h at RT. (R)-l-(Benzylamino)propan-2-ol (45 g, 272.7 mmol, leq) in DCM (lOOmL) was added

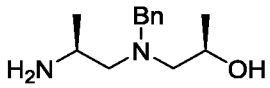
slowly at 10°C and stirred for 16h at RT. The reaction was monitored by TLC, and TLC analysis indicated formation of less polar spot. The reaction mixture was concentrated under reduced pressure to give crude compound. The crude compound was purified by column chromatography using 100-200 silica gel as stationary phase and ethyl acetate in pet ether as mobile phase to afford pure tert-butyl ((S)-l-(benzyl((R)-2-hydroxypropyl)amino)-l-oxopropan-2-yl)carbamate (75 g, 81.8% yield) as colour less liquid. LCMS: [M+H]+ 337.0.

Step 3: (S)-2-amino-N-benzyl-N-((R)-2-hydroxypropyl)propanamide



[00692] To a solution of tert-butyl ((S)-l-(benzyl((R)-2-hydroxypropyl)amino)-1-oxopropan-2-yl)carbamate (55 g, 163.6 mmol, leq) in DCM (550 mL) was added TFA (250 mL, 3272.0 mmol, 20 eq) at 0°C under argon atmosphere. The reaction mixture was stirred for lh at RT. TLC analysis indicated formation of polar spot. The reaction mixture was concentrated under reduced pressure to give crude compound. The residue was diluted with DCM (250 mL), washed with sat. NaHCCb solution (200 mL) and the aqueous layer was extracted with DCM (200 mL). The combined organic layer was washed with water (2 X 150 mL) followed by brine solution (100 mL), dried over Na_2S04 and concentrated under reduced pressure to afford crude (S)-2-amino-N-benzyl-N-((R)-2-hydroxypropyl)propanamide (25 g, crude yield) as colorless liquid. LCMS: [M+H]+ 237.0.

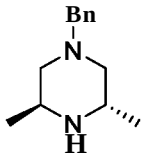
Step 4: (R)-l-(((S)-2-aminopropyl)(benzyl)amino)propan-2-ol



[00693] A stirred solution of (S)-2-amino-N-benzyl-N-((R)-2-hydroxypropyl)propanamide (21 g, 89.0 mmol, leq) in THF (400mL) was cooled to 0°C and BH_3.DMS (10M) (25.5 mL, 254.5 mmol, 2.86 eq) was added dropwise at 0°C under argon atmosphere. Then, the reaction mixture was allowed to stir at RT for 16 h. After cooling to 0°C, the reaction mixture was quenched with HC1 (20%, 490 mL). The reaction was basified with KOH (5N, 164 mL) and KOH (310.8 g, 37.2 eq), and the mixture was heated at reflux for 24h. Then MeOH (100 mL) was added at rt then refluxed for 72 h. The reaction was monitored by TLC, and TLC analysis indicated formation of

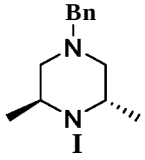
less polar spot. The reaction mixture was cooled to room temperature, and concentrated to remove organic solvents. The aqueous layer was extracted with DCM (250 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2S04 and concentrated under reduced pressure to obtain the crude product, which was purified by column by using neutral alumina as stationary phase and 0-5% MeOH in DCM as mobile phase to afford (R)-l-(((S)-2-aminopropyl)(benzyl)amino)propan-2-ol (14g, 70.80% yield) as pale green liquid. LCMS: [M+l] 223.11.

Step 5: (3S,5S)-1-benzyl-3,5-dimethylpiperazine



[00694] To a stirred solution of (R)-l-(((S)-2-aminopropyl)(benzyl)amino)propan-2-ol (4 g, 18.0 mmol, 1e q) in THF (160 mL) was added TPP (9.45 g, 36.03 mmol, 2eq) at 0°C. After stirring for 10 min, DIAD (7.3 mL, 36.03 mmol, 2 eq) was added at 0°C. The reaction mixture was stirred for 16 h at room temperature. TLC analysis indicated formation of less polar spot. The reaction mixture was concentrated to give crude residue, which was purified by column by using neutral alumina as stationary phase and 0-5% MeOH in DCM as mobile phase to give (3S,5S)-l-benzyl-3, 5-dimethylpiperazine (14 g, 41.7% yield) as pale brown liquid. LCMS: [M+l]+ 205.06.

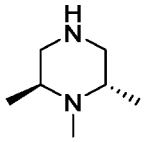
Step 6: (2S,6S)-4-benzyl-l ,2,6-trimethylpiperazine



[00695] A solution of (3S,5S)-l-benzyl-3, 5-dimethylpiperazine (3.5g, 17.15mmol, leq) in DCM: AcOH (35mL:15mL.5mL) was cooled to 0°C and 37% HCHO soln. (2.8mL, 34.31mmol, 2eq) was added dropwise at 0°C under argon atmosphere. Then, the reaction mixture was allowed to react at RT for 3h. The reaction mixture was cooled to 0°C and $NaCNBH_3$ 2.1g, 34.31mol, 2eq) was added slowly at 0°C and allowed to react at RT for 2h. The reaction was monitored by TLC, and TLC analysis indicated formation of less polar spot. The reaction was basified

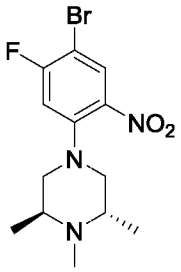
with sat. NaHCCb and extracted with DCM (2 X 250ml). The combined organic layer was washed with water (150mL) and brine solution (100 mL), dried over Na_2SO_4 then concentrated under reduced pressure to give crude compound. The crude compound was purified by silica gel chromatography (silica gel 230-400 mesh) using 2-5% MeOH in DCM as an eluent to afford (2S,6S)-4-benzyl-l,2,6-trimethylpiperazine (3 g, 81.1 % yield) as brown liquid. LCMS: [M+H]+ 219.11.

Step 7: (2S,6S)-l,2,6-trimethylpiperazine



[00696] To a stirred solution of (2S,6S)-4-benzyl-l,2,6-trimethylpiperazine (4.6 g, 21.1 mmol, leq) in methanol (146 mL) was added $Pd(OH)_2$ (20% wt on carbon, 820 mg) and HC1 (4M in dioxane, lmL). Then the reaction mixture was purged with nitrogen for 15 min, and then hydrogenated under par shaker for 18 h. TLC analysis indicated formation of polar spot. The reaction mixture was filtered through celite, and washed with methanol and DCM. The filtrate was concentrated under reduced pressure to afford (2S,6S)-l,2,6-trimethylpiperazine (3 g, 45% crude yield) as a pale yellow liquid. LCMS: [M+H]+ 347.96.

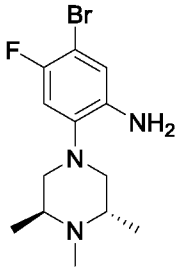
Step 8: (2S, 6S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine



[00697] To a solution of (2S,6S)-4-benzyl-l,2,6-trimethylpiperazine (3 g, 13.4 mmol, 1.3 eq) in ethanol (90 mL) was added TEA (2 mL,15.449 mmol, 1.5 eq) at RT under argon atmosphere, then after 30min, 1-bromo-2,4-difluoro-5 -nitrobenzene (4.5 mL,10.299mmol, leq) was added at RT. Then the reaction mass was heated to 85° C for 16 h. The reaction was monitored by TLC, and TLC analysis indicated formation of polar spot. The reaction mixture was concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (silica gel 230-400 mesh) using 3% methanol in DCM as an eluent to give (2S,6S)-4-(4-bromo-

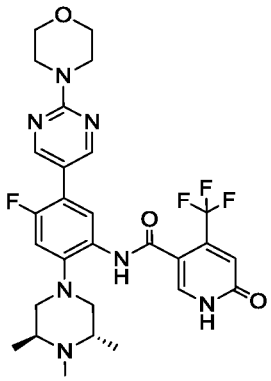
5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (3 g, 46.8% yield) as yellow liquid. LCMS: [M+H]+ 347.96.

Step 9: 5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l -yl)aniline



[00698] A round bottomed flask was charged with (2S,6S)-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (3.5 g, 10.14 mmol, leq), NH_4Cl (3.25 g, 60.86 mmol, 6eq) and Fe powder (3.4 g, 60.9 mmol, 6 eq) and covered with ethanol: water (60 mL: lOmL) at RT. The resulting suspension was then heated to 80°C for 16 h. The reaction was monitored by TLC, and TLC analysis indicated formation of a polar spot. Then, the reaction mixture was cooled to RT and filtered through a celite bed; celite bed was washed with EtOAc (200 mL), then the filtrates were concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using DCM as an eluent to give 5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l-yl)aniline (1.4 g, 41.1% yield) as brown semisolid. LCMS: [M+H]+: 318.0.

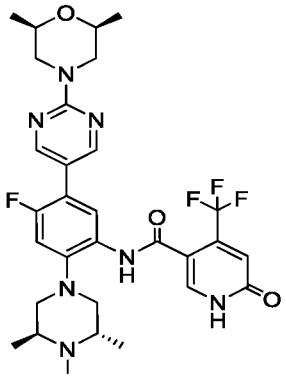
Step 10: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(Mfluoromethyl)-lH^yridine-3 -carboxamide



[00699] The title compound was prepared similar to the sequence described above for the preparation of Example 353 using 5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l-yl)aniline in place of 5-bromo-4-fluoro-2-((3R,5R)-3,4,5-

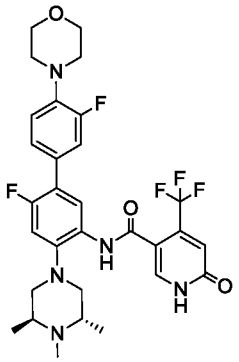
trimethylpiperazin-l-yl)aniline in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.30 (s, 1H), 8.53 (d, *J*=0.6 Hz, 2H), 8.03 (s, 1H), 7.74 (d, *J*=8.6 Hz, 1H), 7.07 (d, *J*=12.3 Hz, 1H), 6.80 (s, 1H), 3.78 - 3.72 (m, 4H), 3.71 - 3.65 (m, 4H), 2.90 (br d, *J*=9.0 Hz, 2H), 2.81 (dt, *J*=3.1, 6.1 Hz, 2H), 2.64 (br dd, *J*=6.2, 10.8 Hz, 2H), 2.20 (s, 3H), 0.97 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+: 590.6.

Example 356: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



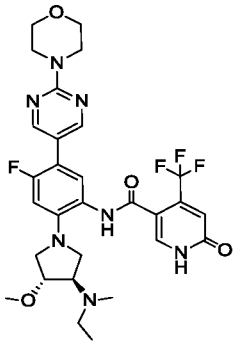
[00700] The title compound was prepared similar to the sequence described above for the preparation of Example 355 using (2-(cis-2,6-dimethylmo ϕ holino)pyrimidin-5-yl)boronic acid in place of 2-(4-mo ϕ holino)pyrimidine-5-boronic acid pinacol ester in the final step. ¾ NMR (500MHz, DMSO-d6) δ = 9.29 (s, 1H), 8.51 (s, 2H), 8.03 (s, 1H), 7.73 (d, *J*=8.6 Hz, 1H), 7.07 (d, *J*=12.3 Hz, 1H), 6.80 (s, 1H), 4.60 - 4.46 (m, 2H), 3.63 - 3.51 (m, 2H), 2.90 (br d, *J*=8.1 Hz, 2H), 2.84 - 2.78 (m, 2H), 2.63 (br dd, *J*=6.2, 10.8 Hz, 2H), 2.58 (dd, *J*=10.8, 13.0 Hz, 2H), 2.20 (s, 3H), 1.16 (d, *J*=6.1 Hz, 6H), 0.97 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+: 618.5.

Example 357: N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^oxamide



[00701] The title compound was prepared similar to the sequence described above for the preparation of Example 355 using 3-fluoro-4-morpholinophenylboronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in the final step. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.28 (s, 1H), 8.04 (s, 1H), 7.75 (br d, *J*=8.4 Hz, 1H), 7.36 - 7.23 (m, 2H), 7.17 - 7.09 (m, 1H), 7.04 (d, *J*=12.7 Hz, 1H), 6.81 (s, 1H), 3.80 - 3.72 (m, 4H), 3.10 - 3.03 (m, 4H), 2.91 (br d, *J*=8.8 Hz, 2H), 2.86 - 2.78 (m, 2H), 2.64 (br dd, *J*=6.1, 10.8 Hz, 2H), 2.20 (s, 3H), 0.97 (d, *J*=6.4 Hz, 6H); LCMS [M+H]+: 606.6.

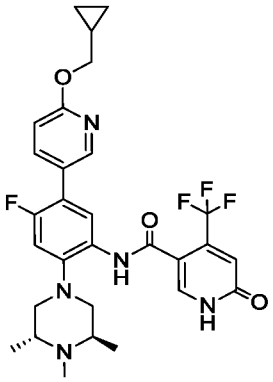
Example 358: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4RJ-3-fethyl(methyl)aminoJ-4-methoxypyrrolidin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00702] The title compound was prepared similar to the procedure described above for the preparation of Example 307 using N-ethylmethylamine in place of N-(2-methoxyethyl)methylamine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.78 (s, 1H), 8.51 (s, 2H), 7.98 (s, 1H), 7.36 (d, *J*=8.8 Hz, 1H), 6.77 (s, 1H), 6.74 (d, *J*=13.8 Hz, 1H), 3.91 - 3.84 (m, 1H), 3.78 - 3.71 (m, 4H), 3.70 - 3.63 (m, 4H), 3.51 - 3.42 (m,

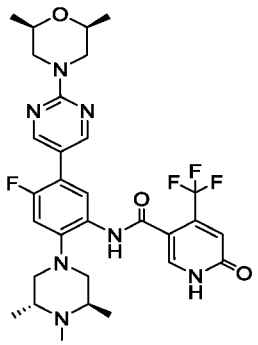
2H), 3.25 (s, 3H), 3.18 (br dd, *J*=6*A*, 10.0 Hz, IH), 3.05 - 2.97 (m, IH), 2.48 - 2.40 (m, IH), 2.17 (s, 3H), 0.95 (t, *J*=7.1 Hz, 3H); LCMS [M+H]+: 620.6.

Example 359: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carb oxamide



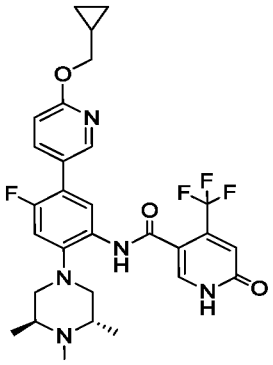
[00703] The title compound was prepared similar to the procedure described above for the preparation of Example 353 using 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 8.91 (s, IH), 8.25 (s, IH), 8.18 (s, IH), 7.94 (d, *J*=8.7 Hz, IH), 7.86 - 7.77 (m, IH), 7.11 (d, *J*=12.2 Hz, IH), 6.92 (d, *J*=8.6 Hz, IH), 6.28 (s, IH), 4.13 (d, *J*=7.2 Hz, 2H), 2.91 (br d, *J*=8.6 Hz, 2H), 2.86 - 2.78 (m, 2H), 2.61 (br dd, *J*=6.2, 10.9 Hz, 2H), 2.21 (s, 3H), 1.32 - 1.21 (m, IH), 0.97 (d, *J*=6.4 Hz, 6H), 0.59 - 0.52 (m, 2H), 0.37 - 0.30 (m, 2H); LCMS [M+H]+: 574.6.

Example 360: N-[4-fluoro-5-[2-[(2R, 6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



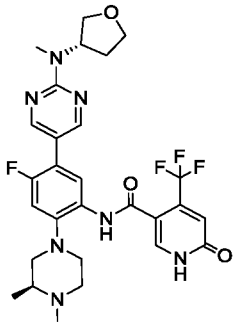
[00704] The title compound was prepared similar to the procedure described above for the preparation of Example 353 using (2-(cis-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.28 (s, IH), 8.51 (s, 2H), 8.04 (s, IH), 7.74 (d, ***J***=8.6 Hz, IH), 7.07 (d, ***J***=12.3 Hz, IH), 6.78 (s, IH), 4.59 - 4.48 (m, 2H), 3.57 (ddd, ***J***=2.3, 6.3, 10.3 Hz, 2H), 2.94 - 2.88 (m, 2H), 2.81 (dt, ***J***=3.0, 6.1 Hz, 2H), 2.63 (br dd, ***J***=6.2, 10.8 Hz, 2H), 2.58 (dd, ***J***=10.8, 13.1 Hz, 2H), 2.20 (s, 3H), 1.16 (d, ***J***=6.2 Hz, 6H), 0.97 (d, ***J***=6.4 Hz, 6H); LCMS [M+H]+: 618.6.

Example 361: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carbomm^de



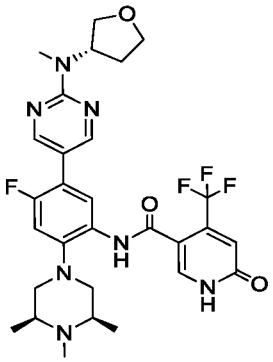
[00705] The title compound was prepared similar to the sequence described above for the preparation of Example 355 using 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine in place of 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester in the final step of the sequence. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.02 (s, IH), 8.25 (s, IH), 8.14 (s, IH), 7.90 (d, ***J***=8.6 Hz, IH), 7.82 (dd, ***J=1.2,*** 8.6 Hz, IH), 7.10 (d, ***J***=12.2 Hz, IH), 6.93 (d, ***J***=8.6 Hz, IH), 6.42 (s, IH), 4.14 (d, ***J***=7.2 Hz, 2H), 2.94 - 2.89 (m, 2H), 2.87 - 2.80 (m, 2H), 2.62 (br dd, ***J=6.2,*** 10.9 Hz, 2H), 2.21 (s, 3H), 1.32 - 1.21 (m, IH), 0.97 (d, ***J***=6.4 Hz, 6H), 0.59 - 0.53 (m, 2H), 0.37 - 0.31 (m, 2H); LCMS [M+H]+: 574.5.

Example 362: N-[4-fluoro-5-[2-[methyl-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



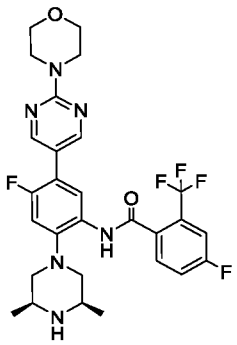
[00706] To a mixture of 2-chloropyrimidine-5-boronic acid (32 mg, 0.2 mmol) and (S)-methyl-(tetrahydro-furan-3-yl)-amine hydrochloride (29 mg, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C for 5 h. Solvents were removed to give crude (S)-(2-(methyl(tetrahydromran-3-yl)amino)pyrirnidin-5-yl)boronic acid as a light yellow semi-solid. LCMS $[M + H]^+$ 224.2. The title compound (light beige solid, 8.3 mg, 14%) was prepared by a procedure similar to that of the last step of Example 273 using crude (S)-(2-(methyl(tetrahydrofuran-3-yl)amino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-1-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.72 (br s, 1H), 8.57 (s, 2H), 8.47 (br d, *J*=8.1 Hz, 1H), 7.88 (s, 1H), 7.05 (br d, *J*=11.0 Hz, 1H), 7.02 (s, 1H), 5.69 - 5.63 (m, 1H), 4.13 (dt, *J*=4.7, 8.5 Hz, 1H), 3.94 - 3.87 (m, 2H), 3.79 (q, *J*=8.1 Hz, 1H), 3.16 (s, 3H), 3.03 - 2.88 (m, 3H), 2.83 (br d, *J*=10.9 Hz, 1H), 2.61 (br t, *J*=10.3 Hz, 1H), 2.43 - 2.29 (m, 5H), 2.23 (br s, 1H), 2.06 - 1.97 (m, 1H), 1.12 (br d, *J*=5.9 Hz, 3H); LCMS $[M+H]^+$ 590.6.

Example 363: N-[4-fluoro-5-[2-[methyl-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-f(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

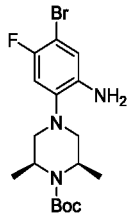


[00707] The title compound (beige solid, 5.3 mg, 9%) was prepared by a procedure similar to that of Example 29 using crude (S)-(2-(methyl(tetrahydrofuran-3-yl)amino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (br s, 1H), 8.55 (s, 2H), 8.45 (br d, *J*=7.6 Hz, 1H), 7.83 (s, 1H), 7.06 - 6.96 (m, 2H), 5.68 - 5.60 (m, 1H), 4.11 (dt, *J*=4.6, 8.4 Hz, 1H), 3.92 - 3.85 (m, 2H), 3.78 (q, *J*=8.0 Hz, 1H), 3.15 (s, 3H), 2.86 - 2.75 (m, 2H), 2.65 (br t, *J*=9.2 Hz, 2H), 2.39 - 2.16 (m, 6H), 2.04 - 1.94 (m, 1H), 1.14 (d, *J*=4.8 Hz, 6H); LCMS $[M + H]^+$ 604.6.

Example 364: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,5-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide

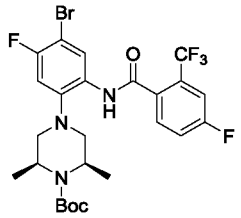


Step 1: tert-butyl (2S,6R)-4-(2-amino-4-bromo-5-fluorophenyl)-2,6-dimethylpiperazine-l-carboxylate



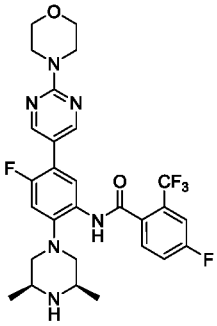
[00708] To a suspension of $K2CO_3$ (366 mg, 2.65 mmol, 0.525 equiv.) in toluene (20 mL) was added cis-2,6-dimethylpiperazine (577 mg, 5.05 mmol), followed by dropwise addition of l-bromo-2,4-difluoro-5 -nitrobenzene (0.63 mL, 5 mmol) over 1 min. The resulting mixture was stirred at 45 °C overnight. After diluting with $\mathbf{H_20}$ (20 mL) to dissolve the insoluble salts, it was extracted with EtOAc (40 mL x 2). The combined extracts were concentrated and dried under vacuum to give the nitro intermediate (3S,5R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-3,5-dimethylpiperazine as an orange solid. LCMS $[M + H]^+$ 332.3. To a solution of the this intermediate in THF (30 mL) was added di-tert-butyl dicarbonate (1.309 g, 6 mmol). The resulting mixture was stirred at rt for 1.5 h. DMAP (73 mg, 0.6 mmol) was added and the resulting mixture was stirred at rt for 1 h. Additional di-tert-butyl dicarbonate (1.309 g, 6 mmol) was added and the resulting mixture was stirred over the weekend at rt. Solvents were removed and the residue was purified by flash chromatography (gradient: EtOAc/hex 0-30%) to give tert-butyl (2S,6R)-4-(4-bromo-5-fluoro-2-nitrophenyl)-2,6-dimethylpiperazine-l-carboxylate as pale yellow crystals (0.946 g). To a solution of the above pale yellow crystal in MeOH (30 mL) was added a suspension of Raney-Nickel (214 mg, 2.5 mmol) in MeOH (5 mL), followed by addition of hydrazine monohydrate (0.73 mL, 15 mmol) over 2 min. After addition, the resulting mixture was stirred at rt for 5 min then heated at 60 °C for 45 min. After filtering and rinsing with MeOH (10 mL), the filtrate was concentrated and purified by flash chromatography (gradient: EtOAc/hex 0-30%) to give tert-butyl (2S,6R)-4-(2-amino-4-bromo-5-fluorophenyl)-2,6-dimethylpiperazine-l-carboxylate as a beige solid (385 mg, 19% yield over 3 steps). LCMS $[M+ H]^+$ 402.4.

Step 2: Preparation of tert-butyl (2S,6R)-4-(4-bromo-5-fluoro-2-(4-fluoro-2-(trifluoromethyl)benzamido)phenyl)-2,6-dimethylpiperazine-l-carboxylate



[00709] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.29 mL, 1.914 mmol) in DCM (10 mL) at rt was added Et_3N (0.534 mL, 3.83 mmol). After addition, the resulting mixture was stirred at rt for 5 min, before a solution of (2S,6R)-tert-butyl 4-(2-amino-4-bromo-5-fluorophenyl)-2,6-dimethylpiperazine-l-carboxylate (385 mg, 0.957 mmol) in DCM (5 mL) was added. The resulting mixture was stirred at rt overnight. After quenching with sat. $NaHCO_3$ (15 mL) and stirring for 10 min at rt, it was extracted with DCM (15 mL x 2). The combined extracts were combined and concentrated to give a light yellow solid. It was triturated with DCM/MeOH (2 mL/8 mL), filtered and dried to give a white solid (463 mg). LCMS $[M+H]^+$ 592.4.

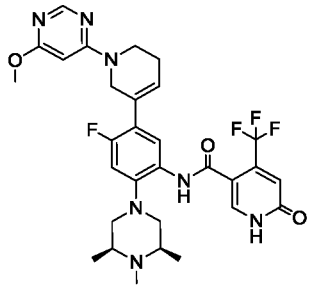
Step 3: N-(2-((3S,5R)-3,5-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide



[00710] tert-Butyl (2S,6R)-4-(5-fluoro-2-(4-fluoro-2-(trifluoromethyl)benzamido)-4-(2-morpholinopyrimidin-5-yl)phenyl)-2,6-dimethylpiperazine-l-carboxylate (444 mg) was prepared according a method similar to that used in the final step of Example 29 using 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (466 mg, 1.6 mmol) and (2S,6R)-tert-butyl 4-(4-bromo-5-fluoro-2-(4-fluoro-2-(trifluoromethyl)benzamido)phenyl)-2, 6-dimethylpiperazine-1-carboxylate (453 mg, 0.765 mmol). LCMS $[M+H]^+$ 677.6. The above solid (444 mg) was redissolved in DCM (10 mL) and treated with TFA (1.2 mL). The resulting mixture was stirred at rt for 4 h and basified with 1 M NaHC03 (15 mL). After stirring at rt for 2 min, it was separated and the aqueous was extracted with DCM (15 mL). The combined DCM extracts were

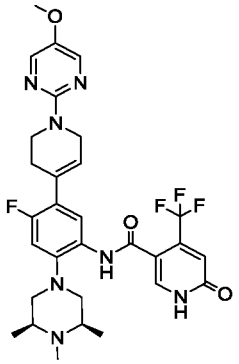
concentrated and dried to give a light brown oil which was purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-20%) to give the title compound as a white solid (263.7 mg, 45% over 2 steps). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.60 (s, IH, NH), 8.58 (s, 2H), 8.56 (d, *J*=8.2 Hz, IH), 7.66 (dd, *J*=5.3, 8.3 Hz, IH), 7.49 (dd, *J*=2.3, 8.8 Hz, IH), 7.37 (t, *J*=8.0 Hz, IH), 7.00 (d, *J*=11.2 Hz, IH), 3.91 - 3.85 (m, 4H), 3.82 - 3.78 (m, 4H), 2.94 - 2.82 (m, 4H), 2.36 (br t, *J*=10.5 Hz, 2H), 1.08 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 577.5.

Example 365: N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



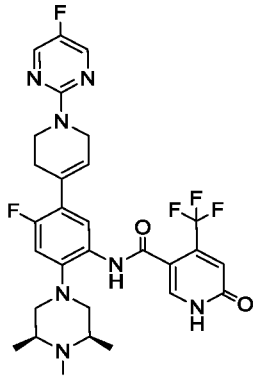
[00711] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (26 mg, 0.051 mmol) and 4-Iodo-6-methoxypyrimidine (13.90 mg, 0.059 mmol) to give the title compound (22 mg, 66% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.14 - 8.06 (m, IH), 7.87 - 7.81 (m, IH), 7.72 - 7.63 (m, IH), 6.92 - 6.85 (m, IH), 6.83 - 6.77 (m, 1H),6.10 - 6.02 (m, IH), 5.96 - 5.92 (m, IH), 4.30 - 4.21 (m, 2H), 3.82 - 3.78 (m, 3H), 3.77 - 3.72 (m, 2H), 2.97 - 2.90 (m, 2H), 2.52 - 2.46 (m, 2H), 2.46 - 2.39 (m, 2H), 2.35 - 2.29 (m, 2H), 2.27 (s, 3H), 1.07 - 1.02 (m, 6H); LCMS [M+H]+ 616.6.

Example 366: N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00712] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihy dropyridine-3 -carboxamide (38 mg, 0.075 mmol) and 2-bromo-5-methoxypyrimidine (16.98 mg, 0.090 mmol) in 2-propanol (2.5 ml). The standard workup and purification provided the title compound as a tan coloured powder (24 mg, 50% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.22 - 8.16 (m, 2H), 7.98 - 7.93 (m, 1H), 7.84 - 7.76 (m, 1H), 6.99 - 6.94 (m, 1H), 6.94 - 6.91 (m, 1H),6.16 - 6.10 (m, 1H), 4.32 - 4.28 (m, 2H), 4.01 - 3.96 (m, 2H), 3.86 - 3.83 (m, 3H), 3.06 - 3.00 (m, 2H), 2.63 - 2.57 (m, 4H), 2.56 - 2.50 (m, 2H), 2.39 - 2.38 (m, 3H), 1.18 - 1.16 (m, 6H); LCMS [M+H]+ 616.7

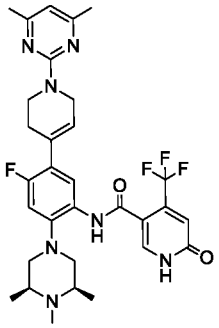
Example 367: N-[4-fluoro-5-[l-(5-fluoropyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00713] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (32 mg,

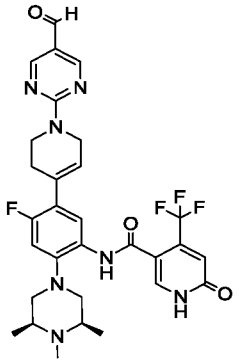
0.063 mmol) and 2-bromo-5-fluoropyrimidine (13.39 mg, 0.076 mmol) in 2-propanol (2.5 ml). Workup and purification provided the title compound as a tan coloured powder (28 mg, 70% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.37 - 8.28 (m, 2H), 7.98 - 7.92 (m, 1H), 7.85 - 7.74 (m, 1H), 6.98 - 6.94 (m, 1H), 6.93 - 6.90 (m, 1H),6.17 - 6.07 (m, 1H), 4.37 - 4.33 (m, 2H), 4.03 (t, *J*=5.6 Hz, 2H), 3.05 - 2.99 (m, 2H), 2.63 - 2.57 (m, 4H), 2.56 - 2.49 (m, 2H), 2.39 - 2.36 (m, 3H),1.19 - 1.16 (m, 6H); LCMS [M+H]+ 604.6.

Example 368: N-[5-[l-(4, 6-dimethylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



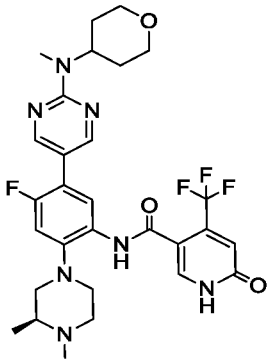
[00714] A procedure similar to that of Example 270 using N-(4-fluoro-5-(l, 2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (30 mg, 0.059 mmol) and 2-bromo-4,6-dimethylpyrimidine (13.27 mg, 0.071 mmol) gave the title compound (28 mg, 73 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.99 - 7.92 (m, 1H), 7.83 - 7.75 (m, 1H), 6.98 - 6.94 (m, 1H), 6.93 - 6.90 (m, 1H), 6.46 - 6.39 (m, 1H),6.16 - 6.08 (m, 1H), 4.41 - 4.37 (m, 2H), 4.09 - 4.03 (m, 2H), 3.07 - 3.00 (m, 2H), 2.63 - 2.52 (m, 6H), 2.39 - 2.37 (m, 3H), 2.33 - 2.30 (m, 6H), 1.17(d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 614.7.

Example 369: N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00715] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50 mg, 0.099 mmol) and 2-bromo-pyrimidine-5-carbaldehyde (22.11 mg, 0.118 mmol) to give the title compound as a beige powder (24 mg, 38% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.82 - 9.72 (m, 1H), 8.87 - 8.76 (m, 2H), 7.99 - 7.92 (m, 1H), 7.85 - 7.77 (m, 1H), 6.99 - 6.94 (m, 1H), 6.93 - 6.90 (m, 1H), 6.19 - 6.10 (m, 1H), 4.58 - 4.52 (m, 2H), 4.28 - 4.19 (m, 2H), 3.08 - 3.01 (m, 2H), 2.68 - 2.63 (m, 2H), 2.63 - 2.57 (m, 2H), 2.56 - 2.48 (m, 2H), 2.39 - 2.36 (m, 3H), 1.18 - 1.15 (m, 6H); LCMS [M+H]+ 614.7.

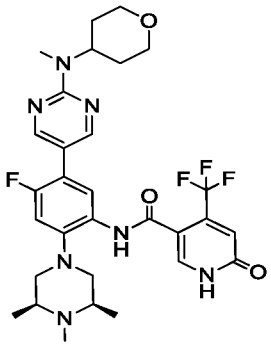
Example 370: N-[4-fluoro-5-[2-[methyl(omn-4-yl)amino]pyrimidin-5-yl]-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00716] To a mixture of 2-chloropyrimidine-5-boronic acid (32 mg, 0.2 mmol) and N-methyl-N-tetrahydro-2H-pyran-4-ylamine (26 μL, 0.21 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 75 °C for 5 h. Solvents were removed to give crude (2-(methyl(tetrahydro-2H-pyran-4-

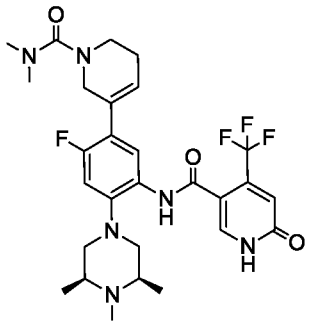
yl)amino)pyrimidin-5-yl)boronic acid as a light yellow solid. LCMS $[M + H]^+$ 238.2. The title compound (white solid, 5.4 mg, 9%) was prepared similar to Example 29 using crude (2-(methyl(tetrahydro-2H-pyran-4-yl)amino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.73 (br s, 1H), 8.57 (s, 2H), 8.52 - 8.40 (m, 1H), 7.87 (br s, 1H), 7.11 - 6.91 (m, 2H), 4.98 (br t, *J*=11.9 Hz, 1H), 4.11 (br dd, *J*=4.0, 11.4 Hz, 2H), 3.61 (br t, *J*=11.6 Hz, 2H), 3.11 (s, 3H), 3.05 - 2.82 (m, 4H), 2.70 - 2.55 (m, 1H), 2.38 (br s, 3H), 2.30 - 2.16 (m, 1H), 1.94 (dq, *J*=4.4, 12.2 Hz, 2H), 1.70 (br d, *J*=11.5 Hz, 2H), 1.13 (br s, 3H); LCMS $[M + H]^+$ 604.5.

Example 371: N-[4-fluoro-5-[2-[methyl(oxan-4-yl)aminoJpyrimidin-5-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



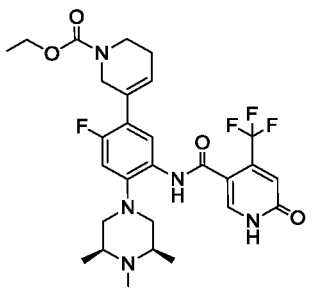
[00717] The title compound (white solid, 4.6 mg, 7%) was prepared similar to Example 31 using crude (2-(methyl(tetrahydro-2H-pyran-4-yl)amino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.72 (br s, 1H), 8.57 (br s, 2H), 8.46 (br s, 1H), 7.86 (br s, 1H), 7.03 (br d, *J*=11.0 Hz, 2H), 4.97 (br t, *J*=11.7 Hz, 1H), 4.11 (br dd, *J*=3.6, 11.2 Hz, 2H), 3.61 (br t, *J*=11.5 Hz, 2H), 3.11 (s, 3H), 2.91 - 2.78 (m, 2H), 2.76 - 2.58 (m, 2H), 2.35 (br s, 4H), 1.94 (dq, *J*=4.0, 12.0 Hz, 3H), 1.70 (br d, *J*=11.5 Hz, 4H), 1.17 (br s, 6H); LCMS $[M+ H]^+$ 618.6.

Example 372: N-[5-[l-(dimethylcarbamoyl)-3, 6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



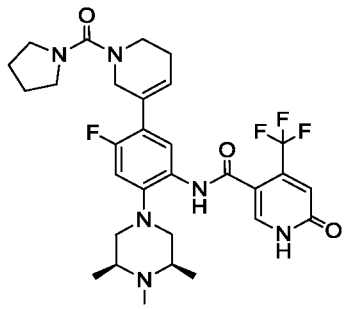
[00718] To a mixture of N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and N,N-diisopropylethylamine (0.017 ml, 0.099 mmol) in DCM (3 ml) at RT, was added dimethylcarbamoyl chloride (5.67 µï, 0.062 mmol). After stirring overnight, additional dimethylcarbamoyl chloride (0.5 eq) was added and the mixture was stirred for an additional 1.5 h. The reaction was quenched with water, and standard workup and purification gave the title compound as a white powder (24 mg, 80% yield). ^{1}H NMR (500MHz, METHANOL-**d4)** δ = 7.98 - 7.90 (m, 1H), 7.81 - 7.71 (m, 1H), 7.00 - 6.94 (m, 1H), 6.94 - 6.90 (m, 1H), 6.16 - 6.03 (m, 1H), 4.11 - 4.03 (m, 2H), 3.45 - 3.41 (m, 2H), 3.07 - 3.01 (m, 2H), 2.93 - 2.88 (m, 6H), 2.63 - 2.57 (m, 2H), 2.57 - 2.50 (m, 2H), 2.44 - 2.39 (m, 2H), 2.39- 2.36 (m, 3H), 1.18 - 1.15 (m, 6H); LCMS [M+H]+ 579.6.

Example 373: ethyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



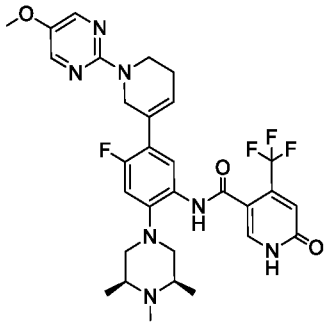
[00719] This example was prepared using a procedure similar to Example 39 from N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (400 mg, 0.661 mmol) and 1-Boc-5,6-dihydro-2H-pyridine-3-boronic acid, pinacol ester (306 mg, 0.991 mmol) followed by deprotection of a portion (50 mg, 0.071 mmol) of the resulting tert-butyl 5-(2-fluoro-5-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-3 ,6-dihy dropyridine- 1(2H)-carboxylate intermediate by stirring in a solution of TFA in DCM (5 ml) at room temperature for 45 min. Standard workup and purification gave the title compound (33 mg, 73% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.80 (m, 1H), 7.69 - 7.60 (m, 1H), 6.89 - 6.82 (m, 1H), 6.82 - 6.77 (m, 1H), 6.02 - 5.95 (m, 1H), 4.15 - 4.06 (m, 2H), 3.54 - 3.42 (m, 2H), 2.95 - 2.89 (m, 2H), 2.54 - 2.40 (m, 4H), 2.28 - 2.25 (m, 3H), 2.24 - 2.19 (m, 2H), 1.40 - 1.37 (m, 9H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 608.4

Example 374: N-[4-fluoro-5-[1-(pyrrolidine-1 -carbonyl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



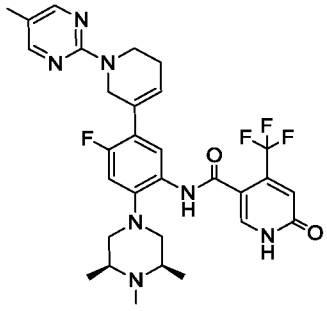
[00720] The procedure followed was similar to that of Example 253 using N-(4-fluoro-5-(l,2,5,64etrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) N,N-diisopropylethylamine (0.017 ml, 0.099 mmol), and 1-pyrrolidinecarbonyl chloride (5.71 µï, 0.052 mmol) in DCM (3 mL) at RT to give the title compound (24 mg, 77% yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.89 (m, 1H), 7.80 - 7.71 (m, 1H), 6.99 - 6.94 (m, 1H), 6.93 - 6.89 (m, 1H), 6.16 - 6.05 (m, 1H),4.15 - 4.05 (m, 2H), 3.51 - 3.41 (m, 6H), 3.07 - 2.96 (m, 2H), 2.64 - 2.50 (m, 4H), 2.43 - 2.33 (m, 5H), 1.93 - 1.83 (m, 4H), 1.18 - 1.11 (m, 6H); LCMS [M+H]+ 605.7.

Example 375: N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00721] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 2-bromo-5-methoxypyrimidine (13.03 mg, 0.069 mmol) to afford, after workup and purification, the title compound (19 mg, 61 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ 8.16 (s, 2H), 7.96 (s, IH), 7.80 (d, *J*=7.82 Hz, IH), 6.98 (d, *J*=12.10 Hz, IH), 6.92 (s, IH), 6.13 (br. s.,lH), 4.46 (br. s., 2H), 3.93 (t, *J*=5.62 Hz, 2H), 3.83 (s, 3H), 3.04 (d, *J*=11.13 Hz, 2H), 2.58-2.64 (m, 2H), 2.55 (d, *J*=5.62 Hz, 2H), 2.37-2.44 (m, 5H), 1.17 (d, *J*=5.99 Hz, 6H); LCMS [M+H]+ 616.7.

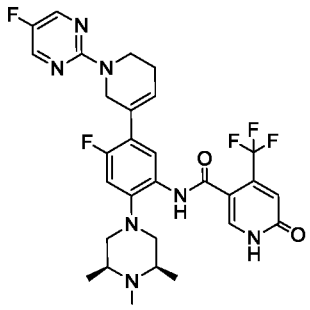
Example 376: N-[4-fluoro-5-[l-(5-methylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00722] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg,

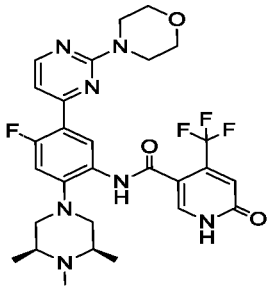
0.049 mmol) and 2-chloro-5-methylpyrimidine (8.87 mg, 0.069 mmol) to give, after workup and purification, the title compound (22 mg, 70 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ 8.22 (s, 2H), 7.96 (s, 1H), 7.80 (d, *J*=7.95 Hz, 1H), 6.98 (d, *J*=12.23 Hz, 1H), 6.92 (s, 1H), 6.15 (br. s.,lH), 4.49 (br. s., 2H), 3.96 (t, *J*=5.75 Hz, 2H), 3.04 (d, *J*=11.13 Hz, 2H), 2.58-2.65 (m, 2H), 2.49-2.56 (m, 2H), 2.55 (d, *J*=4.77 Hz, 2H), 2.41 (d, *J*=3.30 Hz, 2H), 2.38 (s, 3H), 2.16 (s, 3H), 1.17 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 600.7.

Example 377: N-[4-fluoro-5-[l-(5-fluoropyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



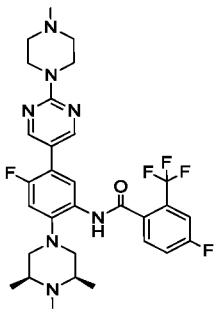
[00723] The procedure followed was similar to Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 2-bromo-5-fluoropyrimidine (10.46 mg, 0.059 mmol) to give, after workup and purification, the title compound (23 mg, 74 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ 8.28-8.36 (m, 2H), 7.96 (s, 1H), 7.79 (d, *J*=7.95 Hz, 1H), 6.98 (d, *J*=12.23 Hz, 1H), 6.92 (s, 1H), 6.15 (br. s., 1H), 4.51 (br. s., 2H), 3.98 (t, *J*=5.75 Hz, 2H), 3.04 (d, *J*=11.13 Hz, 2H), 2.58-2.66 (m, 2H), 2.49-2.57 (m, 2H), 2.41 (d, *J*=3.67 Hz, 2H), 2.38 (s, 3H), 1.17 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 604.5.

Example 378: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^oxamide



[00724] The title compound was prepared similar to the sequence described above for the preparation of Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and 4-[5-(4,4,5,5-Tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo ϕ holine to give, after deprotection of the N-(4-fluoro-5-(6-mo ϕ holinopyridin-3-yl)-2-((3 S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide intermediate, the title compound (48.6 mg, 44% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.58 (d, *J* = 8.3 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 7.92 (s, 1H), 7.13 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.01 (d,J= 13.2 Hz, 1H), 6.92 (s, 1H), 3.84 (d, *J* = 5.0 Hz, 4H), 3.77 - 3.75 (m, 4H), 3.16 (d, *J* = 10.4 Hz, 2H), 2.64 (dd, *J* = 23.5, 12.5 Hz, 4H), 2.40 (s, 3H), 1.18 (d, *J* = 5.9 Hz, 6H); LCMS HSS $[M+l]^{+}$ = 590.55.

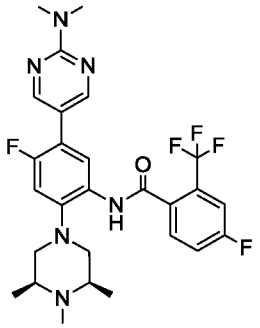
Example 379: 4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-2-(trifluoromethyl)benzamide



[00725] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.61 mL, 4 mmol) in DCM (15 mL) at rt was added Et_3N (1.12 mL, 8 mmol). After addition, the resulting mixture was stirred at rt for 5 min, before a solution of 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (632 mg, 2 mmol) in DCM (10 mL) was added. The resulting mixture was stirred at rt for 2 h. After basic workup with sat. NaHC03, it was purified by flash chromatography (gradient: EtOAc/hex 0-100%) to

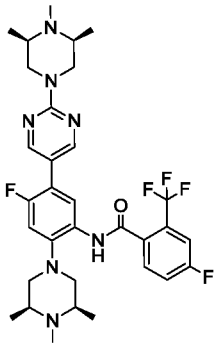
give N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide as a pale beige solid (417 mg, 39%). LCMS $[M + H]^+$ 506.4. The title compound (white solid, 41.2 mg, 68%) was prepared by a procedure similar to examples hereinabove using 2-(4-methylpiperazin-l-yl)pyrimidine-5-boronic acid pinacol ester (60.8 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (50.6 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.60 - 8.53 (m, 4H), 7.66 (dd, *J=5.3,* 8.4 Hz, IH), 7.50 (dd, *J*=2.3, 8.7 Hz, IH), 7.38 (t, *J*=8.0 Hz, IH), 7.00 (d, *J*=11.2 Hz, IH), 3.96 - 3.87 (m, 4H), 2.82 (br d, *J*=11.0 Hz, 2H), 2.62 (t, *J*=10.9 Hz, 2H), 2.50 (t, *J*=5.1 Hz, 4H), 2.36 (s, 3H), 2.27 (s, 3H), 2.26 - 2.19 (m, 2H), 1.10 (d, *J*=6.2 Hz, 6H); LCMS $[M+ H]^+$ 604.6.

Example 380: N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -4-fluoro-2-(trifluoromethyl)benzamide



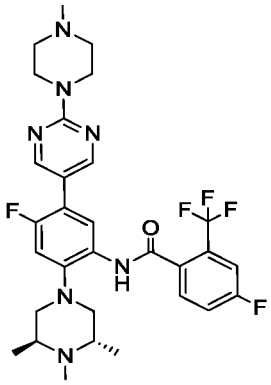
[00726] The title compound (pale beige solid, 44.9 mg, 81%) was prepared through a procedure similar to Example 31 using N,N-dimethyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (50 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (50.6 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.62 - 8.51 (m, 4H), 7.66 (dd, *J*=5.3, 8.4 Hz, IH), 7.49 (dd, *J*=2.3, 8.8 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.00 (d, *J*=11.2 Hz, IH), 3.25 (s, 6H), 2.82 (br d, *J*=11.0 Hz, 2H), 2.62 (br t, *J*=10.8 Hz, 2H), 2.28 (s, 3H), 2.25 - 2.17 (m, 2H), 1.11 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 549.5.

Example 381: 4-fluoro-N-[4-fluoro-2-[(3R, 5SJ-3,4,5-trimethylpiperazin-l -yl]-5-[2-f(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyljbenzamide



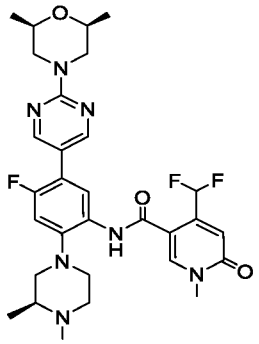
[00727] To a mixture of 2-chloropyrimidine-5-boronic acid (48 mg, 0.3 mmol) and (2R,6S)-l,2,6-trimethylpiperazine (40 mg, 0.315 mmol) in EtOH (2 mL) was added triethylamine (0.07 mL, 0.5 mmol). The resulting mixture was stirred at 80 °C for 1 h. Solvents were removed to give crude (2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)pyrimidin-5-yl)boronic acid as a pale yellow oil (semi-solid). The title compound (light brown solid, 35.3 mg, 55%) was prepared similar to the procedure of Example 31 using crude (2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (50.6 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.60 - 8.52 (m, 4H), 7.66 (dd, *J*=5.3, 8.4 Hz, 1H), 7.50 (dd, *J*=2.4, 8.8 Hz, 1H), 7.38 (dt, *J*=2.3, 8.1 Hz, 1H), 7.00 (d, *J*=11.2 Hz, 1H), 4.65 - 4.59 (m, 2H), 2.87 - 2.76 (m, 4H), 2.62 (t, *J*=11.0 Hz, 2H), 2.32 (s, 3H), 2.29 - 2.19 (m, 7H), 1.21 (d, *J*=6.1 Hz, 6H), 1.10 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 632.7.

Example 382: 4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide

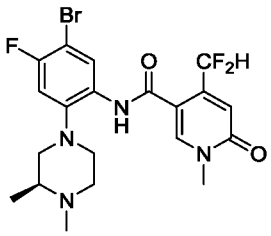


[00728] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.30 niL, 2 mmol) in DCM (9 mL) at rt was added Et_3N (0.56 mL, 4 mmol). After addition, the resulting mixture was stirred at rt for 5 min, before a solution of 5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l-yl)aniline (316 mg, 1 mmol, prepared in a similar manner to examples hereinabove) in DCM (1 mL) was added. The resulting mixture was stirred at rt for 1 h. After quenching with sat. $NaHCO_3$ (5 mL) and stirring for 5 min at rt, the DCM layer was loaded onto samplet and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-10%) to give N-(5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide as a pale beige solid (424 mg, 84%). LCMS $[M + H]^+$ 506.4. The title compound (white solid, 46.3 mg, 77%) was prepared using a procedure similar to Example 31 using 2-(4-methylpiperazin-l-yl)pyrimidine-5-boronic acid pinacol ester (61 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l -yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.1 mmol). ^1H NMR (500MHz, CHLOROFORM-d) δ = 8.62 (s, 1H), 8.56 (s, 2H), 8.53 (d, *J*=8.2 Hz, 1H), 7.67 (dd, *J=5.3,* 8.4 Hz, 1H), 7.49 (dd, *J*=2.3, 8.7 Hz, 1H), 7.36 (t, *J*=8.1 Hz, 1H), 7.00 (d, *J*=11.2 Hz, 1H), 3.96 - 3.87 (m, 4H), 2.94 - 2.78 (m, 4H), 2.66 (br dd, *J*=5.9, 10.6 Hz, 2H), 2.50 (t, *J*=5.0 Hz, 4H), 2.36 (s, 3H), 2.29 (s, 3H), 0.93 (br d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 604.5.

Example 383: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6SJ-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l -yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

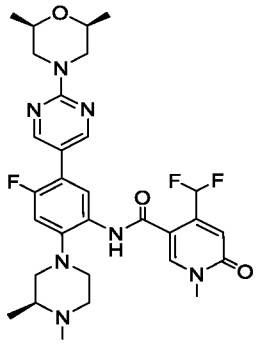


Step 1: (S)-N-(5-bromo-2-(3, 4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide



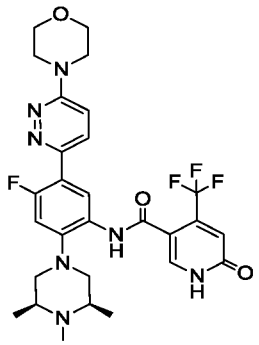
[00729] To a stirred solution of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (8g, 39.40 mmol, leq, prepared in Example 217 Step 6) in DMF (80mL) was added DIPEA (21.7 mL, 118.2 mmol, 3eq), HATU (44.9 g, 118.2 mmol, 3 eq) and then (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (11.94g, 39.4mmol, leq) was added at 0°C under argon atm, and the mixture was stirred for 16 h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200mL) and extracted with EtOAc (2 X 500mL). The organic layer was washed with brine and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% MeOH in EtOAc as an eluent to give (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxarnide (5.5 g, 50%) as a pale brown solid. LCMS: [M+H]+ 487.25.

Step 2: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R)-3, 4-dimethylpiperazin-l -yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

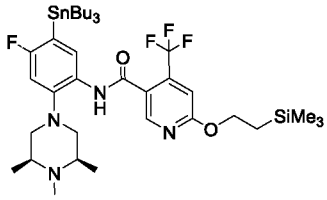


[00730] The title compound was prepared according to a procedure similar to that described in Example 31 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l -methyl-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and (2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (18.24 mg, 0.077 mmol). ¾ NMR (500MHz, DMSO-d6) δ = 9.48 (s, 1H), 8.51 (s, 2H), 8.36 (s, 1H), 7.68 (br d, *J*=8.6 Hz, 1H), 7.50 - 7.17 (m, 1H), 7.09 (br d, *J*=12.0 Hz, 1H), 6.65 (s, 1H), 4.54 (br d, *J*=11.7 Hz, 2H), 3.57 (ddd, *J*=2.3, 6.3, 10.3 Hz, 2H), 3.52 (s, 3H), 3.10 - 2.96 (m, 2H), 2.88 - 2.71 (m, 2H), 2.58 (dd, *J*=10.8, 13.0 Hz, 2H), 2.22 (br s, 2H), 1.20 - 1.11 (m, 1H), 1.16 (d, *J*=6.1 Hz, 5H), 0.98 (br s, 3H); LCMS [M+H]+: 600.6.

Example 384: N-[4-fluoro-5-(6-morpholin-4-ylpyridazin-3-yl)-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide

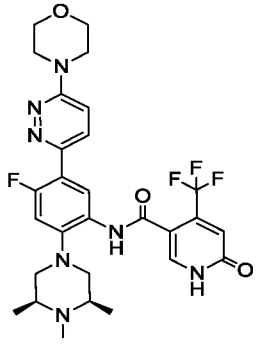


Step 1: N-(4-fluoro-5-(tributylstannyl)-2-((3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



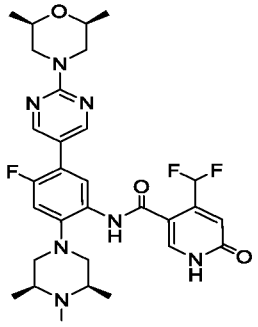
[00731] A stirred solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (10 g, 17.01 mmol, leq, from Example 39) in toluene (60mL) was degassed with argon for 15min, then hexabutylditin (17.3 mL, 34.1 mmol, 2eq) was added, followed by $Pd_2(dppf)_2Cl_2$.DCM (1.39g, 1.706mmol, O.leq) and after that heated to reflux under argon atmosphere for 24h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; and the filtrate was evaporated under reduced pressure. The resulting crude product was purified by column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent and resulted in N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (5.2 g, 36.6% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, MeOD) δ 8.49 (s, 1H), 7.92 - 7.81 (m, 1H), 7.13 (s, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 4.58 - 4.54 (m, 2H), 3.10 (d, *J* = 8.0 Hz, 2H), 2.64 (d, *J* = 5.8 Hz, 4H), 2.43 (s, 3H), 1.65 (d, *J* = 7.7 Hz, 3H), 1.57 (dd, *J* = 15.6, 8.0 Hz, 6H), 1.42 - 1.32 (m, 10H), 1.20 (s, 11H), 1.16 - 1.10 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 9H), 0.11 (s, 9H); LCMS C18 $[M+l]^+$ = 817.75.

Step 2: N-[4-fluoro-5-(6-morpholin-4-ylpyridazin-3-yl)-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide

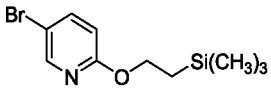


[00732] In N-methyl-2-pyrrolidinone (NMP) (247 μΐ) was dissolved N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (100.9 mg, 0.124 mmol). To the solution was added 4-(6-bromopyridazin-3-yl)morpholine (33.2 mg, 0.136 mmol), lithium chloride (15.73 mg, 0.371 mmol) and bis(triphenylphosphine)palladium(II) dichloride (4.78 mg, 6.80 μηιοΐ) at room temperature and then it was microwaved at the temperature of 120 °C for 2 hours. Standard workup and purification gave the title compound (2.1 mg, 3% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.29 (d, *J* = 7.2 Hz, 1H), 8.02 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 9.7 Hz, 1H), 7.11 (d, *J* = 12.2 Hz, 1H), 6.89 (s, 1H), 3.83 (s, 4H), 3.65 (s, 4H), 2.90 (s, 2H), 2.78 (s, 2H), 2.58 (s, 2H), 1.94 (s, 3H), 1.29 (s, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.67 (s), -119.73 (s); LCMS HSS $[M+l]^{+}$ = 590.55.

Example 385: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



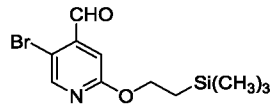
Step 1: 5-bromo-2-(2-(trimethylsilyl)ethoxy)pyridine



[00733] To a stirred solution of TMS ethanol (16.23 ml, 194.8 mmol, 1.5 eq) in dry THF (500 ml) was added NaH (4.68 g, 195.0 mmol, 1.5 eq) at 0°C under argon. The mixture was stirred for 30 min and 5-bromo-2-chloropyridine (25g, 130.2mmol, leq) in dry THF (125 ml) at the same temperature was added. The mixture was then slowly warmed to reflux for 24h, and TLC analysis indicated formation of less polar spot along with 10% of starting material. Then, the reaction mixture cooled to RT was poured into ice water, extracted with EtOAc (2 X 500 ml) and washed with water (2

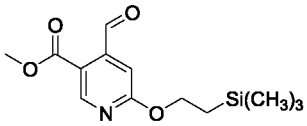
X 250 ml), and brine (2 X 250 ml). The organic layers were combined and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. Crude product was purified by silica gel chromatography (260-400 mesh) using 100% pet ether as an eluent to give 5-bromo-2-(2-(trimethylsilyl)ethoxy)pyridine (22g, 64%) as a pale yellow liquid. TLC: 10% EtOAc in Pet Ether; R_f: 0.8.

Step 2: 5-bromo-2-(2-(trimethylsilyl)ethoxy)isonicotinaldehyde



[00734] To a solution of DiPA (5.76 ml, 57.0 mmol, 1.5 eq) in dry THF (30 ml) was added n-BuLi (2.5M in n-hexane, 15.2ml, 38.09 mmol, 1.3 eq) at -78°C and then allowed to warm to -30°C over 30min. To freshly prepared LDA was added a solution of 5-bromo-2-(2-(trimethylsilyl)ethoxy)pyridine (8 g, 29.3mmol, leq) in dry THF (200 ml) at -78°C under argon atm and was maintained for 1h at the same temperature. Then it was quenched with DMF (2.38g, 32.23mmol, l.leq) added dropwise and stirred at the same temperature for 10 min. TLC analysis indicated formation of polar spots. Then, the reaction mixture was quenched with sat. NH_4C1 (50ml) and extracted with EtOAc (4 x 200ml) then washed with water and brine. The combined organic layer was dried with Na_2S0_4 and concentrated under reduced pressure to give crude 5-bromo-2-(2-(trimethylsilyl)ethoxy)isonicotinaldehyde (7.8g, 88.6%) as a pale yellow liquid. The crude product was used without further purification. TLC: 5% EtOAc in pet ether; R_f: 0.6

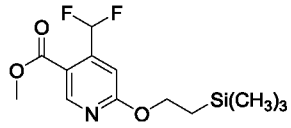
Step 3: methyl 4-formyl-6-(2-(trimethylsilyl)ethoxy)nicotinate



[00735] To a stirred solution of 5-bromo-2-(2-(trimethylsilyl)ethoxy)isonicotinaldehyde (7.8 g, 25.91 mmol, 1 eq) in methanol (80 ml) was added TEA (36.35 ml, 259.1 mmol, 10 eq) at RT in a steel bomb degassed with argon for 10 min, then $Pd_2(dppf)Cl_2DCM$ (2.11g, 2.59mmol, O.leq) was added and the mixture was then heated to 70°C under 250 Psi (CO gas) for 16h. TLC analysis indicated formation of polar spots. The reaction mixture was filtered through celite bed washed with methanol; and the filtrate was evaporated under reduced pressure. The crude compound was purified by flash chromatography using 5% EtOAc in pet ether as

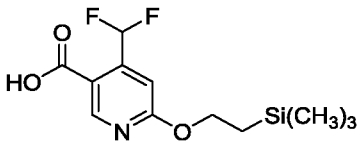
an eluent to afford methyl 4-formyl-6-(2-(trimethylsilyl)ethoxy)nicotinate (3.1g, 39.7%) as a pale yellow liquid. TLC: 5% EtOAc in pet ether; R_f: 0.5.

Step 4: methyl 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinate



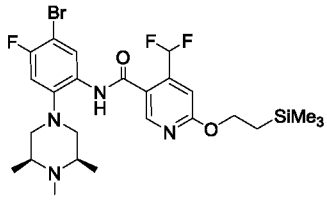
[00736] To a stirred solution of methyl 4-formyl-6-(2-(trimethylsilyl)ethoxy)nicotinate (6.1 g, 21.7 mmol, 1 eq) in DCM (60 ml) was added DAST (5.24 g, 32.56 mmol, 1.5 eq) at -78°C under argon then slowly warmed to RT and stirred for 16h. TLC analysis indicated formation of less polar spots. The reaction mixture was cooled to 0°C quenched with Satd. NaHCCb solution, extracted with DCM (2 x 200 ml) washed with water (2 X 100 ml) and brine (2 X 100 ml). Combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to give crude product methyl 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinate (6 g, 92.87%) as a pale yellow color liquid. The crude product was used without further purification. TLC: 5% EtOAc in pet ether; R_f: 0.6.

Step 5: 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid



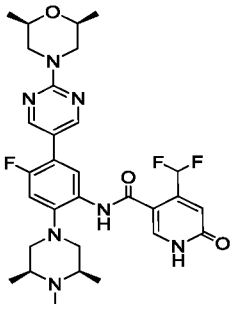
[00737] To a stirred solution of methyl 4-(difiuoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinate (6g, 19.8 mmol, leq) in MeOH:THF:H_2**0** (30:30:10ml) was added LiOH (1.66g, 39.6mmol, 2eq) at RT and was stirred for 16h. TLC analysis indicated formation of polar spot. The solvent was evaporated under reduced pressure, the reaction mixture was cooled to 0°C, acidified with 2N HC1, extracted with EtOAc (2 x 100ml), and washed with water (2X50 ml) and brine (2X50 ml). Combined organic layers were dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. The crude product was washed with pentane to obtain pure 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (4.5g, 78.7%) as an off white solid. TLC: 5% MeOH in DCM; R_f: 0.1.

Step 6: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00738] To a stirred solution of 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (15g, 47.61mmol, leq) in DMF (300mL) was added DIPEA (25.7 mL, 142.8 mmol, 3eq), HATU (54.27g, 142.8 mmol, 3eq) and then 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (14.3 g, 47.61 mmol, 1 eq) added at 0°C under argon atm, and after that stirred for 16h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200 mL) and extracted with EtOAc (2X500mL). The organic layer was washed with brine and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent to result in N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (10 g, 66% yield) as an off white solid. LCMS: [M+H]+ 587.34.

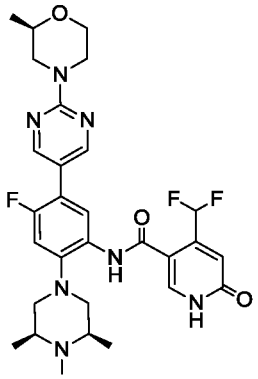
Step 7: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[00739] A microwave vial was charged with N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (25 mg, 0.043 mmol) and (2-((2S,6R)-2,6-

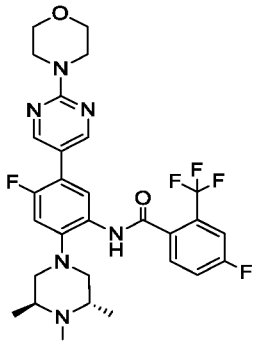
dimethylmorpholino)pyrimidin-5-yl)boronic acid (15.13 mg, 0.064 mmol), potassium phosphate tribasic reagent grade, >=98% (27.1 mg, 0.128 mmol) and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (3.01 mg, 4.25 μηιοΐ). The vial was sealed and evacuated and backfilled with nitrogen (x3). 1,4-Dioxane (0.9 ml) and water (0.100 ml) were added, the vial was evacuated and backfilled with nitrogen and heated with microwave at 110 °C for 2 hours. Aqueous workup [water/DCM] was performed then it was dried over magnesium sulfate and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH40H; collect at 290 nm] to afford the 4-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide intermediate as a clear pale yellow film. This material was dissolved in DCM (2 mL) and treated with TFA (0.163 ml, 2.127 mmol) at room temperature. After 1 hour, LCMS indicated clean deprotection to the desired product. The volatiles were removed in vacuo and the residue cleaned with a catch and release on a PoraPak Rxn CX ion exchange column followed by lyophilization to afford the title compound as a white powder (0.029 mmol, 67.8 % yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.51 (s, 1H), 8.44 (d, *J*=0.7 Hz, 2H), 7.92 (s, 1H), 7.59 (d, *J*=8.7 Hz, 1H), 7.44 - 7.12 (m, 1H), 6.96 (d, *J*=12.3 Hz, 1H), 6.53 (s, 1H), 4.47 (br d, *J*=11.6 Hz, 2H), 3.50 (ddd, *J*=2.3, 6.2, 10.4 Hz, 2H), 2.96 (br d, *J*=10.9 Hz, 2H), 2.51 (dd, *J*=10.8, 13.1 Hz, 2H), 2.39 (br t, *J*=11.0 Hz, 2H), 2.25 (br s, 2H), 2.12 (s, 3H), 1.09 (d, *J*=6.1 Hz, 6H), 0.93 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 600.6.

Example 386: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



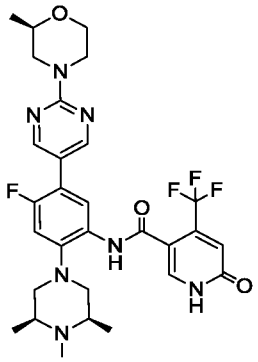
[00740] The procedure used was similar to Example 385 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (25 mg, 0.043 mmol) and (R)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (17.08 mg, 0.077 mmol) to give after workup and purification the title compound (7.2 mg, 29 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.34 (br d, *J=l.6* Hz, IH), 9.52 (s, IH), 8.45 (s, 2H), 7.92 (s, IH), 7.60 (br d, *J*=5.5 Hz, IH), 7.44 - 7.14 (m, IH), 7.03 - 6.92 (m, IH), 6.53 (s, IH), 4.45 (br d, *J*=13.0 Hz, IH), 4.38 (br d, *J*=13.2 Hz, IH), 3.84 (dd, *J*=2.6, 11.5 Hz, IH), 3.50 - 3.40 (m, 2H), 3.01 - 2.89 (m, 3H), 2.61 (dd, *J*=10.4, 13.1 Hz, IH), 2.25 (br s, IH), 2.12 (br s, 3H), 1.09 (d, *J*=6.2 Hz, 3H), 0.94 (br s, 6H); LCMS [M+H]+: 586.6.

Example 387: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



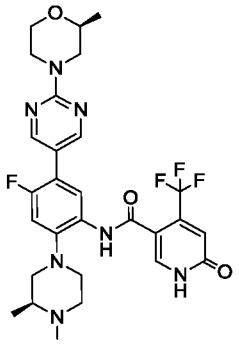
[00741] The title compound (white solid, 44.2 mg, 74%) was prepared by a procedure similar to that of Example 31 using 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (58 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.63 (s, IH), 8.58 (s, 2H), 8.55 - 8.52 (m, IH), 7.67 (dd, *J*=5.3, 8.3 Hz, IH), 7.49 (dd, *J*=2.3, 8.7 Hz, IH), 7.36 (t, *J*=7.9 Hz, IH), 7.01 (d, *J*=11.2 Hz, IH), 3.90 - 3.85 (m, 4H), 3.82 - 3.77 (m, 4H), 2.95 - 2.80 (m, 4H), 2.66 (br dd, *J*=5.9, 10.4 Hz, 2H), 2.30 (s, 3H), 0.93 (br d, *J*=6.1 Hz, 6H); LCMS $[M + H]^+$ 591.5.

Example 388: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



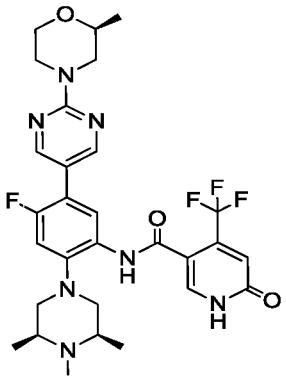
[00742] To a mixture of 2-chloropyrimidine-5-boronic acid (48 mg, 0.3 mmol) and (R)-2-methyl-morpholine, hydrochloride (43 mg, 0.315 mmol) in EtOH (3 mL) was added triethylamine (0.105 mL, 0.75 mmol). The resulting mixture was stirred at 80 °C for 1 h. Solvents were removed to give crude (R)-(2-(2^ ethylmoφηo 1ηo)pyrimidiη-5-yl)boronic acid as a pale yellow solid. LCMS $[M + H]^+$ 224.3. The title compound (pale beige solid, 18.0 mg, 29%) was prepared in a similar manner to Example 31 using crude (R)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (br s, 1H), 8.55 (s, 2H), 8.44 (br d, *J*=8.1 Hz, 1H), 7.87 (s, 1H), 7.06 - 6.97 (m, 2H), 4.64 - 4.54 (m, 2H), 4.01 (dd, *J*=2.6, 11.6 Hz, 1H), 3.70 - 3.60 (m, 2H), 3.15 - 3.04 (m, 1H), 2.82 (br d, *J*=10.8 Hz, 2H), 2.75 (dd, *J*=10.5, 13.1 Hz, 1H), 2.66 (br t, *J*=10.5 Hz, 2H), 2.42 - 2.24 (m, 5H), 1.27 (d, *J*=6.2 Hz, 3H), 1.14 (br d, *J*=5.7 Hz, 6H); LCMS $[M + H]^+$ 604.5.

Example 389: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJ-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-5-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



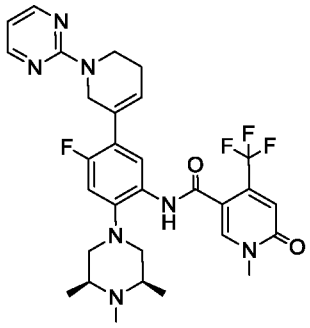
[00743] To a mixture of 2-chloropyrimidine-5-boronic acid (48 mg, 0.3 mmol) and (S)-2-methylmorpholine (33 mg, 0.33 mmol) in EtOH (3 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 80 °C for 1 h. Solvents were removed to give crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid as a yellow solid. LCMS $[M + H]^+$ 224.1. The title compound (pale beige solid, 30.2 mg, 51%) was prepared in a manner similar to the final step of Example 31 using crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.70 (s, 1H), 8.55 (s, 2H), 8.45 (br d, *J*=8.1 Hz, 1H), 7.89 (s, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 7.00 (s, 1H), 4.64 - 4.53 (m, 2H), 4.01 (dd, *J*=2.5, 11.6 Hz, 1H), 3.71 - 3.58 (m, 2H), 3.15 - 3.06 (m, 1H), 3.01 - 2.86 (m, 3H), 2.82 (br d, *J*=10.9 Hz, 1H), 2.75 (dd, *J*=10.6, 13.0 Hz, 1H), 2.60 (br t, *J*=10.5 Hz, 1H), 2.43 - 2.30 (m, 4H), 2.22 (br s, 1H), 1.27 (d, *J*=6.2 Hz, 3H), 1.10 (br d, *J*=6.1 Hz, 3H); LCMS $[M+ H]^+$ 590.6.

Example 390: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-f(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00744] The title compound (pale beige solid, 35.5 mg, 58%) was prepared through a procedure similar to that of Example 31 using crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)- N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.69 (s, 1H), 8.55 (s, 2H), 8.44 (br d, *J*=8.1 Hz, 1H), 7.88 (s, 1H), 7.05 - 6.98 (m, 2H), 4.64 - 4.54 (m, 2H), 4.01 (dd, *J*=2.7, 11.5 Hz, 1H), 3.70 - 3.59 (m, 2H), 3.10 (dt, *J*=3.4, 12.6 Hz, 1H), 2.82 (br d, *J*=11.0 Hz, 2H), 2.75 (dd, *J*=10.5, 13.1 Hz, 1H), 2.65 (br t, *J*=10.9 Hz, 2H), 2.39 - 2.27 (m, 5H), 1.27 (d, *J*=6.2 Hz, 3H), 1.14 (d, *J*=6.1 Hz, 6H); LCMS $[M + H]^{+}$ 604.6.

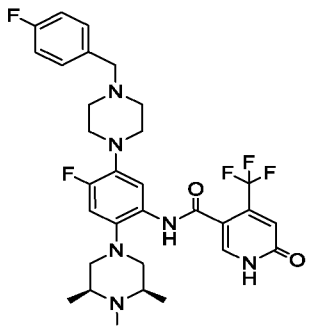
Example 391: N-[4-fluoro-5-(l-pyrimidin-2-yl-3, 6-dihydro-2H-pyridin-5-yl)-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00745] Cesium carbonate (6.68 mg, 0.020 mmol) was added to a solution of N-(4-fluoro-5-(l-(pyrimidin-2-yl)-l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (12 mg, 0.020 mmol) and Mel (1.467 μï, 0.024 mmol) in DMF (1 ml) at

RT. The reaction mixture was continuously stirred at RT. Complete conversion to the desired product was observed after 18 min. The mixture was diluted with DCM (1 ml) and mixed with water (2 ml). The aqueous phase was extracted with DCM (2 x lml), the combined organic phase was washed with water (1 ml x 5), brine, dried over Na_2S04 and concentrated. The crude was purified on Isco column, eluting with DCM containing 0-2 % MeOH and 0-0.2 % NH_4OH to afford the title compound as a white solid. (5.3 mg, 40 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.26 - 8.23 (m, 2H), 8.16 - 8.08 (m, 1H), 7.73 - 7.67 (m, 1H), 6.90 - 6.85 (m, 1H), 6.84 - 6.82 (m, 1H),6.54 - 6.47 (m, 1H), 6.11 - 6.02 (m, 1H), 4.46 - 4.40 (m, 2H), 3.92 - 3.87 (m, 2H), 3.58 - 3.52 (m, 3H), 2.99 - 2.85 (m, 2H), 2.53 - 2.44 (m, 2H), 2.44 - 2.37 (m, 2H), 2.33 - 2.29 (m, 2H), 2.27 - 2.20 (m, 3H), 1.07 - 1.03 (m, 6H); LCMS [M+H]+ 600.8.

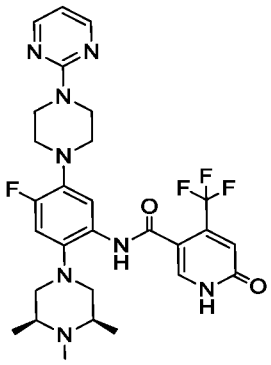
Example 392: N-[4-fluoro-5-[4-[(4-fluorophenyl)methyl]piperazin-l-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00746] 2,2'-Bis(diphenylphosphino)-l, r -binaphthalene (15.4 mg, 0.025 mmol), N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (100 mg, 0.165 mmol), palladium(II) acetate (2.2 mg, 0.001 mmol), l-(4-fluorobenzyl)piperazine (35.3 mg, 0.182 mmol) and $CsCO_3$ (215 mg, 0.661 mmol) were mixed in 1,4-dioxane (3 ml) and the vial was flushed with nitrogen. The reaction mixture was heated in an oil bath at 110 °C for 16 h. The mixture was further heated at 135 °C for 5 h. The reaction mixture was filtered through celite, the filter cake was washed with DCM, the combined filtrate was concentrated onto celite and purified by silica gel chromatography to give N-(4-fluoro-5-(4-(4-fluorobenzyl)piperazin-l-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-

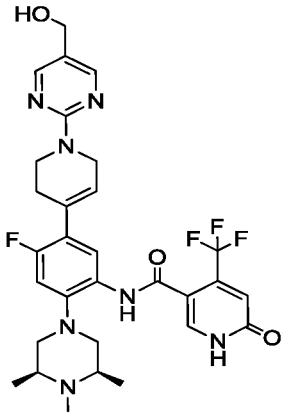
(trimethylsilyl)ethoxy Nicotinamide, which was dissolved in DCM (1.5 mL). TFA (0.5 ml) was added and the mixture was stirred at room temperature for 10 min. Concentration and passing through a cation exchange resin cartridge (Isolute SCX-2 6ml), and eluting with 3% NH_3 in MeOH afforded after removal of solvents the title compound as the free base (11.5 mg, 93 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.92 - 7.87 (m, 1H), 7.58 - 7.50 (m, 1H), 7.36 - 7.30 (m, 2H), 7.02 - 6.93 (m, 3H), 6.81 - 6.77 (m, 1H), 3.66 - 3.57 (m, 2H), 3.08 - 3.02 (m, 4H), 2.93 - 2.88 (m, 2H), 2.85 - 2.73 (m, 2H), 2.71 - 2.64 (m, 4H), 2.63 - 2.57 (m, 2H), 2.53 - 2.47 (m, 3H), 1.15(br d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 619.8.

Example 393: N-[4-fluoro-5-(4-pyrimidin-2-ylpiperazin-l-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



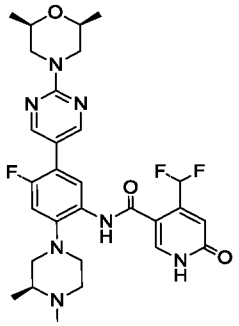
[00747] The procedure used was similar to that of Example 392 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (100 mg, 0.165 mmol) and l-(2-pyrimidyl)piperazine (54.2 mg, 0.330 mmol) to give, after deprotection of the silyoxypyridyl intermediate, the title compound as an off white powder (50 mg, 99% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.37 - 8.31 (m, 2H), 7.99 - 7.93 (m, 1H), 7.72 - 7.64 (m, 1H), 7.09 - 7.01 (m, 1H), 6.92 - 6.85 (m, 1H), 6.64 - 6.56 (m, 1H), 3.98 - 3.92 (m, 4H), 3.14 - 3.08 (m, 4H), 2.99 - 2.91 (m, 2H), 2.79 - 2.69 (m, 2H), 2.67 - 2.61 (m, 2H), 2.52 - 2.44 (m, 3H), 1.22 - 1.17 (m, 6H); LCMS [M+H]+ 589.6.

Example 394: N-[4-fluoro-5-[1-[5-(hydroxymethyl)pyrimidin-2-yl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



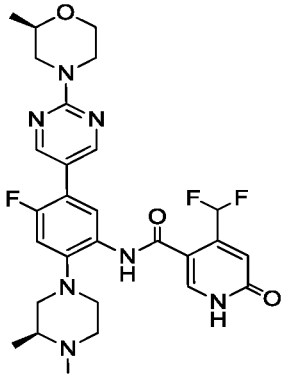
[00748] Sodium borohydride (7.71 mg, 0.204 mmol) was added to a solution of N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) in methanol (3 ml) and water (0.5 ml) at RT. The reaction was complete in 5 min. The mixture was concentrated, taken up in EtOAc, quenched with NH_4C1 solution, the organic phase was separated, the aqueous phase was extracted with EtOAc (5 x 3 ml), dried over Na_2S0_4, concentrated onto celite and purified on Isco (4G), eluting with DCM containing 0-4 % MeOH and 0-0.4 % NH_4OH. The desired product was isolated as an orange red powder (24 mg, 91 %). ^1H NMR (500MHz, METHANOL-d4) δ = 8.29 - 8.22 (m, 2H), 7.87 - 7.82 (m, 1H), 7.72 - 7.64 (m, 1H), 6.92 - 6.86 (m, 1H), 6.84 - 6.80 (m, 1H),6.06 - 5.98 (m, 1H), 4.39 - 4.35 (m, 2H), 4.29 - 4.24 (m, 2H), 3.97 - 3.93 (m, 2H), 3.04 - 2.98 (m, 2H), 2.82 - 2.69 (m, 2H), 2.63 - 2.55 (m, 2H), 2.52 - 2.44 (m, 5H), 1.15 - 1.12 (m, 6H); LCMS [M+H]+ 616.7

Example 395: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH -pyridine-3-carboxamide

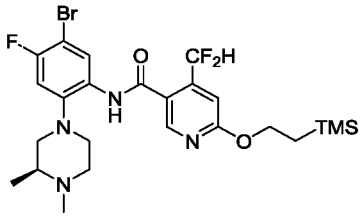


[00749] The title compound (pale beige solid, 35.5 mg, 58%) was prepared by a procedure similar to that of Example 383 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)- N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.69 (s, 1H), 8.55 (s, 2H), 8.44 (br d, *J*=8.1 Hz, 1H), 7.88 (s, 1H), 7.05 - 6.98 (m, 2H), 4.64 - 4.54 (m, 2H), 4.01 (dd, *J*=2.7, 11.5 Hz, 1H), 3.70 - 3.59 (m, 2H), 3.10 (dt, *J*=3.4, 12.6 Hz, 1H), 2.82 (br d, *J*=11.0 Hz, 2H), 2.75 (dd, *J*=10.5, 13.1 Hz, 1H), 2.65 (br t, *J*=10.9 Hz, 2H), 2.39 - 2.27 (m, 5H), 1.27 (d, *J*=6.2 Hz, 3H), 1.14 (d, *J*=6.1 Hz, 6H); LCMS [M + H]$^{+}$ 604.6.

Example 396: 4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phen^l]-6-oxo-1H-pyridine-3-carboxamide

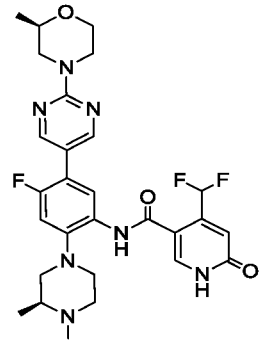


Step 1: (S)-N-(5-bromo-2-(3, 4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00750] To a stirred solution of 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (10 g, 34.59 mmol, 1 eq) in DMF (100 mL) was added DIPEA (18.6 mL, 103.8 mmol, 3 eq), HATU (39.4 g, 103.8 mmol, 3 eq) and then (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (10.4 g, 34.59 mmol, leq) was added at 0°C under argon atm, and after that stirred for 16h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200mL) and extracted with EtOAc (2 X 500mL). The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent to give (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (5 g, 30% yield) as an off white solid. LCMS: [M+H]+ 573.04.

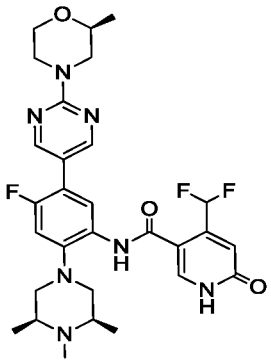
Step 2: 4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6<>xo-lH-py^idine-3-carboxamide



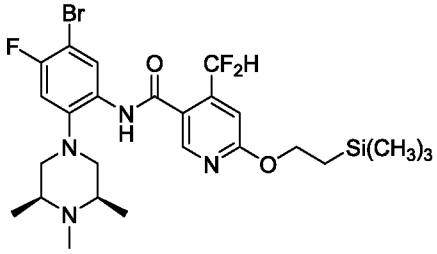
[00751] The procedure followed was similar to that used in Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (25 mg, 0.044 mmol) and (R)-(2-(2-methylmoϕholino)pyrimidin-5-yl)boronic acid (17.50 mg, 0.078 mmol to give the title compound (11 mg, 44. 1 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 12.37 (br s, 1H), 9.55 (s, 1H), 8.52 (s, 2H), 8.00 (s, 1H), 7.69 (d, *J*=8.6 Hz, 1H), 7.48 -

7.21 (m, 1H), 7.06 (d, *J*=12.5 Hz, 1H), 6.59 (s, 1H), 4.57 - 4.40 (m, 2H), 3.91 (dd, *J*=2.4, 11.5 Hz, 1H), 3.57 - 3.49 (m, 2H), 3.06 - 2.96 (m, 3H), 2.85 - 2.74 (m, 2H), 2.67 (dd, *J*=10.5, 13.1 Hz, 1H), 2.42 (t, *J*=10.6 Hz, 1H), 2.35 - 2.28 (m, 1H), 2.20 (s, 4H), 1.16 (d, *J*=6.2 Hz, 3H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 572.6.

Example 397: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



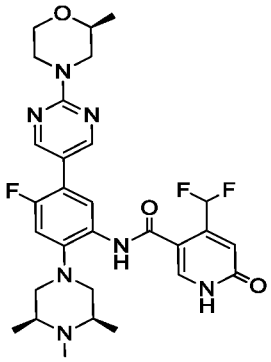
Step 1: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00752] To a stirred solution of 4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (15 g, 47.61 mmol, 1 eq, from Example 385 Step 5) in DMF (300 mL) was added DIPEA (25.7mL, 142.83 mmol, 3 eq), HATU (54.27g, 142.83mmol, 3eq) and then 5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)aniline (14.3g, 47.61 mmol, 1 eq) was added at 0°C under argon atm, and after that stirred for 16 h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200 mL) and extracted with EtOAc (2 X 500mL). The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent afforded

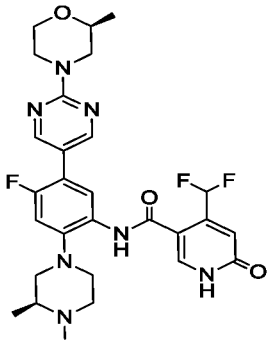
N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (10 g, 66% yield) as an off white solid. LCMS: [M+H]+ 587.34.

Step 2: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrim idin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridme-3-carboxamide



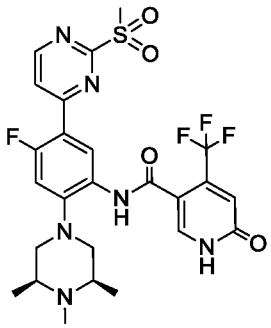
[00753] The title compound (9 mg, 36% yield) was prepared by a procedure similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (25 mg, 0.043 mmol), (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (18.98 mg, 0.085 mmol). ¾ NMR (500 MHz, DMSO-d6) δ = 12.40 (br d, *J*=2.3 Hz, 1H), 9.59 (s, 1H), 8.52 (d, *J*=0.7 Hz, 2H), 7.99 (br s, 1H), 7.67 (br d, *J*=8.4 Hz, 1H), 7.49- 7.20 (m, 1H), 7.04 (br d, *J*=12.3 Hz, 1H), 6.60 (s, 1H), 4.55 - 4.41 (m, 2H), 3.91 (dd, *J*=2.3, 11.3 Hz, 1H), 3.54 - 3.48 (m, 2H), 3.06 - 2.98 (m,3H), 2.68 (dd, *J*=10.5, 13.1 Hz, 1H), 2.47 - 2.42 (m, 2H), 2.32 (br s, 2H), 2.22 - 2.16 (m, 3H), 1.16 (d, *J*=6.1 Hz, 3H), 1.00 (br d, *J*=5.0 Hz, 6H); ^{19}F NMR (471MHz, DMSO-de) δ = -118.73 (br s, IF), -119.35 (br s, 1F).LCMS [M+ H]$^+$ 604.6.

Example 398: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phen^ l]-6-oxo-1H-pyridine-3-carboxamide



[00754] The title compound was prepared by procedure similar to that of Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (25 mg, 0.044 mmol) and (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (19.44 mg, 0.087 mmol) to give the title compound (11.7 mg, 47.0 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.38 (br s, 1H), 9.53 (s, 1H), 8.52 (d, *J*=0.7 Hz, 2H), 8.01 (s, 1H), 7.69 (d, *J*=8.7 Hz, 1H), 7.49 - 7.20 (m, 1H), 7.06 (d, *J*=12.5 Hz, 1H), 6.57 (s, 1H), 4.53 - 4.42 (m, 2H), 3.91 (dd, *J*=2.9, 11.3 Hz, 1H), 3.53 - 3.48 (m, 2H), 3.03 - 2.97 (m, 2H), 2.81 - 2.74 (m, 2H), 2.67 (dd, *J*=10.5, 13.1 Hz, 1H), 2.44 - 2.39 (m, 1H), 2.34 - 2.28 (m, 1H), 2.22 - 2.18 (m, 5H), 1.16 (d, *J*=6.2 Hz, 3H), 0.97 (d, *J*=6.1 Hz, 3H); LCMS [M+H]+: 572.6.

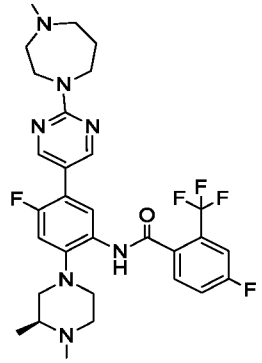
Example 399: N-[4-fluoro-5-(2-methylsulfonylpyrimidin-4-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(Mfluorometh^ l)-1H-pyridine-3-carboxamide



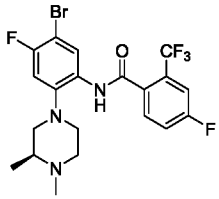
[00755] The title compound (4.5 mg, 6% yield) was prepared in a manner similar to that of Example 384 using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (106 mg, 0.130 mmol) and 4-bromo-2-(methylsulfonyl)pyrimidine (30.8 mg, 0.130 mmol). ^{1}H NMR (500 MHz, MeOD) δ

8.99 (d, *J* = 5.4 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 5.2 Hz, 1H), 7.98 (s, 1H), 7.09 (d, *J* = 13.6 Hz, 1H), 6.93 (s, 1H), 3.44 (s, 3H), 3.25 (d, *J* = 11.7 Hz, 2H), 2.68 (t, *J* = 11.4 Hz, 2H), 2.59 (s, 2H), 2.40 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 6H); LCMS $[M+l]^+$ = 583.5.

Example 400: 4-fluoro-N-[4-fluoro-5-[2-(4-methyl-l, 4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide

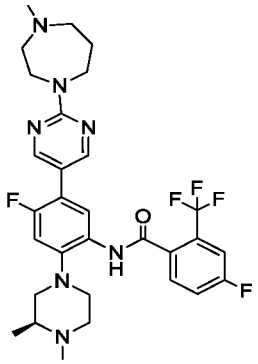


Step 1: Preparation of (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-_1-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide



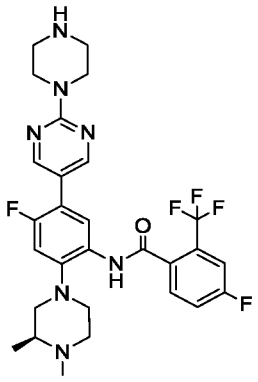
[00756] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.61 mL, 4 mmol) in DCM (15 mL) at rt was added Et_3N (1.12 mL, 8 mmol). After addition, the resulting mixture was stirred at rt for 5 min, before a solution of (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (604 mg, 2 mmol) in DCM (10 mL) was added in 1 min. The resulting dark orange solution was stirred at rt for 2 h. After quenching with sat. NaHCCb (15 mL) and stirring for 2 min at rt, the mixture was extracted with DCM (20 x 2 mL). The extracts were combined, and concentrated to give a light beige solid. It was loaded onto samplet with DCM/MeOH and purified by flash chromatography (gradient: EtOAc/hex 0-100%) to give the title compound as a light yellow solid (822 mg, 82%). LCMS $[M + H]^+$ 492.4.

Step 2: 4-fluoro-N-[4-fluoro-5-[2-(4-methyl-l, 4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00757] The title compound (white solid, 30.5 mg, 51%) was prepared by a procedure similar to Example 31 using crude (2-(4-methyl-l,4-diazepan-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (49.2 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.63 - 8.52 (m, 4H), 7.66 (dd, *J*=5.3, 8.4 Hz, IH), 7.49 (dd, *J*=2.3, 8.8 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.01 (d, *J*=11.2 Hz, IH), 4.04 - 3.94 (m, 2H), 3.87 (t, *J*=6.3 Hz, 2H), 2.98 - 2.80 (m, 4H), 2.76 - 2.69 (m, 2H), 2.63 - 2.52 (m, 3H), 2.40 (s, 3H), 2.33 - 2.24 (m, 4H), 2.12 (br s, IH), 2.04 (quin, *J*=5.8 Hz, 2H), 1.05 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 604.6.

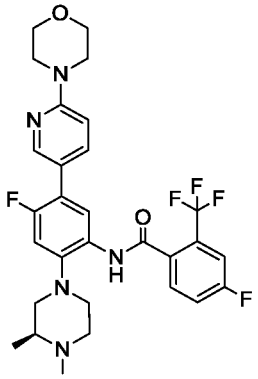
Example 401: 4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00758] The title compound (beige solid, 15.9 mg, 26%) was prepared according to a procedure similar to that of Example 400 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (53 mg, 0.1 mmol) and 2-(4-methylpiperazin-l-yl)pyrimidine-5-boronic acid pinacol ester (61 mg, 0.2 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.61 - 8.54 (m, 4H),

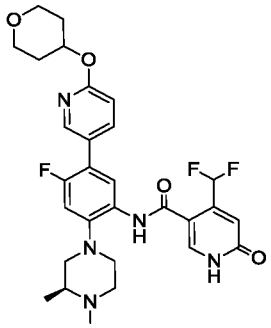
7.67 (dd, *J*=5.3, 8.4 Hz, IH), 7.50 (dd, *J*=2.4, 8.7 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.02 (d, *J*=11.2 Hz, IH), 3.97 - 3.87 (m, 4H), 2.97 - 2.81 (m, 4H), 2.56 (t, *J*=10.5 Hz, IH), 2.50 (t, *J*=5.1 Hz, 4H), 2.36 (s, 3H), 2.32 - 2.25 (m, 4H), 2.12 (br s, IH), 1.05 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 590.3.

Example 402: 4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



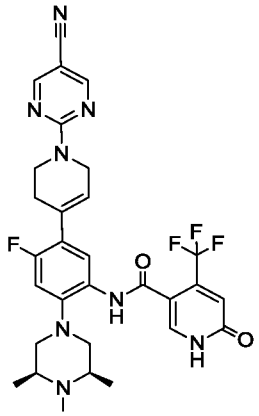
[00759] The title compound (pale beige solid, 38.7 mg, 63%) was prepared by a method similar to that of Example 400 using 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo rpholine (60 mg, 0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifiuoromethyl)benzamide (51 mg, 0.104 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.60 (s, IH), 8.58 (d, *J*=8.2 Hz, IH), 8.48 (s, IH), 7.76 (br d, *J*=8.7 Hz, IH), 7.67 (dd, *J*=5.3, 8.4 Hz, IH), 7.50 (dd, *J*=2.3, 8.8 Hz, IH), 7.38 (dt, *J*=2.3, 8.1 Hz, IH), 7.01 (d, *J*=11.4 Hz, IH), 6.71 (d, *J*=8.9 Hz, IH), 3.88 - 3.82 (m, 4H), 3.61 - 3.55 (m, 4H), 2.99 - 2.81 (m, 4H), 2.57 (br t, *J*=10.5 Hz, IH), 2.39 - 2.24 (m, 4H), 2.20 - 2.07 (m, IH), 1.06 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 576.5.

Example 403: 4-(difluoromethyl)-N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



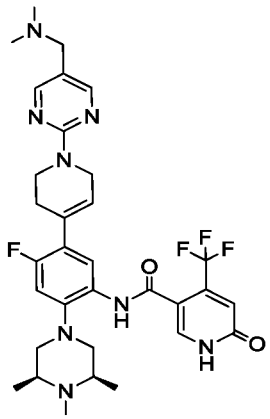
[00760] In a 5 mL microwave vial (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (35 mg, 0.061 mmol), 2-(tetrahydropyran-4-yloxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (27.9 mg, 0.092 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (4.32 mg, 6.10 μητοϊ) and potassium phosphate tribasic reagent grade (0.026 g, 0.122 mmol) were dissolved in 1,4-dioxane (1.098 mL) / water (0.122 mL) (9 : 1 mixture) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 110 °C. The solvent was evaporated and 15 mL of CH2CI2 were added. The suspension was sonicated and extracted from water (15 mL). The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the protected compound. The product was dissolved in 2 mL of dichloromethane and trifluoroacetic acid (70 μϊ, 0.915 mmol) was added. The purple solution was stirred for 1 hour and the solvent was evaporated. The residue was purified using a cation exchange column eluting with MeOH:NH_4OH and freeze dried for 2 days to afford the title compound. ¾ NMR (500 MHz, MeOD) δ 8.28 (s, 1H), 8.02 (s, 1H), 7.85 (t, *J* = 9.9 Hz, 2H), 7.30 (t, *J* = 55.1 Hz, 1H), 7.08 (d, *J* = 12.1 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.80 (s, 1H), 5.25 (tt, *J* = 8.2, 3.9 Hz, 1H), 3.98 (dt, *J* = 9.7, 4.5 Hz, 2H), 3.63 (ddd, *J* = 11.8, 9.3, 2.8 Hz, 2H), 3.10 (dd, *J* = 26.7, 11.0 Hz, 2H), 2.94 (t, *J* = 10.1 Hz, 2H), 2.57 (t, *J* = 10.7 Hz, 2H), 2.44 (s, 1H), 2.39 (s, 3H), 2.13 - 2.06 (m, 2H), 1.81 - 1.74 (m, 2H), 1.13 (d, *J* = 5.9 Hz, 3H); LCMS $[M+l]^+$ = 572.56.

Example 404: N-[5-[l-(5-cyanopyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00761] The procedure used was similar to that of Example 270 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) 2-bromo-5-cyanopyrimidine (13.05 mg, 0.071 mmol) to give the title compound (21 mg, 55% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.59 - 8.47 (m, 2H), 7.87 - 7.78 (m, 1H), 7.74 - 7.63 (m, 1H), 6.88 - 6.83 (m, 1H), 6.82 - 6.79 (m, 1H),6.06 - 5.94 (m, 1H), 4.42 - 4.35 (m, 2H), 4.09 - 4.02 (m, 2H), 2.96 - 2.88 (m, 2H), 2.54 - 2.41 (m, 6H), 2.30 - 2.25 (m, 3H), 1.07 - 1.04 (m, 6H); LCMS [M+H]+ 611.7

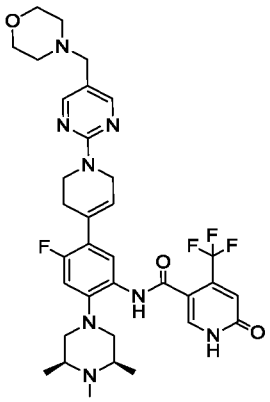
Example 405: N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl] -3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00762] N-(4-Fluoro-5-(l-(5-formylpyrimidin-2-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol), dimethylamine, 2.0M in THF

(0.041 ml, 0.081 mmol) and acetic acid, glacial, 99.8% (9.79 mg, 0.163 mmol) were mixed in anhydrous DCE. A cloudy solution was obtained. After 5 min, sodium triacetoxyborohydride (25.9 mg, 0.122 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat aq NaHCCb solution (basic). The organic (org) phase was separated, the aqueous (aq) phase was extracted with DCM (x2), the combined org phase was washed with brine, dried over Na_2S0_4 and concentrated to afford the crude product. It was purified by silica gel chromatography (4 G), eluting with DCM containing 0-7 % MeOH and 0-0.7 % NH40H to collect the title compound as a white foam (24 mg, 87 %). ¾ NMR (500MHz, METHANOL-d4) δ = 8.37 - 8.30 (m, 2H), 7.98 - 7.93 (m, 1H), 7.84 - 7.75 (m, 1H), 7.00 - 6.94 (m, 1H), 6.94 - 6.89 (m, 1H), 6.17 - 6.09 (m, 1H), 4.42 - 4.35 (m, 2H), 4.11 - 4.04 (m, 2H), 3.48 - 3.42 (m, 2H), 3.07 - 2.99 (m, 2H), 2.63 - 2.52 (m, 6H), 2.39 - 2.36 (m, 3H), 2.34 - 2.30 (m, 6H), 1.18 - 1.14 (m, 6H); LCMS [M+H]+ 643.8.

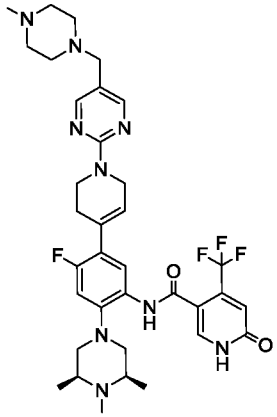
Example 406: N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl] -3, 6-dihydro-2H^yridin-4-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00763] The procedure followed was similar to Example 405 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) and morpholine (5.32 mg, 0.061 mmol) to give the title compound (28 mg, 95% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.37 - 8.31 (m, 2H), 7.98 - 7.92 (m, 1H), 7.84 - 7.76 (m, 1H), 7.00 - 6.94 (m, 1H), 6.93 - 6.89 (m, 1H), 6.17 - 6.09 (m, 1H), 4.42 - 4.35 (m, 2H), 4.06 (t, *J*=5.6 Hz, 2H),

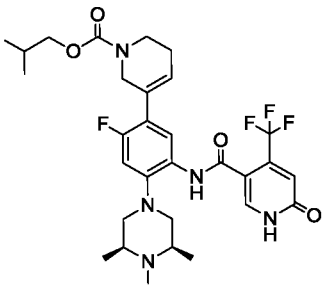
3.72 - 3.68 (m, 4H), 3.44 - 3.40 (m, 2H), 3.07 - 2.99 (m, 2H), 2.64 - 2.53 (m, 6H), 2.51 - 2.44 (m, 4H), 2.41 - 2.37 (m, 3H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 685.7

Example 407: N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



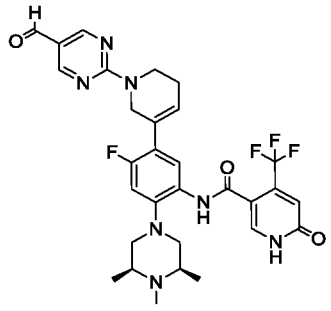
[00764] The procedure followed was similar to Example 405 using N-(4-fluoro-5-(l-(5-fonnylpyrimidin-2-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol), 1-methylpiperazine (6.12 mg, 0.061 mmol) to give the title compound (27.5 mg, 92% yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.36 - 8.29 (m, 2H), 7.99 - 7.94 (m, 1H), 7.84 - 7.75 (m, 1H), 7.00 - 6.94 (m, 1H), 6.93 - 6.88 (m, 1H), 6.17 - 6.08 (m, 1H), 4.42 - 4.34 (m, 2H), 4.10 - 4.03 (m, 2H), 3.44 (s, 2H), 3.03 (br d, *J*=11.0 Hz, 2H), 2.64 - 2.56 (m, 6H), 2.55 - 2.47 (m, 4H), 2.40 - 2.37 (m, 3H), 2.34 - 2.30 (m, 3H), 1.16 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 698.8.

Example 408: 2-methylpropyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl] amino] -4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -3,6-dihydro-2H-pyridine-l-carboxylate



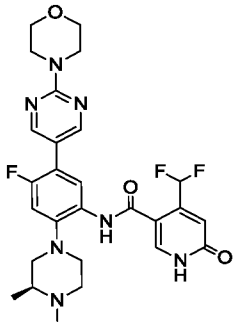
[00765] The procedure followed was similar to Example 253 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and isobutyl chloroformate (7.08 µï, 0.054 mmol) to give the title compound (25 mg, 79% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.93 (m, 1H), 7.82 - 7.73 (m, 1H), 7.01 - 6.95 (m, 1H), 6.93 - 6.88 (m, 1H), 6.14 - 6.08 (m, 1H), 4.34 - 4.23 (m, 2H), 3.95 - 3.89 (m, 2H), 3.70 - 3.60 (m, 2H), 3.08 - 3.00 (m, 2H), 2.64 - 2.51 (m, 4H), 2.40 - 2.34 (m, 5H), 2.04 - 1.92 (m, 1H), 1.19 - 1.15 (m, 6H), 1.01 - 0.96 (m, 6H).

Example 409: N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



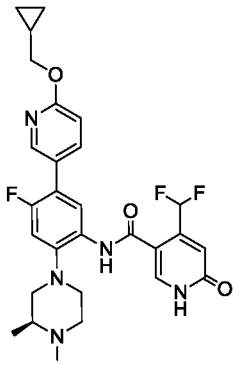
[00766] The procedure used was similar to that of Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (225 mg, 0.443 mmol) and 2-Bromo-pyrimidine-5-carbaldehyde (99 mg, 0.532 mmol) to give the title compound (196 mg, 68 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.81 - 9.70 (m, 1H), 8.86 - 8.76 (m, 2H), 8.01 - 7.92 (m, 1H), 7.86 - 7.77 (m, 1H), 7.04 - 6.98 (m, 1H), 6.95 - 6.88 (m, 1H), 6.25 - 6.15 (m, 1H), 4.77 - 4.69 (m, 2H), 4.21 - 4.13 (m, 2H), 3.10 - 3.02 (m, 2H), 2.66 - 2.53 (m, 4H), 2.51 - 2.43 (m, 2H), 2.41 - 2.36 (m, 3H), 1.20 - 1.16 (m, 6H); LCMS [M+H]+ 614.7.

Example 410: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



[00767] The title compound was prepared according to a sequence similar to Example 39 using 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (41.1 mg, 0.141 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (54 mg, 0.094 mmol) to give the title compound (43.6 mg, 81% yield). ¾ NMR (500 MHz, MeOD) δ 8.54 (s, 2H), 8.02 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 55.1 Hz, 1H), 7.08 (d, *J* = 12.1 Hz, 1H), 6.81 (s, 1H), 3.85 - 3.81 (m, 4H), 3.77 - 3.74 (m, 4H), 3.11 (d, *J* = 11.2 Hz, 1H), 3.06 (d, *J* = 11.5 Hz, 1H), 2.93 (t, *J* = 10.0 Hz, 2H), 2.59 - 2.52 (m, 2H), 2.41 (d, *J* = 7.5 Hz, 1H), 2.37 (s, 3H), 1.12 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (471 MHz, MeOD) δ -120.63 (s), -120.73 - -122.51 (m); LCMS $[M+l]^+$ = 558.65.

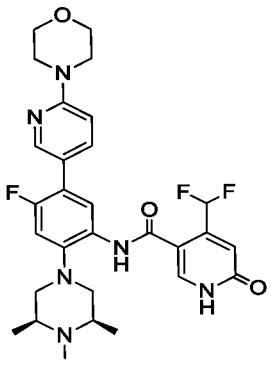
Example 411: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJphenylJ-4-(difluoromethyl)-6-oxo-lH^yridine-3-carboxamide



[00768] The title compound was prepared using by procedures similar to Example 39 using 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (36.5 mg, 0.133 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50.8 mg, 0.089 mmol) to give the title compound

(47.9 mg, 75% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 8.02 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 55.1 Hz, 1H), 7.07 (d, *J* = 12.1 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.80 (s, 1H), 4.15 (d, *J* = 7.1 Hz, 2H), 3.10 (dd, *J* = 26.1, 10.9 Hz, 2H), 2.94 (t, *J* = 10.5 Hz, 2H), 2.57 (t, *J* = 10.9 Hz, 2H), 2.45 (s, 1H), 2.39 (s, 3H), 1.30 (ddd, *J* = 11.9, 7.4, 3.7 Hz, 1H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.64 - 0.59 (m, 2H), 0.36 (q, *J* = 4.7 Hz, 2H); ^{19}F NMR (471 MHz, MeOD) δ -120.63 (s), -121.62 (q, *J* = 292.8 Hz); LCMS [M+l] $^{+}$ = 542.54.

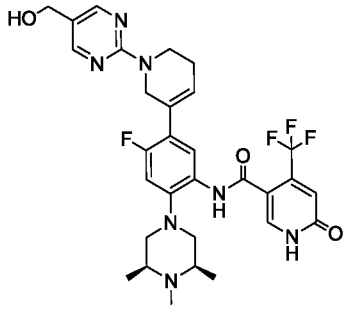
Example 412: 4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[00769] In a 5 mL microwave vial 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo rpholine (36.9 mg, 0.127 mmol), N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (49.9 mg, 0.085 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (6.01 mg, 8.49 μηιοϊ) and potassium phosphate tribasic reagent grade (0.036 g, 0.170 mmol) were dissolved in 1,4-dioxane (1.527 mL) / water (0.170 mL) (9 : 1 mixture) to give a white suspension. The suspension was stirred for 5 min, degassed, purged with N_2, and microwaved for 60 min at 110 °C. The solvent was evaporated and 15 mL of CH2CI2 were added. The suspension was sonicated and extracted from water (15 mL). The solvent was evaporated in vacuo yielding the crude product that was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH4AC/CH2CI2) to afford the protected intermediate. The product was dissolved in 2 mL of dichloromethane and trifluoroacetic acid (97 μϊ, 1.273 mmol) was added. The solution was stirred for 1 hour and the solvent was evaporated. The residue was

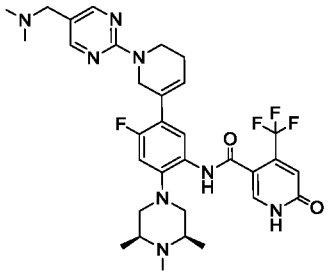
purified using a cation exchange column eluting with MeOH:NH_4OH and freeze dried for 2 days to afford the title compound. ^1H NMR (500 MHz, MeOD) δ 8.31 (s, 1H), 8.01 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.31 (t, *J* = 55.1 Hz, 1H), 7.04 (d, *J* = 12.2 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 6.80 (s, 1H), 3.82 - 3.80 (m, 4H), 3.55 - 3.51 (m, 4H), 3.06 (d, *J* = 11.0 Hz, 2H), 2.61 (t, *J* = 11.0 Hz, 2H), 2.55 (d, *J* = 5.0 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.0 Hz, 6H); LCMS $[M+l]^+$ = 569.40.

Example 413: N-[4-fluoro-5-[1-[5-(hydroxymethyl)pyrimidin-2-yl] -3, 6-dihydro-2H-pyridin-5-yl] -2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl] phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



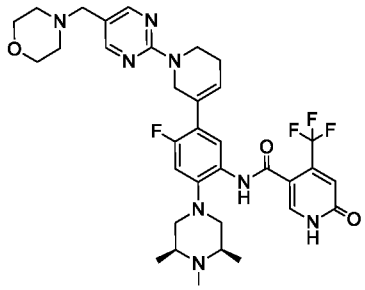
[00770] To a mixture of N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-l, 2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) in MeOH (3 ml) and water (0.5 ml) at ambient temperature was added sodium borohydride (7.71 mg, 0.204 mmol). The reaction was stirred at RT for 5 min, quenched with NH_4Cl solution, MeOH was removed, and the aq phase was extracted with chloroform/IPA 4:1 solution (4 x 2 ml). The combined org phase was dried over Na_2SO_4, concentrated onto celite and purified using sgc (4 g column), eluting with DCM containing 0-8 % MeOH and 0-0.8 % NH_4OH. The desired product was isolated as an orange red powder (20 mg, 76% yield). ^1H NMR (500MHz, METHANOL-d4) δ = 8.29 - 8.22 (m, 2H), 7.87 - 7.80 (m, 1H), 7.73 - 7.61 (m, 1H), 6.90 - 6.84 (m, 1H), 6.82 - 6.76 (m, 1H), 6.08 - 5.99 (m, 1H), 4.46 - 4.41 (m, 2H), 4.38 - 4.33 (m, 2H), 3.94 - 3.86 (m, 2H), 2.97 - 2.89 (m, 2H), 2.55 - 2.40 (m, 4H), 2.33 - 2.25 (m, 5H), 1.08 - 1.03 (m, 6H); LCMS [M+H]+ 616.7

Example 414: N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl] -3, 6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00771] The procedure followed was similar to Example 405 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(mfluoromethyl)- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) and dimethylamine (2.0M in THF, 0.041 ml, 0.081 mmol), to afford the title compound (24.5 mg, 89% yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ 8.17-8.24 (m, 2H), 7.85 (s, 1H), 7.68 (d, *J*=7.95 Hz, 1H), 6.86 (d, *J*=12.23 Hz, 1H), 6.79 (s, 1H), 6.04 (br. s., 1H), 4.44 (br. s., 2H), 3.90 (t, *J*=5.75 Hz, 2H), 3.30 (s, 2H), 2.92 (d, *J*=11.13 Hz, 2H), 2.46-2.53 (m, 2H), 2.38-2.44 (m, 2H), 2.30 (d, *J*=3.55 Hz, 2H), 2.25 (s, 3H), 2.18 (s, 6H), 1.05 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 643.8.

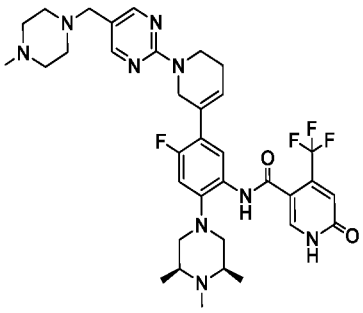
Example 415: N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl] -3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3, 4, 5-trimethylpiperazin-l -yl]phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00772] The procedure followed was similar to Example 405 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) and morpholine (7.10 mg, 0.081 mmol) to give

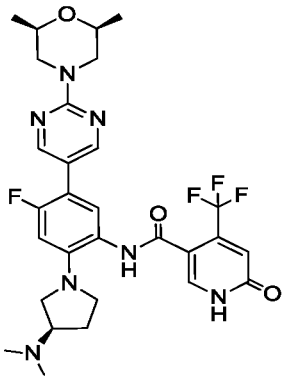
the title compound (20 mg, 68 % yield). ^{1}H NMR (500 MHz, METHANOL-d4) δ 8.30 (s, 2H), 7.94 (s, IH), 7.78 (d, *J*=7.95 Hz, IH), 6.96 (d, *J*=12.23 Hz, IH), 6.90 (s, IH), 6.14 (br. s., IH), 4.53 (br. s., 2H), 3.99 (t, *J*=5.75 Hz, 2H), 3.68 (t, *J*=4.46 Hz, 4H), 3.39 (s, 2H), 3.02 (d, *J*=11.13 Hz, 2H), 2.56-2.63 (m, 2H), 2.49-2.55 (m, 2H), 2.46 (br. s., 4H), 2.39 (d, *J*=3.42 Hz, 2H), 2.36 (s, 3H), 1.15 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 685.9.

Example 416: N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

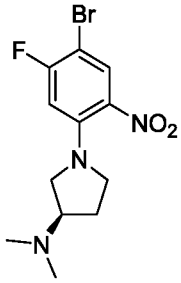


[00773] A procedure similar to that used in Example 405 with N-(4-fluoro-5-(1-(5-formylpyrimidin-2-yl)- 1,2,5,6-tetrahydropyridin-3 -yl)-2-((3 S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.041 mmol) and 1-methylpiperazine (4.08 mg, 0.041 mmol) gave the title compound (24 mg, 80% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.22 - 8.16 (m, 2H), 7.88 - 7.83 (m, IH), 7.72 - 7.64 (m, IH), 6.90 - 6.84 (m, IH), 6.82 - 6.77 (m, IH), 6.07 - 6.00 (m, IH), 4.47 - 4.41 (m, 2H), 3.92 - 3.88 (m, 2H), 3.33 - 3.29 (m, 2H), 2.96 - 2.89 (m, 2H), 2.64 - 2.45 (m, 5H), 2.45 - 2.38 (m, 5H), 2.37 - 2.27 (m, 4H), 2.26 - 2.24 (m, 3H), 2.21 - 2.19 (m, 3H), 2.12 - 2.12 (m, IH), 1.05 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 698.8

Example 417: N-[4-fluoro-2-[(3S)-3-(dimethylamino)pyrrolidin-l-yl]-5-[2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

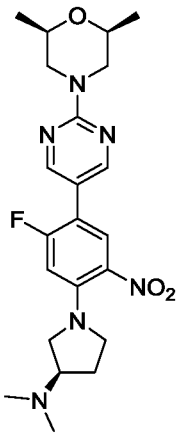


Step 1: (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



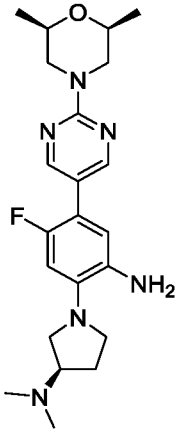
[00774] A solution of l-bromo-2,4-difluoro-5-nitrobenzene (2.7 mL, 21 mmol) in toluene (5 mL) was added dropwise to a rapidly stirring mixture of (3R)-(+)-3-(dimethylamino)pyrrolidine (2.4 g, 21 mmol) and potassium carbonate (1.4 g, 10 mmol) in toluene (50 mL) at room temperature. After stirring for 20 minutes the reaction was warmed to 45 °C for 30 minutes. After the reaction was cooled to room temperature the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)- 1-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (6.4 g, 91 %). LCMS [M+H]+: 332.1.

Step 2: (R)-l-(4-(2-(cis-2, 6-dimethylmorpholino)pyrimidin-5-yl)-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine



[00775] A vial was charged with a mixture of (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.050 g, 0.15 mmol), (2-(cis-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (0.050 g, 0.21 mmol), XPhos Pd G2 (2 mg, 3.0 μηιοϊ) and XPhos (1.5 mg, 3.0 μηιοϊ). The vial was sealed with a septum, evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and 2 M aqueous sodium carbonate (0.4 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 95 °C in an aluminum block for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford (R)-l-(4-(2-(cis-2,6-dimethylmo rpholino)pyrimidin-5-yl)-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3-amine (0.066 g, 99 %). LCMS [M+H]+: 445.6.

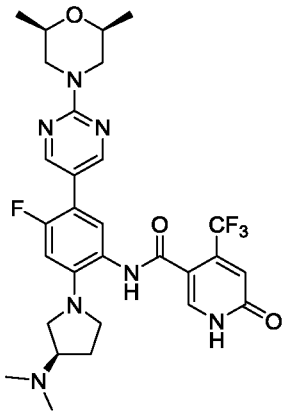
Step 3: (R)-l-(2-amino-4-(2-(cis-2, 6-dimethylmorpholino)pyrimidin-5-yl)-5-fluorophenyl)-N,N-dimethylpyrrolidin-3-amine



[00776] A mixture of (R)-l-(4-(2-(cis-2,6-dimethylmorpholino)pyrimidin-5-yl)-5-fluoro-2-nitrophenyl)-N,N-dimethylpyrrolidin-3 -amine (0.066 g, 0.15 mmol)

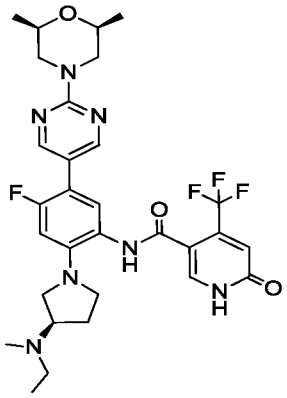
and tin(II) chloride (0.11 g, 0.60 mmol in EtOH (5 niL) was heated to 75 °C for 1 h. The reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded (R)-l-(2-amino-4-(2-(cis-2,6-dimethylmorpholino)pyrimidin-5-yl)-5-fluorophenyl)-N,N-dimethylpyrrolidin-3 -amine (0.050 g, 81 %). LCMS [M+H]+: 415.5.

Step 4: N-(2-((R)-3-(dimethylamino)pyrrolidin-l-yl)-5-(2-(cis-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



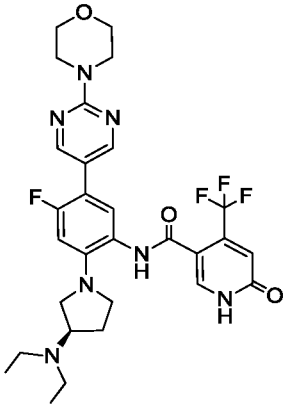
[00777] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.028 g, 0.090 mmol) was activated with HATU (0.035 g, 0.090 mmol) and N,N-diisopropylethylamine (0.02 mL, 0.090 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of (R)-l-(2-amino-4-(2-(cis-2,6-dimethylmo rpholino)pyrimidin-5-yl)-5-fluorophenyl)-N,N-dimethylpyl rolidin-3-amine (0.025 g, 0.060 mmol) in DMF (1 mL) and the reaction was heated to 55 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-7.5% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with TFA (1 mL) at room temperature. After stirring for 2 h the volatiles were removed under a stream of air and the title compound was isolated by a catch and release protocol using a SCX2 silica cartridge to afford the title compound (0.019 g, 52 %). ^1H NMR (500MHz, DMSO-d6) δ = 12.53 (br s, 1H), 9.81 (s, 1H), 8.48 (s, 2H), 7.95 (br s, 1H), 7.29 (br d, *J*=8.8 Hz, 1H), 6.80 (s, 1H), 6.66 (br d, *J*=14.2 Hz, 1H), 4.52 (br d, *J*=12.6 Hz, 2H), 3.60 - 3.53 (m, 4H), 2.60 - 2.53 (m, 4H), 2.15 (s, 6H), 2.11 - 2.00 (m, 1H), 1.69 (quin, *J*=9.9 Hz, 1H), 1.16 (br d, *J*=6.1 Hz, 6H), 1.09 - 0.97 (m, 1H); LCMS [M+H]+: 604.6.

Example 418: N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S)-3-[ethyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



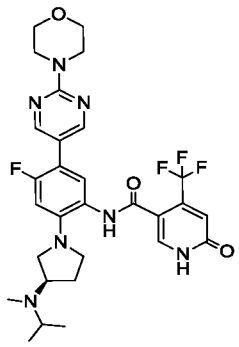
[00778] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using (R)-N-ethyl-N-methylpyrrolidin-3-amine in place of (3R)-(+)-3-(dimethylamino)pyrrolidine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.53 (br s, IH), 9.79 (s, IH), 8.48 (s, 2H), 7.94 (br s, IH), 7.30 (br d, *J*=8.8 Hz, IH), 6.80 (s, IH), 6.66 (d, *J*=13.9 Hz, IH), 4.52 (br d, *J*=12.7 Hz, 2H), 3.60 - 3.53 (m, 2H), 3.40 - 3.36 (m, *J*=9.2 Hz, 3H), 3.26 - 3.20 (m, 2H), 2.89 (br d, *J*=5.1 Hz, IH), 2.60 - 2.53 (m, 3H), 2.45 - 2.38 (m, 2H), 2.14 (s, 3H), 2.11 - 2.04 (m, IH), 1.74 - 1.64 (m, IH), 1.16 (d, *J*=6.1 Hz, 6H), 0.95 (br t, *J*=7.0 Hz, 3H); LCMS [M+H]+: 618.5.

Example 419: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-l-yl]phenyl]-6<>xo-4-(Mfluor^methyl)-1H-pyridine-3-carboxamide



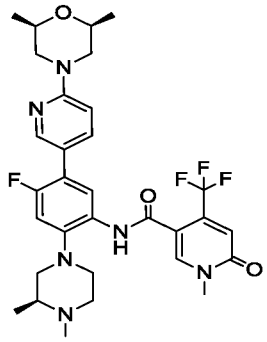
[00779] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using diethylamine in place of N-ethylmethyl amine in Step 1 and (2-morpholinopyrimidin-5-yl)boronic acid in Step 2. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.44 (br s, 1H), 9.78 (s, 1H), 8.50 (s, 2H), 7.95 (br s, 1H), 7.31 (br d, *J*=8.6 Hz, 1H), 6.79 (s, 1H), 6.66 (d, *J*=13.9 Hz, 1H), 3.75 - 3.72 (m, 4H), 3.69 - 3.66 (m, 4H), 3.37 - 3.35 (m, 3H), 3.25 - 3.18 (m, 2H), 2.58 - 2.52 (m, 5H), 2.10 - 2.03 (m, 1H), 1.73 - 1.64 (m, 1H), 0.99 (br d, *J*=6.2 Hz, 3H), 0.91 (t, *J*=7.0 Hz, 6H); LCMS [M+H]+: 604.5.

Example 420: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(propan-2-yl)amino]pyrrolidin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl) -1H-pyridine-3-carboxamide



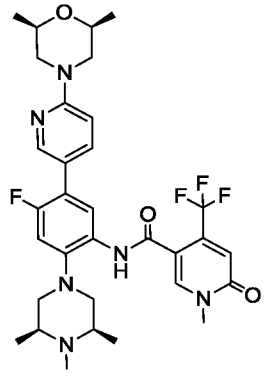
[00780] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using N-isopropyl-N-methylamine in place of N-ethylmethylamine in Step 1 and (2-morpholinopyrimidin-5-yl)boronic acid in Step 2. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.79 (s, 1H), 8.50 (s, 2H), 7.94 (br s, 1H), 7.30 (br d, *J*=8.8 Hz, 1H), 6.79 (s, 1H), 6.66 (d, *J*=14.1 Hz, 1H), 3.75 - 3.71 (m, 4H), 3.70 - 3.66 (m, 4H), 3.41 - 3.35 (m, 3H), 3.25 - 3.20 (m, 1H), 3.09 - 3.01 (m, 2H), 2.95 - 2.88 (m, 1H), 2.05 (s, 3H), 1.71 - 1.62 (m, 1H), 0.98 (br d, *J*=6.5 Hz, 6H); LCMS [M+H]+: 604.5.

Example 421: N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00781] The title compound (white solid, 26.0 mg, 42%) was prepared by a procedure similar to Example 209 using (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (47 mg, 0.15 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.4 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.32 (s, IH), 8.26 (s, IH), 7.93 (d, *J*=8.3 Hz, IH), 7.79 (br d, *J*=9.0 Hz, IH), 7.09 (d, *J*=12.1 Hz, IH), 6.95 (s, IH), 6.92 (d, *J*=8.6 Hz, IH), 4.16 (br d, *J*=12.6 Hz, 2H), 3.78 - 3.70 (m, 2H), 3.67 (s, 3H), 3.15 - 3.04 (m, 2H), 2.96 (br t, *J*=10.2 Hz, 2H), 2.63 - 2.51 (m, 4H), 2.49 - 2.43 (m, IH), 2.40 (br s, 3H), 1.27 (d, *J*=6.2 Hz, 6H), 1.15 (d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^{+}$ 617.6.

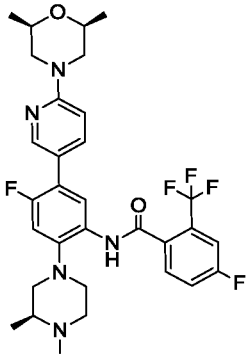
Example 422: N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-f(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00782] The title compound (white solid, 26.4 mg, 42%) was prepared through a procedure similar to Example 209 using (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (47 mg, 0.15 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-

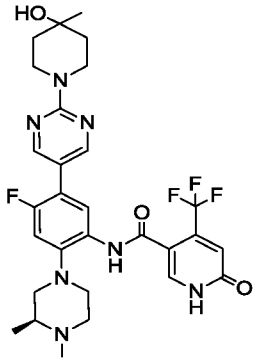
oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (51.8 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.31 (s, IH), 8.26 (s, IH), 7.93 (d, *J*=8.3 Hz, IH), 7.79 (br d, *J*=8.8 Hz, IH), 7.09 (d, *J*=12.0 Hz, IH), 6.95 (s, IH), 6.92 (d, *J*=8.7 Hz, IH), 4.16 (br d, *J*=12.1 Hz, 2H), 3.78 - 3.70 (m, 2H), 3.66 (s, 3H), 3.09 (br d, *J*=8.4 Hz, 2H), 2.73 - 2.51 (m, 6H), 2.44 (br s, 3H), 1.27 (d, *J*=6.2 Hz, 6H), 1.21 (br s, 6H); LCMS [M + H]$^+$ 631.6.

Example 423: 4-fluoro-N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3R)-3,4^iimethylpiperazm-l-yl]phenyl]-2-(trifluoromethyl)benzamide



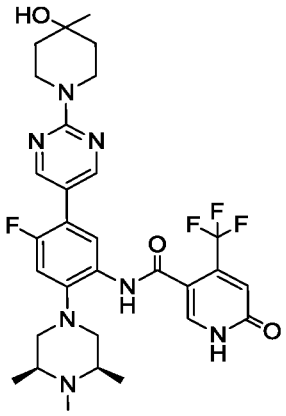
[00783] The title compound (formic acid salt, off white solid, 43.0 mg, 66%) was prepared by a method similar to that of Example 400 using (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (47 mg, 0.15 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (49.2 mg, 0.1 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 8.52 - 8.35 (m, IH), 8.33 (s, IH), 8.05 (d, *J*=8.1 Hz, IH), 7.84 - 7.77 (m, 2H), 7.67 (br d, *J*=8.9 Hz, IH), 7.58 (br t, *J*=7.9 Hz, IH), 7.18 (br d, *J*=11.7 Hz, IH), 6.93 (d, *J*=8.2 Hz, IH), 4.17 (br d, *J*=12.7 Hz, 2H), 3.78 - 3.70 (m, 2H), 3.51 - 3.41 (m, IH), 3.41 - 3.35 (m, IH), 3.31 - 3.08 (m, 5H), 2.94 - 2.77 (m, 4H), 2.55 (br t, *J*=11.6 Hz, 2H), 1.40 - 1.32 (m, 3H), 1.27 (br d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 604.6.

Example 424: N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



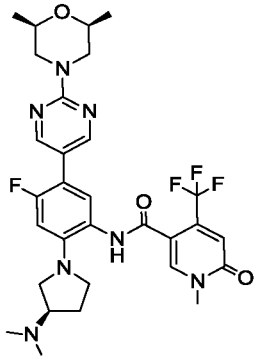
[00784] To a mixture of 2-chloropyrimidine-5-boronic acid (48 mg, 0.3 mmol) and 4-methylpiperidin-4-ol (36 mg, 0.315 mmol) in EtOH (2 mL) was added triethylamine (0.070 mL, 0.5 mmol). The resulting mixture was stirred at 80 °C for 1 h and solvents were removed to give crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid as a yellow solid. LCMS $[M + H]^+$ 238.4. The title compound (light beige solid, 34.7 mg, 57%) was prepared according to a method similar to Example 40 using crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide (49 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.51 (s, 2H), 7.99 (s, IH), 7.91 (br d, *J*=8.2 Hz, IH), 7.10 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 4.29 (td, *J*=4.0, 13.2 Hz, 2H), 3.63 - 3.53 (m, 2H), 3.14 - 3.03 (m, 2H), 2.99 - 2.91 (m, 2H), 2.61 - 2.52 (m, 2H), 2.47 - 2.42 (m, IH), 2.39 (s, 3H), 1.71 - 1.58 (m, 4H), 1.28 (s, 3H), 1.14 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 604.5.

Example 425: N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00785] The title compound (light beige solid, 29.2 mg, 47%) was prepared by a procedure similar to Example 31 using crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (51 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.51 (s, 2H), 7.98 (s, IH), 7.90 (d, *J*=8.2 Hz, IH), 7.09 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 4.29 (td, *J*=4.2, 13.3 Hz, 2H), 3.58 (ddd, *J*=3.5, 10.3, 13.3 Hz, 2H), 3.07 (br d, *J*=11.0 Hz, 2H), 2.67 - 2.53 (m, 4H), 2.40 (s, 3H), 1.70 - 1.58 (m, 4H), 1.28 (s, 3H), 1.18 (d, *J*=6.0 Hz, 6H); LCMS $[M + H]^+$ 618.5.

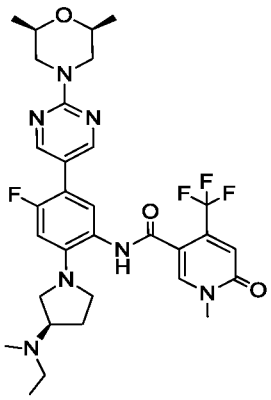
Example 426: N-[4-fluoro-2-[(3S)-3-(dimethylamino)pyrrolidin-l-yl]-5-[2-[(2R, 6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl] phenyl] -l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00786] The title compound was prepared similar to the procedure described above for the preparation of Example 417 Step 4 using (R)-l-(2-amino-4-(2-((2S,6R)-2,6-dimethylmorpholino)pyrirnidin-5-yl)-5-fluorophenyl)-N,N-dimethylpyrrolidin-3-anline

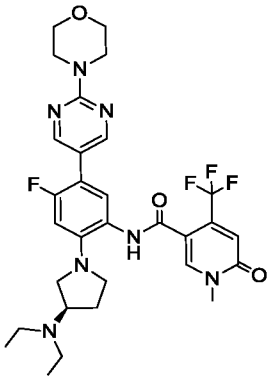
(25 mg, 0.060 mmol) and [l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (20.00 mg, 0.090 mmol) to give the title compound (37.3 mg, 34% yield). ¾ NMR (500MHz, DMSO-d6) δ = 9.79 (s, IH), 8.47 (s, 2H), 8.33 (s, IH), 7.28 (d, *J*=8.8 Hz, IH), 6.86 (s, IH), 6.69 (d, *J*=13.8 Hz, IH), 4.52 (br d, *J*=12.0 Hz, 2H), 3.60 - 3.52 (m, 7H), 3.25 - 3.19 (m, 2H), 2.67 - 2.56 (m, 7H), 2.14 (s, 6H), 2.10 - 2.03 (m, IH), 1.75 - 1.65 (m, IH), 1.16 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+: 618.5.

Example 427: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S)-3-[ethyl(methyl)amino]pyrrolidin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



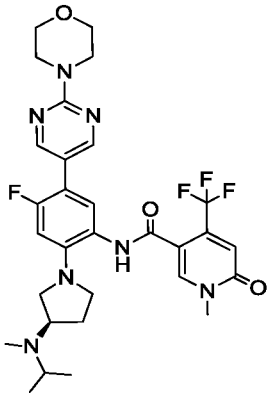
[00787] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 4. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.78 (s, IH), 8.47 (s, 2H), 8.32 (s, IH), 7.28 (d, *J*=8.7 Hz, IH), 6.86 (s, IH), 6.69 (d, *J*=13.9 Hz, IH), 4.52 (br d, *J*=11.7 Hz, 2H), 3.59 - 3.52 (m, 5H), 3.42 - 3.36 (m, 4H), 3.27 - 3.20 (m, IH), 2.93 - 2.84 (m, IH), 2.60 - 2.53 (m, 3H), 2.44 - 2.38 (m, 2H), 2.13 (s, 3H), 2.11 - 2.05 (m, IH), 1.73 - 1.65 (m, IH), 1.16 (d, *J*=6.2 Hz, 6H), 0.95 (t, *J*=7.1 Hz, 3H); LCMS [M+H]+: 632.6.

Example 428: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-l-ylJphenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00788] The title compound was prepared according to a sequence similar to the preparation of Example 417 using (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N,N-diethylpyrrolidin-3-amine (19 mg, 0.046 mmol) that was dissolved in N,N-Dimethylformamide (DMF) (1 ml) and treated with a solution of activated acid [1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (15.20 mg, 0.069 mmol) to give the title compound (28.3 mg, 35% yield for final step). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.76 (s, 1H), 8.49 (s, 2H), 8.33 (s, 1H), 7.29 (d, *J*=8.7 Hz, 1H), 6.86 (s, 1H), 6.68 (d, *J*=13.8 Hz, 1H), 3.75 - 3.72 (m, 4H), 3.70 - 3.65 (m, 4H), 3.54 (s, 3H), 3.40 - 3.35 (m, 4H), 3.25 - 3.17 (m, 2H), 2.57 - 2.52 (m, 5H), 2.11 - 2.03 (m, 1H), 1.73 - 1.64 (m, 1H), 0.91 (t, *J*=7.0 Hz, 6H); LCMS [M+H]+: 618.5.

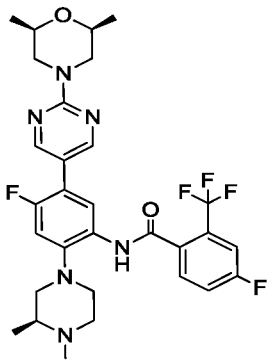
Example 429: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(propan-2-yl)amino]pyrrolidin-l-yl] phenyl] -l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00789] The title compound was prepared according to a sequence similar to Example 417 using (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-

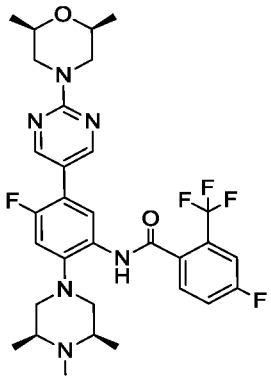
isopropyl-N-methylpyrrolidin-3-amine (18 mg, 0.043 mmol) that was dissolved in DMF and [l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (9.60 mg, 0.043 mmol) in the final step to give the title compound (26.8 mg, 49% yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.78 (s, 1H), 8.49 (s, 2H), 8.32 (s, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 6.86 (s, 1H), 6.68 (d, *J*=13.9 Hz, 1H), 3.75 - 3.72 (m, 4H), 3.69 - 3.66 (m, 4H), 3.54 (s, 3H), 3.26 - 3.20 (m, 2H), 3.12 - 3.01 (m, 1H), 2.97 - 2.87 (m, 1H), 2.12 - 2.03 (m, 4H), 1.71 - 1.62 (m, 1H), 0.92 (br d, *J*=6. 1 Hz, 6H); LCMS [M+H]+: 618.6.

Example 430: 4-fluoro-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-y l]pyrimidin-5-yl]-2-[(3R)-3, 4-dimethylpiperazin-l -yl]phenyl]-2-(trifluoromethyljbenzamide



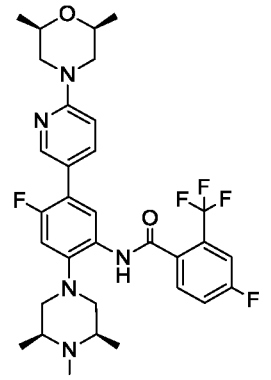
[00790] The title compound (formic acid salt, white solid, 36.2 mg, 55%) was prepared according to a procedure similar to that used in Example 400 using (2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (36 mg, 0.15 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (49 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.37 (br s, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.82 (dd, *J*=5.4, 8.4 Hz, 1H), 7.68 (dd, *J*=2.2, 9.0 Hz, 1H), 7.58 (dt, *J*=2.3, 8.3 Hz, 1H), 7.20 (d, *J*=11.9 Hz, 1H), 4.68 - 4.63 (m, 2H), 3.71 - 3.64 (m, 2H), 3.43 - 3.37 (m, 1H), 3.31 - 3.22 (m, 2H), 3.16 - 3.04 (m, 3H), 2.91 - 2.80 (m, 1H), 2.79 - 2.75 (m, 3H), 2.68 - 2.60 (m, 2H), 1.33 (br d, *J*=6.4 Hz, 3H), 1.26 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 605.5.

Example 431: 4-fluoro-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-y l]pyrimidin-5-yl]-2-[(3S, 5R)-3, 4, 5-trimethylpiperazin-l -yl]phenyl]-2-(trifluoromethyljbenzamide



[00791] The title compound (formic acid salt, white solid, 36.5 mg, 39%) was prepared by a procedure similar to Example 400 using (2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)boronic acid (36 mg, 0.15 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-**d4)** δ = 8.56 (s, 2H), 8.42 (br s, IH), 8.05 (d, *J*=8.2 Hz, IH), 7.81 (dd, *J=5.3,* 8.4 Hz, IH), 7.68 (br d, *J*=8.9 Hz, IH), 7.58 (br t, *J*=8.1 Hz, IH), 7.20 (br d, *J*=11.9 Hz, IH), 4.65 (br d, *J*=13.2 Hz, 2H), 3.67 (br dd, *J*=6.4, 7.9 Hz, 2H), 3.26 (br d, *J*=13.0 Hz, 4H), 2.94 - 2.82 (m, 2H), 2.77 (br d, *J*=9.4 Hz, 3H), 2.68 - 2.60 (m, 2H), 1.37 (br d, *J*=4.5 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^{+}$ 619.5.

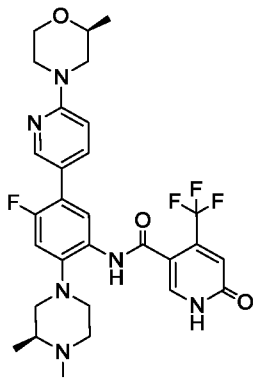
Example 432: 4-fluoro-N-[4-fluoro-5-[6-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3S, 5R)-3, 4, 5-trimethylpiperazin-l -yl]phenyl]-2-(trifluoromethyljbenzamide



[00792] The title compound (white solid, 35.8 mg, 56%) was prepared by a procedure similar to Example 400 using (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (47 mg, 0.15 mmol) and

N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.33 (s, IH), 8.03 (d, *J*=8.3 Hz, IH), 7.82 - 7.75 (m, 2H), 7.66 (dd, *J*=2.3, 9.1 Hz, IH), 7.57 (dt, *J*=2.3, 8.3 Hz, IH), 7.08 (d, *J*=12.0 Hz, IH), 6.93 (d, *J*=9.0 Hz, IH), 4.17 (br d, *J*=11.6 Hz, 2H), 3.78 - 3.71 (m, 2H), 3.06 (br d, *J*=11.4 Hz, 2H), 2.63 (br t, *J*=ll.l Hz, 2H), 2.58 - 2.43 (m, 4H), 2.35 (br s, 3H), 1.27 (d, *J*=6.2 Hz, 6H), 1.17 (d, *J*=6.2 Hz, 6H); LCMS [M + H]$^+$ 618.5.

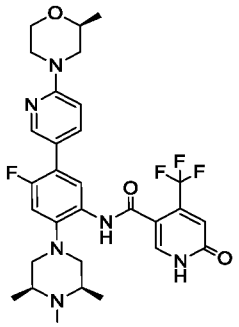
Example 433: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJ-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00793] To a 5 mL microwave vial charged with 2-chloro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (479 mg, 2 mmol), (S)-2-methylmorpholine (223 mg, 2.2 mmol) and Hunig base (0.70 mL, 4 mmol) was added NMP (1 mL). The resulting solution was heated at 140 °C for 2 h and purified by flash chromatography twice (gradient: EtOAc/hex 0-100% and EtOAc/hex 0-50% respectively) to give (S)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine as a crystalline light beige solid (102 mg). LCMS for boronic acid [M + H]$^+$ 223.2. The title compound (pale beige solid, 21.1 mg, 34%) was prepared by a method similar to Example 400 using (S)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (50 mg) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.32 (s, IH), 7.98 (s, IH), 7.93 (br d, *J*=8.3 Hz, IH), 7.79 (br d, *J*=8.9 Hz, IH), 7.09 (d, *J*=12.1 Hz, IH), 6.95 - 6.90 (m, 2H), 4.16 (br d, *J*=12.7 Hz,

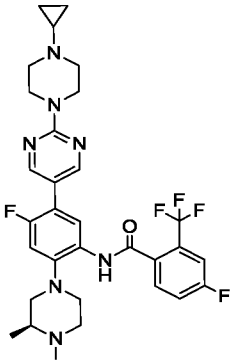
1H), 4.10 - 3.99 (m, 2H), 3.76 - 3.66 (m, 2H), 3.16 - 3.03 (m, 2H), 3.02 - 2.90 (m, 3H), 2.67 - 2.53 (m, 3H), 2.47 (br s, 1H), 2.44 - 2.38 (m, 3H), 1.26 (d, *J*=6.2 Hz, 3H), 1.15 (br d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^+$ 589.5.

Example 434: N-[4-fluoro-5-[6-[(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-f(3S, 5R)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



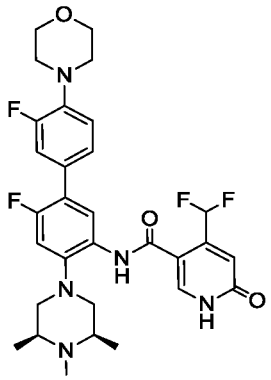
[00794] The title compound (pale beige solid, 26.5 mg, 40%) was prepared by a procedure similar to Example 400 using (S)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)mo rpholine (50 mg, 80% purity, 0.16 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.32 (s, 1H), 7.97 (s, 1H), 7.92 (br d, *J*=8.4 Hz, 1H), 7.79 (br d, *J*=8.8 Hz, 1H), 7.07 (d, *J*=12.1 Hz, 1H), 6.95 - 6.90 (m, 2H), 4.16 (br d, *J*=12.7 Hz, 1H), 4.10 - 3.99 (m, 2H), 3.75 - 3.66 (m, 2H), 3.07 (br d, *J*=10.5 Hz, 2H), 2.96 (dt, *J*=3.4, 12.3 Hz, 1H), 2.70 - 2.56 (m, 5H), 2.41 (s, 3H), 1.26 (d, *J*=6.2 Hz, 3H), 1.19 (d, *J*=5.7 Hz, 6H); LCMS [M + H]$^+$ 603.6.

Example 435: N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl] phenyl] -4-fluoro-2-(trifluoromethyl)benzamide



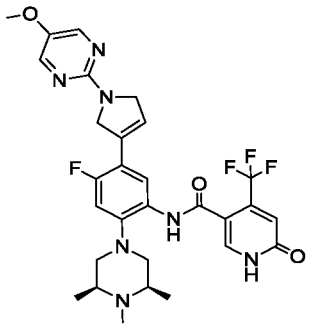
[00795] To a mixture of 2-chloropyrimidine-5-boronic acid (633 mg, 4 mmol) and 1-cyclopropylpiperazine (0.56 mL, 4.4 mmol) in EtOH (8 mL) was added triethylamine (0.84 mL, 6 mmol). The resulting mixture was stirred at 75 °C for 1 h, concentrated and dried to give crude (2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid as a beige solid (1.319g, 75% purity assuming full conversion). LCMS $[M + H]^+$ 249.2. The title compound (beige solid, 15.9 mg, 25%) was prepared according to a procedure similar to Example 40 using crude (2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.03 (d, *J*=8.2 Hz, IH), 7.80 (dd, *J*=5.3, 8.4 Hz, IH), 7.66 (dd, *J*=2.3, 9.0 Hz, IH), 7.57 (dt, *J*=2.3, 8.3 Hz, IH), 7.13 (d, *J*=12.0 Hz, IH), 3.91 - 3.84 (m, 4H), 3.16 - 3.04 (m, 2H), 2.99 - 2.88 (m, 2H), 2.77 - 2.70 (m, 4H), 2.58 (t, *J*=10.8 Hz, IH), 2.49 (dt, *J*=2.6, 11.5 Hz, IH), 2.39 - 2.32 (m, 4H), 1.76 - 1.72 (m, IH), 1.13 (d, *J*=6.2 Hz, 3H), 0.60 - 0.48 (m, 4H); LCMS $[M+ H]^+$ found 616.6.

Example 436: 4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



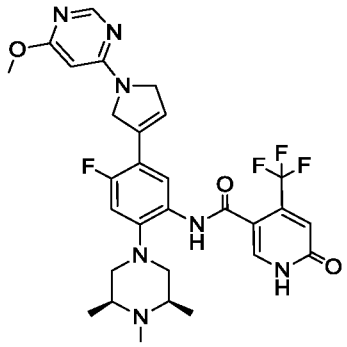
[00796] A sequence similar to Example 397 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (92.3 mg, 0.157 mmol) and 3-fluoro-4-morpholinophenylboronic acid (42.4 mg, 0.189 mmol) was employed to give, after deprotection of the N-(3',6-difluoro-4'^ ophenoHpho -4-((38,5R)-3,4,5-trimethylpiperazin- 1-yl)-[1,1'-biphenyl]-3-yl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide intermediate, (108 mg, 0.157 mmol) the title compound (13.6 mg, 14.15 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.39 (br. s., 1H), 9.56 (s, 1H), 7.99 (s, 1H), 7.69 (d, *J*=8.68 Hz, 1H), 7.21-7.49 (m, 2H), 7.09-7.16 (m, 1H), 7.00 (d, *J*=12.72 Hz, 1H), 6.59 (s, 1H), 3.71-3.81 (m, 4H), 3.00-3.09 (m, 6H), 2.48 (br. s., 1H), 2.33 (d, *J*=6.60 Hz, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 588.5.

Example 437: N-[4-fluoro-5-[1-(5-methoxypyrimidin-2-yl)-2,5-dihydropyrrol-3-yl] -2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



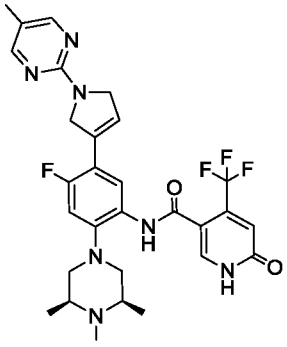
[00797] The procedure used was similar to Example 270 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and 2-bromo-5-methoxypyrimidine (10.72 mg, 0.057 mmol) to give the title compound (13.5 mg, 53% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 8.04-8.11 (m, 2H), 7.86 (s, 1H), 7.77 (d, *J*=8.07 Hz, 1H), 6.91 (d, *J*=12.96 Hz, 1H), 6.80 (s, 1H), 6.37 (br. s., 1H), 4.53-4.62 (m, 2H), 4.38 (br. s., 2H), 3.73 (s, 3H), 2.94 (d, *J*=11.37 Hz, 2H), 2.46-2.53 (m, 2H), 2.37-2.44 (m, 2H), 2.37-2.44 (m, 2H), 2.25 (s, 3H), 1.05 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 602.7.

Example 438: N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-2,5-dihydropyrrol-3-yl] -2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00798] The procedure used was similar to Example 270 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-ihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and 4-iodo-6-Methoxy pyrimidine (13.39 mg, 0.057 mmol) to give the title compound (19 mg, 74% yield). ¾ NMR (500MHz, METHANOL-d4) δ 8.19-8.28 (m, 1H), 7.99 (s, 1H), 7.89 (d, *J*=7.95 Hz, 1H), 7.04 (d, *J*=12.96 Hz, 1H), 6.93 (s, 1H), 6.49 (br. s., 1H), 5.86 (br. s., 1H), 4.26-4.72 (m, 4H), 3.93 (s, 3H), 3.07 (d, *J*=11.25 Hz, 2H), 2.58-2.65(m, 2H), 2.55 (d, *J*=6.11 Hz, 2H), 2.38 (s, 3H), 1.17 (d, *J*=5.99Hz, 6H); LCMS [M+H]+ 602.7.

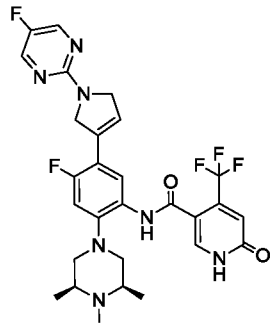
Example 439: N-[4-fluoro-5-[l-(5-methylpyrimidin-2-yl)-2, 5-dihydropyrrol-3-yl] -2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00799] A procedure similar to Example 270 was employed using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and

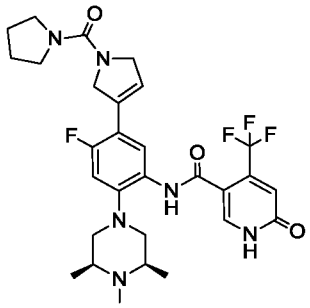
2-Chloro-5-methylpyrimidine (7.29 mg, 0.057 mmol) to give the title compound (16.5 mg, 63 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 8.26 (s, 2H), 8.04 (s, IH), 7.91 (d, *J*=7.95 Hz, IH), 7.03 (d, *J*=12.96 Hz, IH), 6.87 (s, IH), 6.48-6.53 (m, IH), 6.50 (br. s., IH), 4.72 (br. s., 2H), 4.52 (br. s., 2H), 3.07 (d, *J*=11.25 Hz, 2H), 2.58-2.65 (m, 2H), 2.53 (d, *J*=6.36 Hz, 2H), 2.37 (s, 3H), 2.19 (s, 3H), 1.16-1.18 (m, 6H), 1.17 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 586.7

Example 440: N-[4-fluoro-5-[1-(5-fluoropyrimidin-2-yl)-2,5-dihydropyrrol-3-yl] -2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



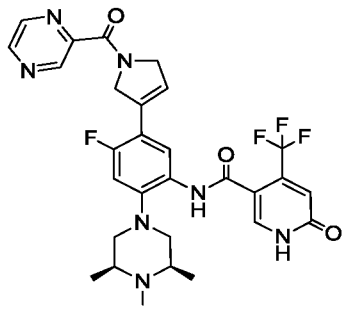
[00800] A procedure similar to that of Example 270 was employed using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and 2-Bromo-5-fluoropyrimidine (7.17 mg, 0.041 mmol) to give the title compound (17.5 mg, 70 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.40 - 8.31 (m, 2H), 8.04 - 7.97 (m, IH), 7.94 - 7.85 (m, IH), 7.08 - 7.00 (m, IH), 6.95 - 6.88 (m, IH), 6.53 - 6.46 (m, IH), 5.51 (s, IH), 4.75 - 4.68 (m, 2H), 4.56 - 4.48 (m, 2H), 3.12 - 3.03 (m, 2H), 2.66 - 2.58 (m, 2H), 2.56 - 2.49 (m, 2H), 2.41 - 2.36 (m, 3H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 590.7.

Example 441: N-[4-fluoro-5-[1-(pyrrolidine-1 -carbonyl)-2,5-dihydropyrrol-3-yl] -2-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



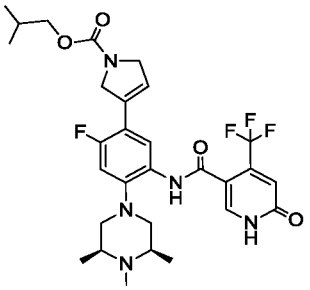
[00801] The procedure followed was similar to Example 253 using N-(5-(2,5-dihydro- 1H-pyrrol-3 -yl)-4-fluoro-2-((3 S,5R)-3,4,5 -trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (24 mg, 0.049 mmol) and 1-pyrrolidinecarbonyl chloride (5.37 µï, 0.049 mmol) to give the title compound (22 mg, 73 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.03 - 7.93 (m, 1H), 7.87 - 7.76 (m, 1H), 7.06 - 6.98 (m, 1H), 6.94 - 6.87 (m, 1H), 6.41 - 6.30 (m, 1H), 4.71 - 4.62 (m, 2H), 4.51 - 4.43 (m, 2H), 3.54 - 3.47 (m, 4H), 3.10 - 3.02 (m, 2H), 2.64 - 2.57 (m, 2H), 2.56 - 2.49 (m, 2H), 1.97 - 1.88 (m, 4H), 1.20 - 1.15 (m, 6H); LCMS [M+H]+ 591.7.

Example 442: N-[4-fluoro-5-[1-(pyrazine-2-carbonyl)-2,5-dihydropyrrol-3-yl] -2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



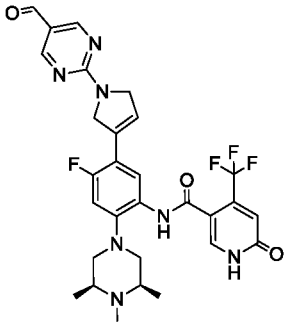
[00802] The procedure followed was similar to Example 253 using N-(5-(2,5-dihydro- 1H-pyrrol-3 -yl)-4-fluoro-2-((3 S,5R)-3,4,5 -trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and pyrazine-2-carbonyl chloride (10.83 mg, 0.076 mmol) to give the title compound (11 mg, 34 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 9.17 - 9.09 (m, 1H), 8.78 - 8.70 (m, 2H), 8.02 - 7.94 (m, 1H), 7.93 - 7.75 (m, 1H), 7.09 - 6.99 (m, 1H), 6.96 - 6.91 (m, 1H), 6.50 - 6.36 (m, 1H), 5.14 - 5.07 (m, 1H), 4.72 - 4.65 (m, 1H), 3.13 - 3.03 (m, 2H), 2.65 - 2.52 (m, 4H), 2.41 - 2.36 (m, 3H), 1.17 (t, *J*=6.5 Hz, 6H); LCMS [M+H]+ 600.6.

Example 443: 2-methylpropyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-2,5-dihydropyrrole-l-carboxylate



[00803] The procedure employed was similar to Example 253 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and isobutyl chloroformate (6.62 µï, 0.051 mmol) to give the title compound (25 mg, 79 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.01 - 7.93 (m, 1H), 7.87 - 7.77 (m, 1H), 7.05 - 6.98 (m, 1H), 6.95 - 6.90 (m, 1H), 6.42 - 6.32 (m, 1H), 4.63 - 4.53 (m, 2H), 4.43 - 4.31 (m, 2H), 3.94 (t, *J*=7.2 Hz, 2H), 3.10 - 3.03 (m, 2H), 2.65 - 2.58 (m, 2H), 2.58 - 2.49 (m, 2H), 2.08 - 1.92 (m, 1H), 1.21 - 1.15 (m, 6H), 1.05 - 0.97 (m, 6H); LCMS [M+H]+ 594.4

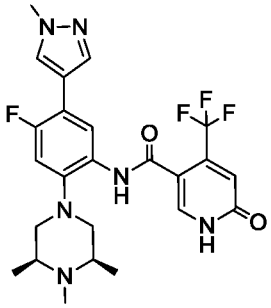
Example 444: N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-2,5-dihydropyrrol-3-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



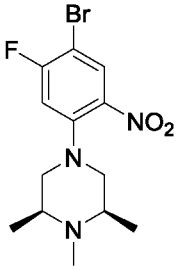
[00804] The procedure followed was similar to Example 270 using N-(5-(2,5-dihydro- 1H-pyrrol-3 -yl)-4-fluoro-2-((3 S,5R)-3,4,5 -trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (200 mg, 0.405 mmol) and

2-bromo-pyrimidine-5-carbaldehyde (91 mg, 0.486 mmol) to give the title compound (212 mg, 83 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 12.85 - 12.28 (m, 1H), 9.88 - 9.77 (m, 1H), 9.57 - 9.46 (m, 1H), 8.93 - 8.84 (m, 2H), 8.03 - 7.91 (m, 1H), 7.73 (br d, *J*=8.3 Hz, 1H), 7.06 - 6.96 (m, 1H), 6.87 - 6.78 (m, 1H), 6.51 - 6.43 (m, 1H), 4.82 - 4.72 (m, 2H), 4.64 - 4.56 (m, 2H), 3.10 - 3.01 (m, 2H), 2.48 - 2.42 (m, 2H), 2.39 - 2.30 (m, 2H), 2.23 - 2.17 (m, 3H), 1.01 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 600.6.

Example 445: N-[4-fluoro-5-(1-methylpyrazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide



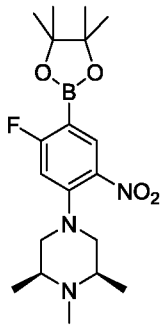
Step 1: cis-4-(4-Bromo-5-fluoro-2-nitrophenyl)-1,2, 6-trimethylpiperazine



[00805] A solution of 1-bromo-2,4-difluoro-5-nitrobenzene (5.0 g, 21 mmol) in toluene (5 mL) was added dropwise to a rapidly stirring mixture of cis-1,2,6-trimethylpiperazine (2.7 g, 21 mmol) and potassium carbonate (1.4 g, 10 mmol) in toluene (50 mL) at room temperature. After stirring for 20 minutes the reaction was warmed to 45 °C for 30 minutes. After the reaction was cooled to room temperature the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] afforded

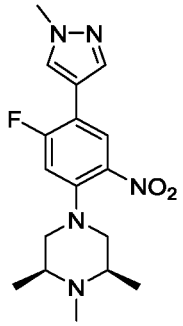
cis-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (6.8 g, 93 % yield). LCMS [M+H]+: 346.3.

Step 2: cis-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2,6-trimethylpiperazine



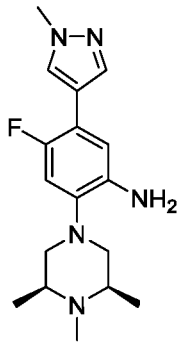
[00806] Two reaction vials containing magnetic stir bars were charged with cis-4-(4-bromo-5-fluoro-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.55 g, 1.6 mmol), bis(pinacolato)diboron (0.73 g, 2.9 mmol), potassium acetate (0.44 g, 4.5 mmol) and [l,l'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.12 g, 0.16 mmol). The vials were sealed with septa. After evacuating and back filling the vials with nitrogen gas 1,4-dioxane (10 mL) and DMSO (0.2 mL) were added via syringe and the reaction vials were evacuated and back filled an additional time. The reaction vials were heated to 100 °C for 3 h. After cooling to room temperature the reaction mixtures were combined and passed through a pad of celite eluting with DCM. The filtrate was concentrated to near dryness and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford cis-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2,6-trimethylpiperazine (0.95 g, 76 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 8.06 (d, *J*=6.4 Hz, 1H), 7.02 (d, *J*=12.0 Hz, 1H), 3.14 (br d, *J*=12.6 Hz, 2H), 2.72 (br t, *J*=11.6 Hz, 2H), 2.28 - 2.22 (m, 2H), 2.19 (s, 3H), 1.29 (s, 12H), 1.01 (d, *J*=6.1 Hz, 6H).

Step 3: cis-4-(5-Fluoro-4-(l-methyl-lH-pyrazol-4-yl)-2-nitrophenyl)-l,2,6-trimethylpiperazine



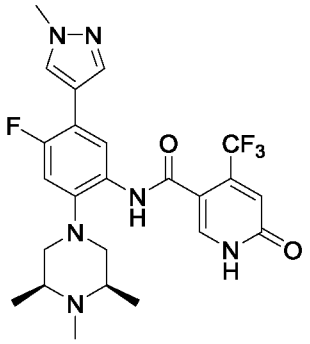
[00807] A 30 mL vial was charged with a mixture of cis-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2,6-trimethylpiperazine (0.045 g, 0.11 mmol), 4-bromo-l-methyl-lH-pyrazole (0.020 g, 0.13 mmol), XPhos Pd G2 (1.8 mg, 2.3 μηοϊ) and XPhos (1.1 mg, 2.3 μηοϊ). The vial was sealed with a septum and evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and 2 M aqueous sodium carbonate (0.5 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 95 °C for 20 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford cis-4-(5-fluoro-4-(l-methyl-lH-pyrazol-4-yl)-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.014 g, 35 %). LCMS [M+H]+: 348.1.

Step 4: 4-fluoro-5-(l-methyl-lH-pyrazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline



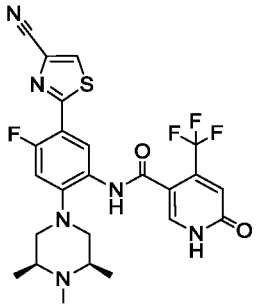
[00808] A solution of cis-4-(5-fluoro-4-(l-methyl-lH-pyrazol-4-yl)-2-nitrophenyl)-l,2,6-trimethylpiperazine (0.014 g, 0.04 mmol) and tin(II) chloride (0.030 g, 0.14 mmol) in a mixture of EtOH (3 mL) and MeOH (1 mL) was heated to 65 °C for 4 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5 - 10% MeOH/DCM + 0.5% NH_4OH] to afford 4-fluoro-5-(l-methyl-lH-pyrazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.009 g, 70 %). LCMS [M+H]+: 318.5.

Step 5: N-(4-fluoro-5-(1-methyl- lH-pyrazol-4-yl)-2-(cis -3,4,5-trimethylpiperazin-l - yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



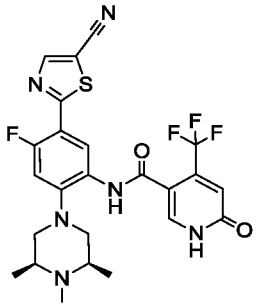
[00809] 4<†jifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.017 g, 0.057 mmol) was activated with HATU (0.022 g, 0.057 mmol) and N,N-diisopropylethylamine (10 µï, 0.057 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of 4-fluoro-5-(l-methyl-lH-pyrazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.009 g, 0.030 mmol) in DMF (0.5 mL) and the reaction was heated to 50 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with TFA (0.5 mL) at room temperature. After stirring for 2 h the volatiles were removed under a stream of air and the title compound was isolated with a catch and release protocol using a SCX2 silica cartridge to afford the title compound N-(4-fluoro-5-(l-methyl-lH-pyrazol-4-yl)-2-(cis-3,4,5-†jimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.011 g, 77 %). ^1H NMR (500MHz, DMSO-d6) δ = 12.56 (br s, 1H), 9.45 (s, 1H), 8.05 (s, 1H), 7.94 (s, 1H), 7.86 (d, *J*=8.3 Hz, 1H), 7.74 (s, 1H), 6.99 (d, *J*=12.6 Hz, 1H), 6.80 (s, 1H), 3.89 (s, 3H), 2.98 (br d, *J*=10.9 Hz, 2H), 2.44 (br t, *J*=10.9 Hz, 2H), 2.36 - 2.28 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 507.6.

Example 446: N-[5-(4-cyano-l, 3-thiazol-2-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6-oxo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



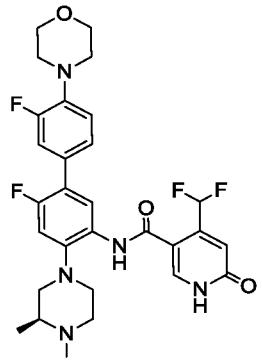
[00810] The title compound was prepared similar to the procedure described above for the preparation of Example 445 using 2-bromo-4-cyanothiazole in place of 4-bromo-l-methyl-lH-pyrazole in Step 3. ^{1}H NMR (500 MHz, DMSO-d6) δ = 9.68 (s, IH), 8.95 (s, IH), 8.39 (d, *J*=8.1 Hz, IH), 7.97 (s, IH), 7.13 (d, *J*=13.3 Hz, IH), 6.82 (s, IH), 3.18 (br d, *J*=11.6 Hz, 2H), 2.38 - 2.33 (m, 2H), 2.20 (s, 3H), 1.01 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 535.5.

Example 447: N-[5-(5-cyano-l ,3-thiazol-2-yl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



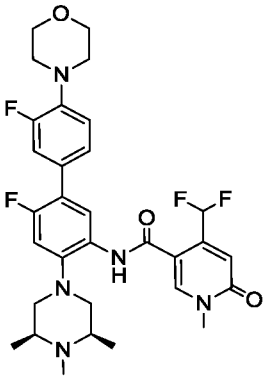
[00811] The title compound was prepared similar to the procedure described above for the preparation of Example 445 using 2-bromo-5-cyanothiazole in place of 4-bromo-l-methyl-lH-pyrazole in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.71 (s, IH), 8.79 (d, *J*=2.1 Hz, IH), 8.48 (d, *J*=8.2 Hz, IH), 7.94 (s, IH), 7.16 (d, *J*=13.3 Hz, IH), 6.83 (s, IH), 3.22 (br d, *J*=11.4 Hz, 3H), 2.37 (br s, 3H), 2.20 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 535.5.

Example 448: 4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



[00812] The procedure followed was similar to Example 396 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (96 mg, 0.167 mmol) and 3-fiuoro-4-morpholinophenylboronic acid (111 mg, 0.493 mmol) to give, after deprotection of the intermediate (S)-4-(difluoromethyl)-N-(4-(3,4-dimethylpiperazin-l-yl)-3',6-difluoro-4'-morpholino-[l ,1'-biphenyl]-3-yl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide the title compound (69.0 mg, 0.118 mmol, 70.3 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.35 (br. s., 1H), 9.54 (s, 1H), 8.00 (s, 1H), 7.71 (d, *J*=8.68 Hz, 1H), 7.21-7.48 (m, 3H), 7.09-7.16 (m, 1H), 7.04 (d, *J*=12.72 Hz, 1H), 6.59 (s, 1H), 3.73-3.79 (m, 4H), 2.99-3.09 (m, 6H), 2.72-2.89 (m, 2H), 2.40-2.47 (m, 1H), 2.29-2.39 (m, 1H), 2.23 (br. s., 3H), 0.98 (d, *J*=5.62 Hz, 3H); LCMS [M+H]+ 574.5.

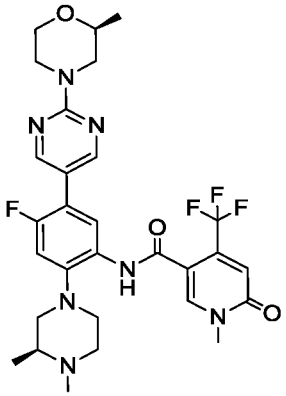
Example 449: 4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyrM ne-3-carboxamide



[00813] To a mixture of N-(3^6-difluoro-4'-morpholino-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)-[1,1'-biphenyl]-3-yl)-4-(difluoromethyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (70 mg, 0.095 mmol) and cesium carbonate (46.6 mg,

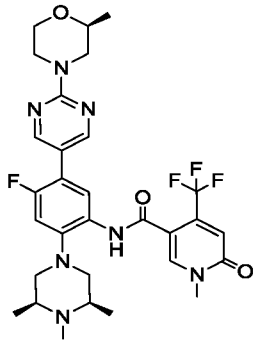
0.143 mmol) in N,N-dimethylformamide (4 ml) was added iodomethane (10 μï, 0.161 mmol) at room temperature. The reaction mixture was stirred for 15 minutes at room temperature and followed by LCMS. Successive portions of 10 and 5 μL of Mel were added at 15 min intervals and the reaction was worked up and the product was purified to give the title compound (0.022 mmol, 22.71 % yield) as an off-white powder. ^{1}H NMR (500MHz, DMSO-d6) δ 9.47 (s, 1H), 8.32-8.35 (m, 1H), 7.69 (d, *J*=8.56 Hz, 1H), 7.20-7.48 (m, 3H), 7.13 (t, *J*=7.30 Hz, 1H), 7.02 (d, *J*=12.47 Hz, 1H), 6.64 (s, 1H), 3.72-3.80 (m, 4H), 3.47-3.55 (m, 3H), 3.35 (d, *J*=2.69 Hz, 1H), 2.97-3.10 (m, 6H), 2.45 (br. s., 1H), 2.36 (br. s., 2H), 2.19 (br. s., 3H), 1.01 (d, *J*=5.62 Hz, 6H). LCMS [M+H]+ 602.5.

Example 450: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l -yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



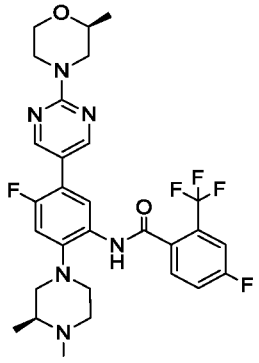
[00814] The title compound (light beige solid, 31.6 mg, 52%) was prepared in a manner similar to Example 31 using crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.27 (s, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.12 (d, *J*=12.1 Hz, 1H), 6.95 (s, 1H), 4.65 - 4.54 (m, 2H), 4.01 - 3.96 (m, 1H), 3.69 - 3.59 (m, 5H), 3.15 - 3.04 (m, 3H), 3.01 - 2.89 (m, 2H), 2.77 - 2.70 (m, 1H), 2.64 - 2.50 (m, 2H), 2.43 (br s, 1H), 2.38 (s, 3H), 1.25 (d, *J*=6.2 Hz, 3H), 1.14 (d, *J*=6.4 Hz, 3H); LCMS $[M + H]^+$ 604.5.

Example 451: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-f(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00815] The title compound (off white solid, 12.9 mg, 21%) was prepared in a manner similar to Example 31 using crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (52 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.26 (s, 1H), 7.91 (d, *J*=8.3 Hz, 1H), 7.11 (d, *J*=12.0 Hz, 1H), 6.94 (s, 1H), 4.64 - 4.52 (m, 2H), 3.98 (dd, *J*=2.6, 11.4 Hz, 1H), 3.68 - 3.58 (m, 5H), 3.12 - 3.03 (m, 3H), 2.76 - 2.54 (m, 5H), 2.41 (br s, 3H), 1.26 - 1.23 (m, 3H), 1.19 (br d, *J*=4.3 Hz, 6H); LCMS $[M + H]^{+}$ 618.5.

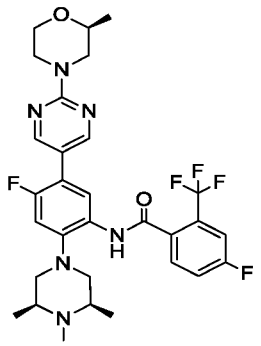
Example 452: 4-fluoro-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l -yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide



[00816] The title compound (formic acid salt, beige solid, 28.1 mg, 43%) was prepared using a similar procedure to Example 400 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-

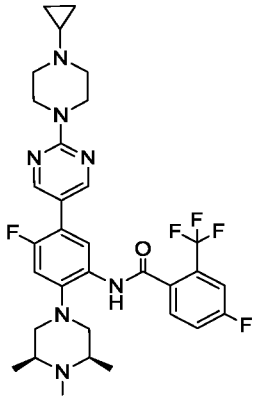
(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (49 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.40 (br s, IH), 8.03 (d, *J*=8.3 Hz, IH), 7.80 (dd, *J=5.3,* 8.3 Hz, IH), 7.65 (dd, *J*=1.7, 8.9 Hz, IH), 7.56 (t, *J*=8.2 Hz, IH), 7.17 (d, *J*=11.9 Hz, IH), 4.63 - 4.52 (m, 2H), 3.97 (br dd, *J*=2.3, 11.5 Hz, IH), 3.66 - 3.57 (m, 2H), 3.35 (br d, *J*=11.0 Hz, IH), 3.27 - 3.18 (m, 2H), 3.15 - 2.98 (m, 4H), 2.84 (br d, *J*=10.8 Hz, IH), 2.76 - 2.68 (m, 4H), 1.30 (br d, *J*=6.1 Hz, 3H), 1.23 (d, *J*=6.1 Hz, 3H); LCMS [M + H]$^+$ 591.5.

Example 453: 4-fluoro-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S, 5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



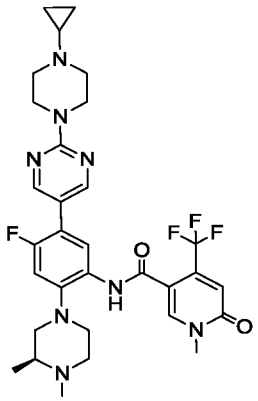
[00817] The title compound (formic acid salt, beige solid, 35.8 mg, 54%) was prepared according to a procedure similar to Example 400 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.46 (br s, IH), 8.03 (d, *J*=8.2 Hz, IH), 7.78 (dd, *J*=5.4, 8.3 Hz, IH), 7.65 (br d, *J*=8.9 Hz, IH), 7.56 (br t, *J*=8.1 Hz, IH), 7.16 (d, *J*=11.9 Hz, IH), 4.65 - 4.52 (m, 2H), 3.99 - 3.94 (m, IH), 3.67 - 3.56 (m, 2H), 3.18 (br s, 2H), 3.12 - 2.96 (m, 3H), 2.87 - 2.76 (m, 2H), 2.75 - 2.68 (m, IH), 2.66 (s, 3H), 1.30 (br d, *J*=5.7 Hz, 6H), 1.23 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 605.5.

Example 454: N-[5-[2-(4-cyclopropylpiperazin-l -yl)pyrimidin-5-yl]-4-fluoro-2-f(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide



[00818] The title compound (beige solid, 4.2 mg, 7%) was prepared according a procedure similar to Example 400 using crude (2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.03 (d, *J*=8.3 Hz, IH), 7.78 (dd, *J*=5.3, 8.5 Hz, IH), 7.66 (dd, *J*=2.2, 9.2 Hz, IH), 7.58 (t, *J*=8.3 Hz, IH), 7.11 (d, *J*=12.0 Hz, IH), 3.91 - 3.84 (m, 4H), 3.07 (br d, *J*=11.4 Hz, 2H), 2.74 (t, *J*=5.1 Hz, 4H), 2.63 (t, *J*=11.2 Hz, 2H), 2.52 - 2.43 (m, 2H), 2.34 (s, 3H), 1.76 - 1.72 (m, IH), 1.17 (d, *J*=6.2 Hz, 6H), 0.58 - 0.49 (m, 4H); LCMS $[M + H]^+$ 630.6.

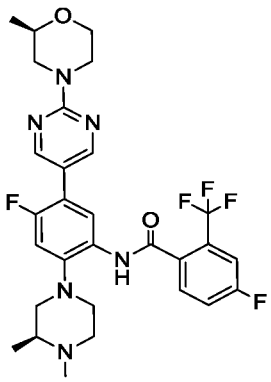
Example 455: N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-ylJ-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00819] The title compound (light beige solid, 28.3 mg, 44%) was prepared according to a procedure similar to Example 400 using crude (2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and (S)-N-(5-

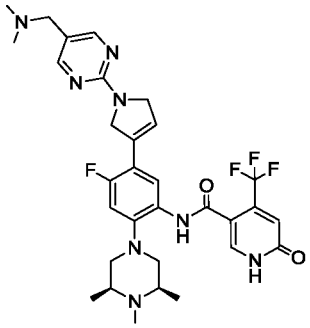
bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (49 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.54 (s, 2H), 8.27 (s, IH), 7.92 (d, *J*=8.2 Hz, IH), 7.12 (d, *J*=12.0 Hz, IH), 6.95 (s, IH), 3.86 (br s, 4H), 3.66 (s, 3H), 3.15 - 3.03 (m, 2H), 3.00 - 2.89 (m, 2H), 2.78 - 2.69 (m, 4H), 2.62 - 2.51 (m, 2H), 2.43 (br s, IH), 2.38 (s, 3H), 1.74 (br d, *J*=3.9 Hz, IH), 1.14 (d, *J*=6.2 Hz, 3H), 0.58 - 0.53 (m, 2H), 0.53 - 0.49 (m, 2H); LCMS [M + H]$^+$ 629.6.

Example 456: 4-fluoro-N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide



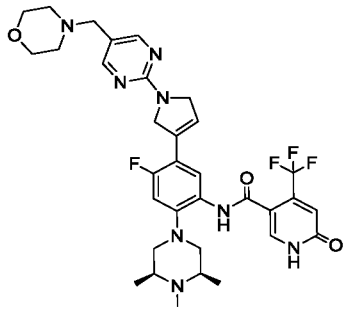
[00820] The title compound (formic acid salt, beige solid, 25.0 mg, 38%) was prepared according to a procedure similar to Example 400 using crude (R)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (49 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.03 (d, *J*=8.3 Hz, IH), 7.79 (dd, *J*=5.4, 8.4 Hz, IH), 7.66 (dd, *J*=2.3, 9.0 Hz, IH), 7.57 (dt, *J*=2.3, 8.3 Hz, IH), 7.13 (d, *J*=12.0 Hz, IH), 4.65 - 4.54 (m, 2H), 3.99 (dd, *J*=2.5, 11.6 Hz, IH), 3.68 - 3.59 (m, 2H), 3.15 - 3.01 (m, 3H), 2.99 - 2.88 (m, 2H), 2.74 (dd, *J*=10.5, 13.2 Hz, IH), 2.57 (t, *J*=10.8 Hz, IH), 2.52 - 2.44 (m, IH), 2.37 - 2.31 (m, 4H), 1.25 (d, *J*=6.2 Hz, 3H), 1.13 (d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^+$ 591.5.

Example 457: N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-2, 5-dihydropyrrol-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00821] The procedure followed was similar to Example 148 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-2,5-dihydro-lH-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.050 mmol) and dimethyl amine, 2.0M in THF (0.050 ml, 0.100 mmol) to give the title compound (23 mg, 70 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.40 - 8.34 (m, 2H), 8.04 - 7.97 (m, 1H), 7.95 - 7.85 (m, 1H), 7.08 - 7.00 (m, 1H), 6.95 - 6.89 (m, 1H), 6.55 - 6.46 (m, 1H), 4.76 - 4.72 (m, 2H), 4.57 - 4.53 (m, 2H), 3.46 - 3.42 (m, 2H), 3.11 - 3.05 (m, 2H), 2.65 - 2.58 (m, 2H), 2.56 - 2.48 (m, 2H), 2.40 - 2.36 (m, 3H), 2.33 - 2.28 (m, 6H), 1.17 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 629.8.

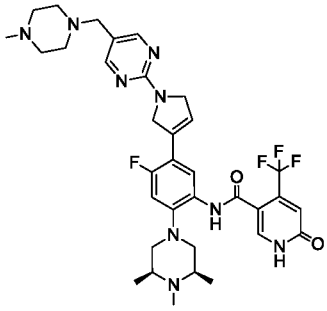
Example 458: N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl] -2,5-dihydropyrrol-3-yl] -2-[(3R,5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00822] The procedure employed was similar to that of Example 148 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-2,5-dihydro-lH-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.050 mmol) and morpholine (8.72 mg, 0.100 mmol) to give the title compound (10 mg, 28 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ =

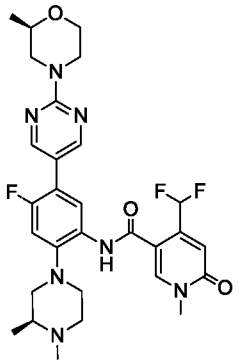
8.41 - 8.32 (m, 2H), 8.03 - 7.98 (m, 1H), 7.94 - 7.86 (m, 1H), 7.08 - 7.00 (m, 1H), 6.95 - 6.89 (m, 1H), 6.55 - 6.47 (m, 1H), 4.76 - 4.71 (m, 2H), 4.57 - 4.51 (m, 2H), 3.75 - 3.68 (m, 4H), 3.46 - 3.42 (m, 2H), 3.12 - 3.04 (m, 2H), 2.66 - 2.59 (m, 2H), 2.57 - 2.52 (m, 2H), 2.51 - 2.44 (m, 4H), 2.41 - 2.37 (m, 3H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 671.8.

Example 459: N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



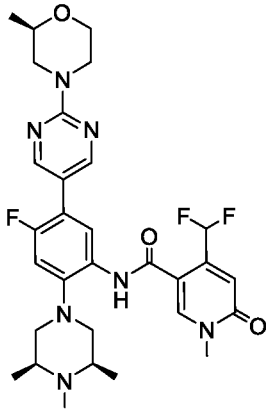
[00823] The procedure followed was similar to Example 148 using N-(4-fluoro-5-(l-(5-formylpyrimidin-2-yl)-2,5-dihydro-lH-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.050 mmol) and 1-methylpiperazine (10.02 mg, 0.100 mmol) to give the title compound (25 mg, 69 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.38 - 8.32 (m, 2H), 8.02 - 7.97 (m, 1H), 7.95 - 7.87 (m, 1H), 7.07 - 7.01 (m, 1H), 6.95 - 6.88 (m, 1H), 6.54 - 6.47 (m, 1H), 4.78 - 4.71 (m, 2H), 4.58 - 4.51 (m, 2H), 3.49 - 3.44 (m, 2H), 3.12 - 3.03 (m, 2H), 2.80 - 2.40 (m, 12H), 2.38 - 2.35 (m, 3H), 2.34 - 2.29 (m, 3H), 1.19 - 1.15 (m, 6H); LCMS [M+H]+ 584.6.

Example 460: 4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l -yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

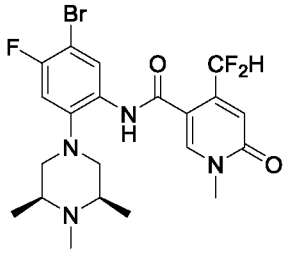


[00824] The title compound (8.1 mg, 33.7% yield) was prepared according to a procedure similar to that described for Example 383 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and (R)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (45.8 mg, 0.205 mmol). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.47 (s, IH), 8.52 (s, 2H), 8.36 (s, IH), 7.68 (d, *J*=8.4 Hz, IH), 7.47 - 7.18 (m, IH), 7.08 (d, *J*=12.2 Hz, IH), 6.65 (s, IH), 4.52 (br d, *J*=13.1 Hz, IH), 4.44 (br d, *J*=13.2 Hz, IH), 3.91 (br dd, *J*=2.4, 11.4 Hz, IH), 3.52 (s, 4H), 3.08 - 2.95 (m, 3H), 2.86 - 2.79 (m, IH), 2.76 (br d, *J*=11.0 Hz, IH), 2.67 (dd, *J*=10.5, 13.0 Hz, IH), 2.42 (br t, *J*=10.5 Hz, IH), 2.38 - 2.29 (m, IH), 2.20 (s, 3H), 1.16 (d, *J*=6.2 Hz, 3H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 586.6.

Example 461: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-5-ylj'-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yljphenyl]'-1-methyl-6-oxopyridine-3-carboxamide

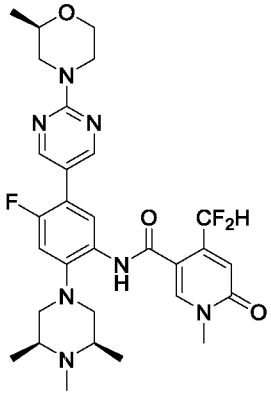


Step 1: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide



[00825] To a stirred solution of 4-(difluoromethyl)-l -methyl-6-oxo- 1,6-dihydropyridine-3-carboxylic acid (4g, 19.7mmol, leq, from Example 34, Step 4) in DMF (40mL) was added DIPEA (9.9mL, 59.0mmol, 3eq), HATU (22.4g, 59.1mmol, 3eq) and then 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (6.2g, 19.7mmol, leq) was dropwise added at 0°C-rt for 16h. TLC analysis indicated formation of polar spots. The reaction mixture was diluted with ice water (lOOmL) and extracted with EtOAc (2 X lOOmL). The organic layer was washed with brine and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (neutral alumina) using 0-5% MeOH in DCM as an eluent to afford (2.5g, 30%) as a pale brown solid. LCMS: [M+H]+ 501.07.

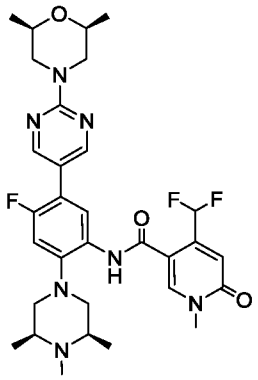
Step 2: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide



[00826] The title compound (11.0 mg, 46% yield) was prepared according to a procedure similar to that described for Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(difluoromethyl)-l -methyl-6-oxo- 1,6-dihydropyridine-3-carboxamide (20 mg, 0.040 mmol), (R)-(2-(2-

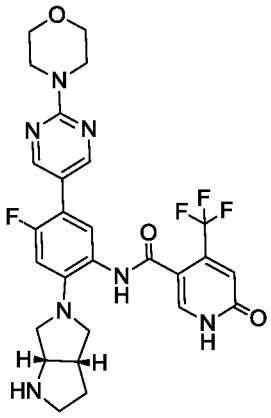
methylmorpholino)pyrimidin-5-yl)boronic acid (35.6 mg, 0.160 mmol). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.51 (br s, IH), 8.52 (s, 2H), 8.35 (s, IH), 7.67 (d, *J*=8.6 Hz, IH), 7.51 - 7.21 (m, IH), 7.06 (d, *J*=12.3 Hz, IH), 6.65 (s, IH), 4.52 (br d, *J*=13.0 Hz, IH), 4.45 (br d, *J*=13.0 Hz, IH), 3.92 (dd, *J*=2.4, 11.7 Hz, IH), 3.53 (s, 3H), 3.04 (br d, *J*=11.4 Hz, 2H), 3.01 - 2.96 (m, IH), 2.72 - 2.64 (m, IH), 2.48 - 2.43 (m, 2H), 2.37 - 2.31 (m, 2H), 2.19 (s, 3H), 1.17 (d, *J*=6.1 Hz, 3H), 1.01 (d, *J*=6.0Hz, 6H); LCMS [M+H]+: 600.6.

Example 462: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-m ethyl-6-oxopyridine-3-carboxamide



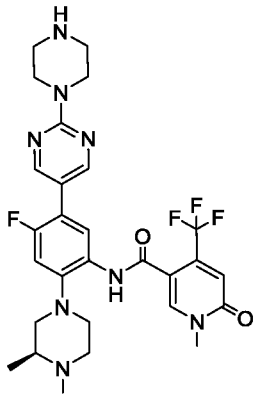
[00827] The title compound (4.8 mg, 20% yield) was prepared according to a procedure similar to that of Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (20 mg, 0.040 mmol), (2S,6R)-2,6-dimethyl-4-(5-(4,4,5, 5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)mo rpholine (19. 10 mg, 0.060 mmol). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.40 (s, IH), 8.28 (s, IH), 8.18 (br s, IH), 7.64 - 7.56 (m, 2H), 7.44 - 7.12 (m, IH), 6.96 (br d, *J*=12.3 Hz, IH), 6.88 (br d, *J*=8.8 Hz, IH), 6.57 (s, IH), 4.12 (br d, *J*=12.3 Hz, 2H), 3.61 - 3.51 (m, 2H), 3.45 (s, 3H), 2.95 (br d, *J*=10.9 Hz, 2H), 2.28 (br d, *J*=7.6 Hz, 2H), 2.11 (s, 3H), 1.10 (br d, *J*=6.1 Hz, 6H), 0.93 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 613.6.

Example 463: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3aR, 6aR)-2,3,3a,4,6,6a-hexahydro-lH-pyrrolo[2, 3-c]pyrrol-5-yl]phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



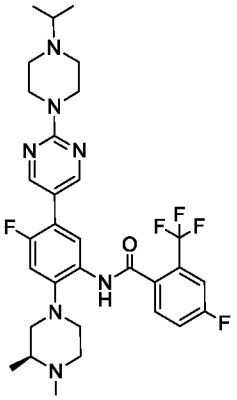
[00828] The title compound (22.5 mg, 1.219 % yield) was obtained as an off-white powder from tert-butyl (3aS,6aS)-5-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)hexahydropyrrolo[3,4-b]pyrrole-l(2H)-carboxylate (1.31 g, 2.70 mmol) and 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.96 g, 3.12 mmol) followed by TFA deprotection of the silyloxypyridine intermediate using a procedure similar to that described for the final step of Example 39. The tert-butyl (3aS,6aS)-5-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)hexahydropyrrolo[3,4-b]pyrrole-l(2H)-carboxylate was obtained from a route starting with l-Boc-3as-6as-octahydropyrrolo-3-4-b-pyrrole and l-bromo-2,4-difluoro-5-nitrobenzene through a route similar to that described in Example 34. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.70 (br. s., IH), 8.51 (s, 2H), 8.06 (s, IH), 7.50 (d, *J*=8.68 Hz, IH), 6.82 (d, *J*=13.20 Hz, IH), 6.74 (s, IH), 3.74 (d, *J*=5.01 Hz, 7H), 3.68 (d, *J*=4.89 Hz, 7H), 3.17-3.29 (m, 9H), 3.09 (d, *J*=9.05 Hz, 2H), 2.97 (dd, *J*=4.46, 9.72 Hz, 2H), 2.88 (dd, *J*=6.60, 10.39 Hz, 2H), 2.68-2.81 (m, 3H), 1.82 (dd, *J*=7.64, 12.17 Hz, IH), 1.48-1.58 (m, IH); LCMS [M+H]+ 574.5.

Example 464: N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



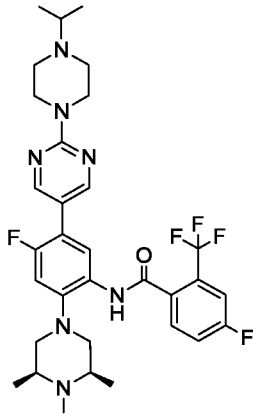
[00829] Intermediate tert-butyl (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-(l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)phenyl)pyrimidin-2-yl)piperazine-l-carboxylate (brown solid) was prepared according to a procedure similar to that of Example 31 using 2-(4-Boc-piperazino)pyrimidine-5-boronic acid pinacol ester (234 mg, 0.6 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (202 mg, 0.4 mmol). LCMS [M + H]$^+$ 689.6. Followed by deprotection using TFA (1.2 mL) in DCM (20 mL) and removal of the solvents, the residue was passed through porapak (20 cc, rinsed with DCM/2 M NH_3/MeOH), purified by prep-HPLC and Biotage Isolute SCX-2 column to give the title compound as a light yellow solid (117.4 mg, 49% over 2 steps). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.27 (s, 1H), 7.92 (d, *J*=8.2 Hz, 1H), 7.12 (d, *J*=12.1 Hz, 1H), 6.95 (s, 1H), 3.91 - 3.83 (m, 4H), 3.67 (s, 3H), 3.14 - 3.03 (m, 2H), 2.99 - 2.89 (m, 6H), 2.60 - 2.49 (m, 2H), 2.44 - 2.34 (m, 4H), 1.13 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 589.6.

Example 465: 4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-ylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-2-(trifluoromethyl)benzamide



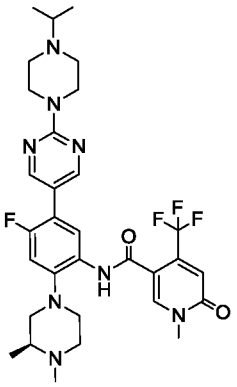
[00830] To a mixture of 2-chloropyrimidine-5-boronic acid (633 mg, 4 mmol) and 1-isopropylpiperazine (0.57 mL, 4.4 mmol) in EtOH (8 mL) was added triethylanune (0.84 mL, 6 mmol). The resulting mixture (a cloudy suspension, never observed to clear) was stirred at 75 °C for 1 h. Solvents were removed and the residue was dried under high vacuum to give crude (2-(4-isopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid as a beige solid (1.272g, 79% purity assuming full conversion). LCMS $[M + H]^+$ found 251.4. The title compound (light beige solid, 34.1 mg, 54%) was prepared by a procedure similar to Example 400 using crude (2-(4-isopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.03 (d, *J*=8.2 Hz, 1H), 7.80 (dd, *J=5.3,* 8.4 Hz, 1H), 7.66 (dd, *J*=2.1, 9.0 Hz, 1H), 7.57 (t, *J*=8.3 Hz, 1H), 7.13 (d, *J*=12.0 Hz, 1H), 3.91 (br s, 4H), 3.14 - 3.03 (m, 2H), 3.00 - 2.88 (m, 2H), 2.83 - 2.73 (m, 1H), 2.67 (br t, *J*=4.7 Hz, 4H), 2.58 (br t, *J*=10.8 Hz, 1H), 2.52 - 2.41 (m, 1H), 2.39 - 2.31 (m, 4H), 1.18 - 1.11 (m, 9H); LCMS $[M + H]^+$ 618.6.

Example 466: 4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00831] The title compound (pale beige solid, 34.3 mg, 54%) was prepared by a procedure similar to that of Example 31 using crude (2-(4-isopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and (N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.03 (d, *J*=8.3 Hz, IH), 7.78 (dd, *J*=5.3, 8.4 Hz, IH), 7.66 (dd, *J*=2.2, 9.0 Hz, IH), 7.57 (dt, *J*=2.2, 8.2 Hz, IH), 7.11 (d, *J*=12.0 Hz, IH), 3.91 (br s, 4H), 3.06 (br d, *J*=11.4 Hz, 2H), 2.84 - 2.74 (m, IH), 2.72 - 2.60 (m, 6H), 2.47 (br s, 2H), 2.38 - 2.31 (m, 3H), 1.17 (br d, *J*=6.4 Hz, 6H), 1.15 (br d, *J*=6.5 Hz, 6H); LCMS $[M + H]^+$ 632.7.

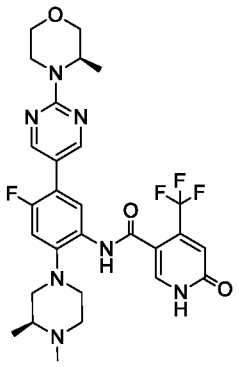
Example 467: N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00832] The title compound (beige solid, 25.4 mg, 40%) was prepared according to a procedure similar to that of Example 31 using crude (2-(4-isopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.27 mmol) and (S)-N-(5-

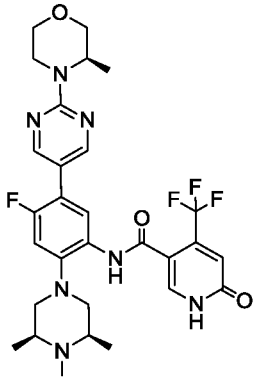
bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.27 (s, IH), 7.92 (d, *J*=8.3 Hz, IH), 7.12 (d, *J*=12.1 Hz, IH), 6.95 (s, IH), 3.91 (br s, 4H), 3.67 (s, 3H), 3.15 - 3.03 (m, 2H), 2.99 - 2.87 (m, 2H), 2.85 - 2.75 (m, IH), 2.68 (br s, 4H), 2.61 - 2.50 (m, 2H), 2.45 - 2.34 (m, 4H), 1.18 - 1.11 (m, 9H); LCMS [M + H]$^+$ 631.6.

Example 468: N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l-ylJ-5-[2-[(3R)-3-methylmorpholin-4-ylJpyrimidin-5-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide



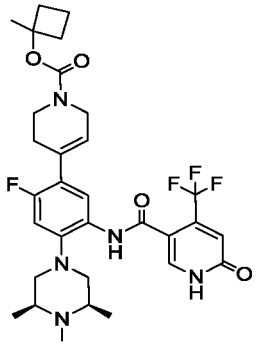
[00833] To a mixture of 2-chloropyrimidine-5-boronic acid (633 mg, 4 mmol) and (R)-3-methylmorpholine (0.55 mL, 4.8 mmol) in EtOH (8 mL) was added triethylamine (0.84 mL, 6 mmol). The resulting mixture was stirred for 1 h at 75 °C for 5 h. Solvents were removed to give a dark orange oil that was dried under high vacuum to give crude (R)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid as a yellow foam (953 mg, 84% purity assuming 90% conversion based on LCMS). LCMS [M+ H]$^+$ 224.3. The title compound (beige solid, 6.3 mg, 10%) was prepared by a procedure similar to that used in Example 31 using crude (R)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.3 mmol x 2) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-4-(trifluoromethyl)-l,6-&hydropyridine-3-carboxamide (49.1 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.01 (s, IH), 7.93 (br d, *J*=8.2 Hz, IH), 7.13 (br d, *J*=l 1.7 Hz, IH), 6.90 (s, IH), 4.75 (br d, *J*=5.3 Hz, IH), 4.38 (br d, *J*=12.6 Hz, IH), 4.02 - 3.96 (m, IH), 3.80 (br d, *J*=11.5 Hz, IH), 3.76 - 3.69 (m, IH), 3.63 - 3.53 (m, IH), 3.21 - 2.63 (m, 8H), 2.54 (br s, 3H), 1.31 (d, *J*=6.7 Hz, 3H), 1.21 (br s, 3H); LCMS [M+ H]$^+$ 590.6.

Example 469: N-[4-fluoro-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



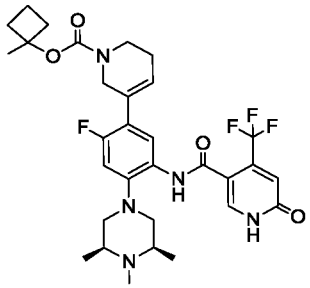
[00834] The title compound (light beige solid, 6.4 mg, 10%) was prepared according to a procedure similar to that described in Example 31 using crude (R)-(2-(3-methylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol x 2) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.00 (s, IH), 7.92 (br d, *J*=8.1 Hz, IH), 7.12 (br d, *J*=11.9 Hz, IH), 6.91 (s, IH), 4.79 - 4.72 (m, IH), 4.41 - 4.36 (m, IH), 4.00 (br dd, *J*=3.5, 11.3 Hz, IH), 3.81 (d, *J*=11.5 Hz, IH), 3.73 (dd, *J*=2.9, 11.6 Hz, IH), 3.57 (dt, *J*=2.9, 11.9 Hz, IH), 3.12 (br d, *J*=11.0 Hz, 2H), 2.95 - 2.68 (m, 4H), 2.52 (br s, 3H), 1.32 (d, *J*=6.7 Hz, 3H), 1.24 (d, *J*=4.8 Hz, 6H); LCMS [M + H]$^{+}$ 604.5.

Example 470: (1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



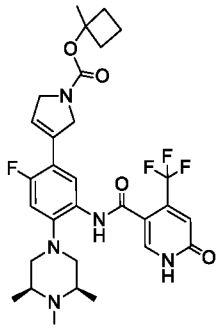
[00835] The procedure followed was similar to that described in Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (35 mg, 0.069 mmol) in dichloromethane (DCM) (3 ml) was added triethylamine (0.019 ml, 0.138 mmol) and a solution of 1-methylcyclobutyl (4-nitrophenyl) carbonate (22 mg, 0.070 mmol, prepared as described in *J. Med. Chem.* **2016,** *59* (18), pp 8345-8368) to give the title compound (18 mg, 38% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.80 (m, 1H), 7.70 - 7.61 (m, 1H), 6.87 - 6.82 (m, 1H), 6.81 - 6.77 (m, 1H), 5.92 - 5.83 (m, 1H), 4.04 - 3.92 (m, 2H), 3.61 - 3.47 (m, 2H), 2.94 - 2.89 (m, 2H), 2.51 - 2.39 (m, 6H), 2.31 - 2.23 (m, 5H), 2.08 - 2.00 (m, 2H), 1.78 - 1.69 (m, 1H), 1.65 - 1.56 (m, 1H), 1.50 - 1.45 (m, 3H), 1.07 - 1.03 (m, 6H); LCMS [M+H]+ 620.7.

Example 471: (1-methylcyclobutyl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



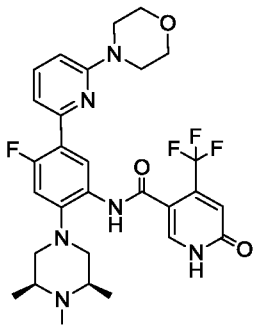
[00836] The procedure followed was similar to Example 470 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (35 mg, 0.069 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (21.66 mg, 0.069 mmol) to give the title compound (19 mg, 41% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.80 (m, 1H), 7.70 - 7.59 (m, 1H), 6.88 - 6.82 (m, 1H), 6.81 - 6.77 (m, 1H), 6.03 - 5.96 (m, 1H), 4.17 - 4.06 (m, 2H), 3.56 - 3.42 (m, 2H), 2.96 - 2.89 (m, 2H), 2.53 - 2.39 (m, 4H), 2.29 - 2.20 (m, 7H), 2.07 - 1.98 (m, 2H), 1.76 - 1.67 (m, 1H), 1.65 - 1.55 (m, 1H), 1.50 - 1.42 (m, 3H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 620.8.

Example 472: (1-methylcyclobutyl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate



[00837] The procedure followed was similar to Example 470 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (19.09 mg, 0.061 mmol) to give the title compound (27 mg, 70 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 - 7.81 (m, 1H), 7.74 - 7.62 (m, 1H), 6.94 - 6.85 (m, 1H), 6.83 - 6.77 (m, 1H), 6.29 - 6.18 (m, 1H), 4.47 - 4.34 (m, 2H), 4.27 - 4.13 (m, 2H), 2.99 - 2.89 (m, 2H), 2.53 - 2.38 (m, 4H), 2.34 - 2.22 (m, 5H), 2.10 - 2.00 (m, 2H), 1.79 - 1.68 (m, 1H), 1.66 - 1.56 (m, 1H), 1.49 (d, *J*=3.8 Hz, 3H), 1.08 - 1.00 (m, 6H); LCMS [M+H]+ 606.7.

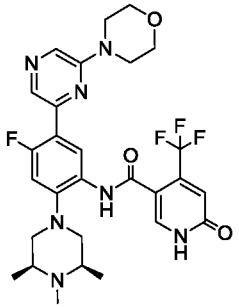
Example 473: N-[4-fluoro-5-(5-morpholin-4-ylpyridin-2-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ne-3-carboxamide



[00838] The procedure followed was similar to Example 384 using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (103 mg, 0.126 mmol) and 4-(6-bromopyridin-2-yl)morpholine (33.8 mg, 0.139 mmol) to give the title

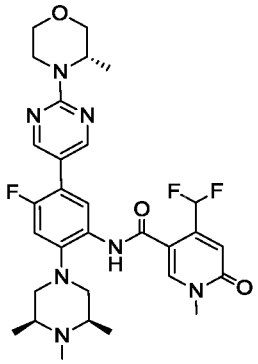
compound (74.3 mg, 28% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.51 (d, *J* = 8.3 Hz, 1H), 7.91 (s, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.99 (d, *J* = 12.9 Hz, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 3.83 - 3.80 (m, 4H), 3.58 - 3.56 (m, 4H), 3.11 (d, *J* = 10.4 Hz, 2H), 2.67 - 2.59 (m, 4H), 2.40 (s, 3H), 1.18 (d, *J* = 5.7 Hz, 6H); LCMS [M+l] $^+$ = 587.46.

Example 474: N-[4-fluoro-5-(5-morpholin-4-ylpyrazin-2-yl)-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



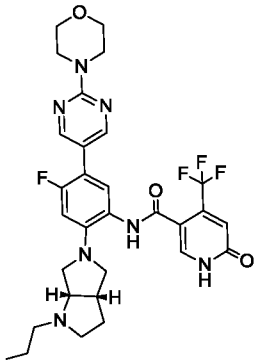
[00839] The title compound (74.4 mg, 38.3 mg) was prepared similar to the sequence described above for the preparation of Example 384 using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (103 mg, 0.126 mmol) and 4-(6-bromopyrazin-2-yl)morpholine (33.9 mg, 0.139 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.51 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 2.1 Hz, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 7.04 (d, *J* = 13.0 Hz, 1H), 6.91 (s, 1H), 3.84 - 3.81 (m, 4H), 3.69 - 3.66 (m, 4H), 3.14 (d, *J* = 11.4 Hz, 2H), 2.63 (t, *J* = 11.1 Hz, 2H), 2.56 (d, *J* = 6.4 Hz, 2H), 2.37 (s, 3H), 1.17 (d, *J* = 6.1 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -63.75 (s), -116.22 (s); LCMS [M+l] $^+$ = 588.44.

Example 475: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(3R)-3-methylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



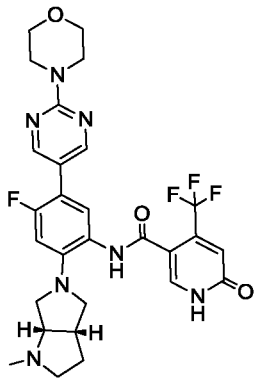
[00840] The title compound (10.6 mg, 44.6% yield) was prepared according to a procedure similar to that described in Example 31 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (20 mg, 0.040 mmol) and (S)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid (35.6 mg, 0.160 mmol). ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (br s, IH), 8.52 (s, 2H), 8.34 (s, IH), 7.67 (d, *J*=8.6 Hz, IH), 7.50 - 7.18 (m, IH), 7.05 (d, *J*=12.2 Hz, IH), 6.64 (s, IH), 4.65 (br dd, *J*=2.3, 6.7 Hz, IH), 4.33 - 4.24 (m, IH), 3.93 (br dd, *J*=3.1, 11.2 Hz, IH), 3.73 (d, *J*=11.4 Hz, IH), 3.60 (dd, *J*=2.9, 11.4 Hz, IH), 3.52 (s, 3H), 3.44 (dt, *J*=2.8, 11.8 Hz, IH), 3.19 (dt, *J*=3.7, 13.0 Hz, IH), 3.03 (br d, *J*=11.0 Hz, 2H), 2.48 - 2.43 (m, 2H), 2.39 - 2.30 (m, 2H), 2.18 (s, 3H), 1.21 (d, *J*=6.7 Hz, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 600.5.

Example 476: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3aR, 6aR)-l-propyl-2, 3,3a, 4,6, 6a-hexahydropyrrolo[2, 3-c]pyrrol-5-yl]phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00841] To a solution of N-(4-fluoro-2-(hexahydropyrrolo[3,4-b]pyrrol-5(lH)-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamideTFA (70 mg, 0.064 mmol, obtained from Example 463) in 1,2-dichloroethane (DCE) (3 ml) was added propionaldehyde (19.4 mg, 0.334 mmol) and acetic acid (36 mg, 0.599 mmol) at room temperature. The reaction mixture was stirred for 15 minutes and then sodium triacetoxyborohydride (54.0 mg, 0.255 mmol) was added. After 90 min the reaction mixture was poured into 20 mL of a saturated solution of NaHCCb. The product was extracted using DCM (3x30mL). The organic phase was dried over MgSC>4 and after filtration and solvent removal the crude material was dry loaded and purified by Flash chromatography [0-30% MeOH/DCM] to afford the N-(4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-(l-propylhexahydropyrrolo[3,4-b]pyrrol-5(lH)-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (10.7 mg, 0.016 mmol, 25.6 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.58 (br. s., 1H), 9.63 (br. s., 1H), 8.51 (s, 2H), 8.02 (br. s., 1H), 7.53 (d, *J*=7.83 Hz, 1H), 6.76-6.88 (m, 2H), 3.72-3.78 (m, 5H), 3.65-3.70 (m, 5H), 3.19 (br. s., 1H), 3.11 (br. s., 1H), 2.92-3.07 (m, 3H), 2.74 (d, *J*=9.78 Hz, 1H), 2.43 (br. s., 1H), 2.36 (br. s., 1H), 2.19 (br. s., 2H), 1.98 (br. s., 1H), 1.61 (br. s., 1H), 1.35 (br. s., 1H), 1.23 (br. s., 1H), 0.81-0.96 (m, 1H), 0.77 (t, *J*=7.09 Hz, 3H); LCMS [M+H]+ 616.6.

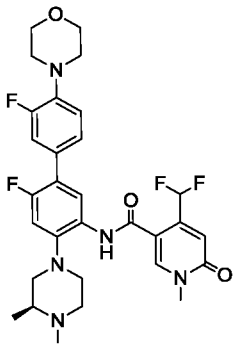
Example 477: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3aR, 6aR)-l-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2, 3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00842] A similar procedure was used as for Example 476 with N-(4-fluoro-2-(hexahy dropyrrolo [3,4-b] pyrrol -5 (1H)-yl)-5 -(2-mo rpholinopyrimidin-5 -yl)phenyl)-6-

oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamideTFA (87 mg, 0.079 rnmol) and formaldehyde solution, 37% weight in water (36 mg, 0.444 rnmol) to afford the title compound (21.2 mg, 0.034 rnmol, 42.8 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 12.56 (br. s., 1H), 9.69 (s, 1H), 8.51 (s, 2H), 8.01 (s, 1H), 7.50 (d, *J*=8.68 Hz, 1H), 6.76-6.83 (m, 2H), 3.71-3.76 (m, 5H), 3.65-3.69 (m, 5H), 3.34-3.40 (m, 2H), 3.19-3.29 (m, 3H), 3.10 (dd, *J*=4.59, 9.48 Hz, 1H), 3.04 (dd, *J*=4.83, 10.33 Hz, 1H), 2.94 (t, *J*=7.58 Hz, 1H), 2.71-2.82 (m, 2H), 2.61-2.68 (m, 1H), 2.32 (s, 1H), 2.15-2.24 (m, 4H), 1.93-2.01 (m, 1H), 1.53-1.63 (m, 1H); LCMS [M+H]+ 588.5.

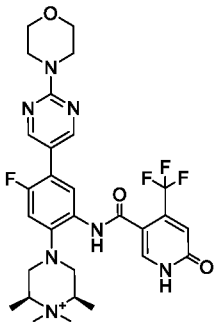
Example 478: 4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[00843] To a suspension of (S)-4-(difluoromethyl)-N-(4-(3,4-dimethylpiperazin-l-yl)-3',6-difluoro-4'-mo rpholino-[l, 1'-biphenyl]-3-yl)-6-oxo-l,6-dihydropyridine-3-carboxamide (39 mg, 0.068 rnmol) and cesium carbonate (24.37 mg, 0.075 rnmol) in N,N-dimethylformamide (3 ml) was added Mel (4.66 µï, 0.075 rnmol) at room temperature. The reaction mixture was stirred for 90 min at room temperature. Then the reaction mixture was poured into water and the product was extracted by DCM (3x20mL). The organic phase was dried over $MgSO_4$ and after filtration and solvent removal the crude material was dissolved in MeOH and passed through a PoraPak Rxn CX (20cc-2g) cartridge in a catch and elute method. The cartridge was washed with MeOH (20mL) and the solution of product in MeOH was added onto the cartridge. The cartridge was rinsed with MeOH (2x20mL) and the product was released with a solution of lOmL (NH_3 in MeOH at 7N) in 10 mL of MeOH to afford the free base of (S)-4-(difluoromethyl)-N-(4-(3,4-dimethylpiperazin-l-yl)-3',6-difluoro-4'-mo ϕ holino-[l, 1'-biphenyl]-3-yl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (32.4 mg, 0.052

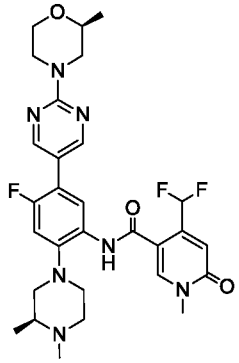
mmol, 76 % yield) as a white powder. ¾H NMR (500MHz, DMSO-d6) δ = 9.46 (s, 1H), 8.35 (s, 1H), 7.70 (d, *J*=8.80 Hz, 1H), 7.21-7.34 (m, 3H), 7.09-7.17 (m, 1H), 7.05 (d, *J*=12.72 Hz, 1H), 6.64 (s, 1H), 3.73-3.79 (m, 4H), 3.52 (s, 3H), 3.00-3.10 (m, 6H), 2.72-2.89 (m, 2H), 2.43 (t, *J*=10.27 Hz, 1H), 2.35 (d, *J*=6.36 Hz, 1H), 2.21 (br. s., 4H), 0.98 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 588.4.

Example 479: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 5SJ-3,4,4,5-tetramethylpiperazin-4-ium-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



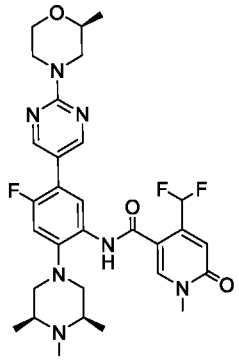
[00844] To a suspension of N-(4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (60 mg, 0.102 mmol) in acetonitrile (3 ml) was added iodomethane (8.24 µï, 0.132 mmol) at room temperature. The reaction mixture was stirred for 15 minutes at room temperature and then DCM (3.00 mL) was added to dissolve all the product. After 30 minutes, Mel (60 µï, 0.961 mmol) was added at room temperature and stirred for overnight. The solvents were removed under vacuum and the product was triturated in **Et_20 .** After filtration the pale yellow powder gave the (2R,6S)-4-(5-fluoro-4-(2-morpholinopyriinidin-5-yl)-2-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3 -carboxamido)phenyl)- 1,1,2,6-tetramethylpiperazin- 1-ium, Iodide, I-[BC] (61.2 mg, 0.079 mmol, 77 % yield). ¾ NMR (500MHz, DMSO-d6) δ = 12.60 (br. s., 1H), 9.54 (s, 1H), 8.54 (s, 2H), 7.99 (d, *J*=8.56 Hz, 2H), 7.33 (d, *J*=l 1.98 Hz, 1H), 6.84 (s, 1H), 3.82-3.90 (m, 2H), 3.74-3.78 (m, 5H), 3.66-3.70 (m, 5H), 3.14-3.27 (m, 5H), 3.11 (s, 3H), 2.88 (s, 3H), 1.34 (d, *J*=6.60 Hz, 7H); LCMS [M]+ 604.5.

Example 480: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l -yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide



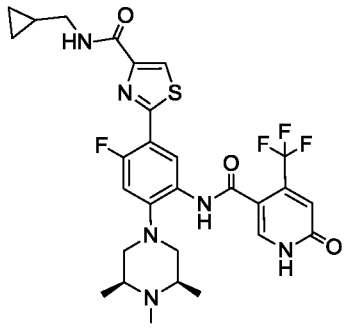
[00845] The title compound (light beige solid, 31.6 mg, 52%) was prepared by a procedure similar to that of Example 40 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.27 (s, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.12 (d, *J*=12.1 Hz, 1H), 6.95 (s, 1H), 4.65 - 4.54 (m, 2H), 4.01 - 3.96 (m, 1H), 3.69 - 3.59 (m, 5H), 3.15 - 3.04 (m, 3H), 3.01 - 2.89 (m, 2H), 2.77 - 2.70 (m, 1H), 2.64 - 2.50 (m, 2H), 2.43 (br s, 1H), 2.38 (s, 3H), 1.25 (d, *J*=6.2 Hz, 3H), 1.14 (d, *J*=6.4 Hz, 3H); LCMS $[M + H]^{+}$ 604.5.

Example 481: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl] -2-[(3S,5R)-3,4,5-trimethylpiperazin-l -yljphenyl] -1-methyl-6-oxopyridine-3-carboxamide

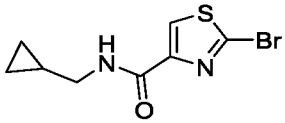


[00846] The title compound (off white solid, 12.9 mg, 21%) was prepared using a procedure similar to that in Example 29 using crude (S)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide (52 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.26 (s, 1H), 7.91 (d, *J*=8.3 Hz, 1H), 7.11 (d, *J*=12.0 Hz, 1H), 6.94 (s, 1H), 4.64 - 4.52 (m, 2H), 3.98 (dd, *J*=2.6, 11.4 Hz, 1H), 3.68 - 3.58 (m, 5H), 3.12 - 3.03 (m, 3H), 2.76 - 2.54 (m, 5H), 2.41 (br s, 3H), 1.26 - 1.23 (m, 3H), 1.19 (br d, *J*=4.3 Hz, 6H); LCMS $[M + H]^+$ 618.5.

Example 482: N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenylj-l ,3-thiazole-4-carboxamide

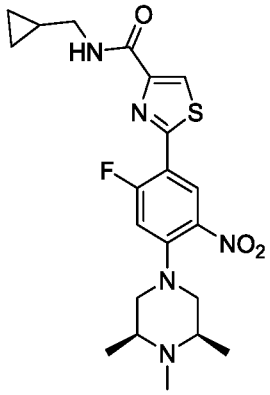


Step 1: 2-bromo-N-(cyclopropylmethyl)thiazole-4-carboxamide



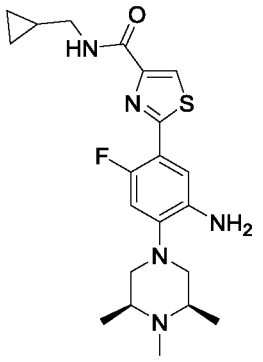
[00847] 2-Bromo-4-thiazolecarboxylic acid (0.10 g, 0.48 mmol) was activated with HATU (0.27 g, 0.72 mmol) and N,N-diisopropylethylamine (0.13 mL, 0.72 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a stirring solution of aminomethylcyclopropane (0.06 mL, 0.72 mmol) in DMF (1 mL) at room temperature. After stirring at room temperature for 18 h the DMF was removed under reduced pressure. The residue was partitioned between DCM (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The decanted organic layer was concentrated onto celite and purified by flash chromatography [EtOAc/hexanes] to afford 2-bromo-N-(cyclopropylmethyl)thiazole-4-carboxamide (0.10 g, 82 %). LCMS [M+H]+: 261.2.

Step 2: N-(cyclopropylmethyl)-2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazole-4-carboxamide



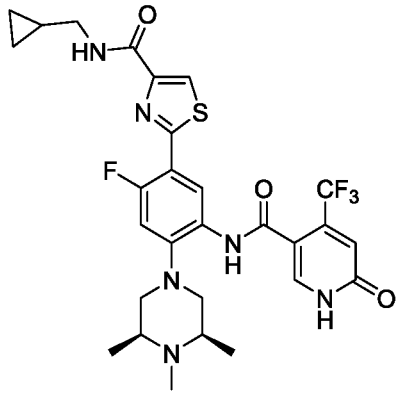
[00848] A reaction vial was charged with a mixture of cis-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2,6-trimethylpiperazine (0.050 g, 0.13 mmol), 2-bromo-N-(cyclopropylmethyl)thiazole-4-carboxamide (0.040 g, 0.14 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.013 mmol). The vial was sealed with a septum then evacuated and backfilled with nitrogen. 1,4-Dioxane (3 mL) and 2 M aqueous sodium carbonate (1.0 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated in an aluminum block at 95 °C for 5 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford N-(cyclopropylmethyl)-2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazole-4-carboxamide (0.026 g, 45 %). LCMS [M+H]+: 448.4.

Step 3: 2-(5-amino-2-fluoro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)thiazole-4-carboxamide



[00849] A solution of N-(cyclopropylmethyl)-2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazole-4-carboxamide (0.026 g, 0.058 mmol) and tin(II) chloride (0.033 g, 0.17 mmol) in a mixture of EtOH (3 mL) and MeOH (1 mL) was heated to 75 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash [0.5 - 10% MeOH/DCM + 0.5% NH_4OH] to afford 2-(5-amino-2-fluoro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)thiazole-4-carboxamide (0.017 g, 70 %). LCMS [M+H]+: 418.4.

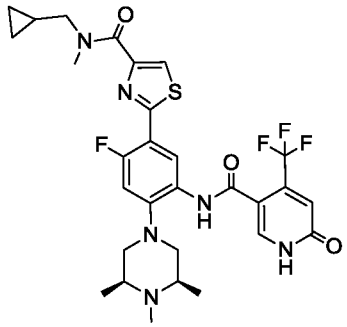
Step 4: N-(cyclopropylmethyl)-2-(2-fluoro-5-(6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamido)-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazole-4-carboxamide



[00850] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.025 g, 0.081 mmol) was activated with HATU (0.031 g, 0.081 mmol) and N,N-diisopropylethylamine (0.014 mL, 0.081 mmol) in DMF (0.5 mL) at room temperature. The solution of activated acid was added to a solution of 2-(5-amino-2-fluoro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)thiazole-4-carboxamide (0.017 g, 0.041 mmol) in DMF (0.5 mL) and the reaction was heated to 50 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyloxy protected pyridine intermediate was dissolved in DCM (2 mL) and treated with TFA (0.7 mL) at room temperature. After stirring for 18 h the volatiles were removed under a stream of air and the product was isolated with a catch and release protocol using a SCX2 silica cartridge. The product was further purified by reverse phase chromatography [5-95% MeCN / 10 mM NH_4HCO_3] to afford the title compound N-(cyclopropylmethyl)-2-(2-fluoro-5-(6-oxo-4-

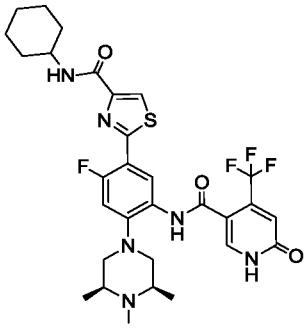
(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazole-4-carboxamide (0.008 g, 32 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.56 (br s, 1H), 9.71 (s, 1H), 8.44 (br t, *J*=5.9 Hz, 1H), 8.37 - 8.28 (m, 2H), 8.00 (s, 1H), 7.10 (d, *J*=13.1 Hz, 1H), 6.83 (s, 1H), 3.22 - 3.12 (m, 6H), 2.34 (br d, *J*=6.0 Hz, 2H), 2.19 (s, 3H), 1.10 - 1.04 (m, 1H), 1.01 (br d, *J*=5.9 Hz, 6H), 0.46 - 0.41 (m, 2H), 0.29 - 0.23 (m, 2H); LCMS [M+H]+: 607.3.

Example 483: N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-4-carboxamide



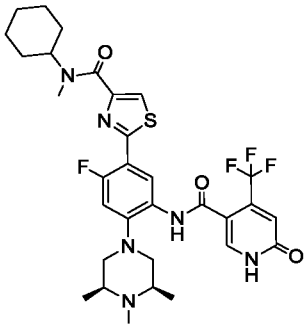
[00851] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using 1-cyclopropyl-N-methylmethanamine in place of aminomethyl cyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.67 - 9.59 (m, 1H), 8.42 - 8.33 (m, 1H), 8.14 (s, 1H), 7.97 - 7.85 (m, 1H), 7.11 (br d, J=12.7 Hz, 1H), 6.81 (s, 1H), 3.19 - 3.11 (m, 4H), 3.07 (s, 3H), 2.39 - 2.32 (m, 2H), 2.19 (s, 3H), 1.17 - 1.10 (m, 1H), 1.00 (br d, *J*=6.7 Hz, 6H), 0.53 - 0.41 (m, 2H), 0.29 (br s, 1H), 0.19 - 0.10 (m, 1H); LCMS [M+H]+: 621.5.

Example 484: N-Cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-4-carboxamide



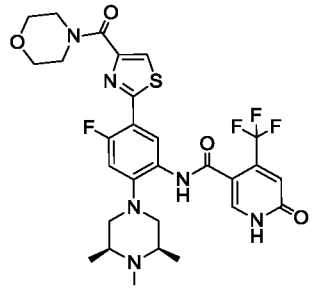
[00852] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using cyclohexylamine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.60 (br s, 1H), 9.71 (s, 1H), 8.36 - 8.28 (m, 2H), 8.00 - 7.94 (m, 2H), 7.09 (d, *J*=13.3 Hz, 1H), 6.83 (s, 1H), 3.85 - 3.71 (m, 2H), 3.16 (br d, *J*=\ 1.1 Hz, 2H), 2.33 (br s, 2H), 2.19 (s, 3H), 1.86 - 1.79 (m, 2H), 1.71 (br d, *J*=12.5 Hz, 2H), 1.59 (br d, *J*=13.2 Hz, 1H), 1.44 - 1.26 (m, 5H), 1.20 - 1.10 (m, 3H), 1.01 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 635.5.

Example 485: N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-4-carboxamide



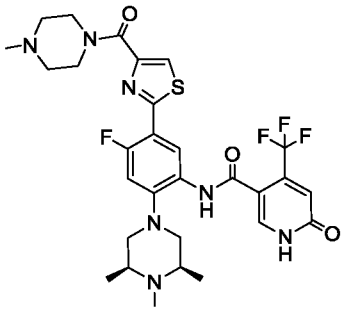
[00853] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using N-methylcyclohexylamine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.64 (br s, 1H), 8.43 - 8.31 (m, 1H), 8.17 - 8.08 (m, 1H), 7.99 - 7.92 (m, 1H), 7.87 (br s, 1H), 7.17 - 6.99 (m, 1H), 6.82 (s, 1H), 4.40 - 4.28 (m, 1H), 4.00 - 3.86 (m, 1H), 3.15 (br d, *J*=10.8 Hz, 3H), 2.89 (s, 3H), 2.36 (br d, *J*=1.6 Hz, 3H), 2.20 (s, 3H), 1.78 (br d, *J*=8.8 Hz, 3H), 1.73 - 1.62 (m, 4H), 1.62 - 1.51 (m, 3H), 1.02 (br d, *J*=5.7 Hz, 6H); LCMS [M+H]+: 649.5.

Example 486: N-[4-fluoro-5-[4-(morpholine-4-carbonyl)-l, 3-thiazol-2-yl]-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



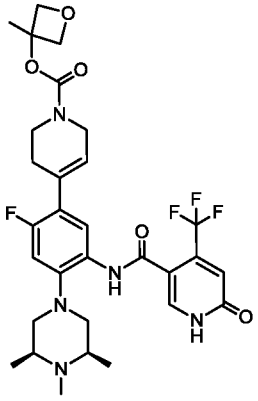
[00854] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using morpholine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.64 (s, IH), 8.40 (d, *J*=8.2 Hz, IH), 8.21 (s, IH), 7.90 (s, IH), 7.10 (d, *J*=13.2 Hz, IH), 6.81 (s, IH), 3.74 - 3.64 (m, 8H), 3.14 (br d, *J*=11.0 Hz, 3H), 2.36 (br t, *J*=6.8 Hz, 3H), 2.20 (s, 3H), 1.02 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+: 623.4.

Example 487: N-[4-fluoro-5-[4-(4-methylpiperazine-l -carbonyl)-l ,3-thiazol-2-yl]-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



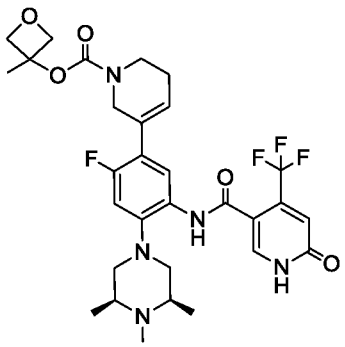
[00855] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using 1-methylpiperazine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.65 (s, IH), 8.41 (d, *J*=8.1 Hz, IH), 8.17 (s, IH), 7.88 (s, IH), 7.10 (d, *J*=13.1 Hz, IH), 6.81 (s, IH), 3.66 (br s, 4H), 3.14 (br d, *J*=11.0 Hz, 2H), 2.37 (br s, 5H), 2.20 (br s, 6H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 636.5.

Example 488: (3-methyloxetan-3-yl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



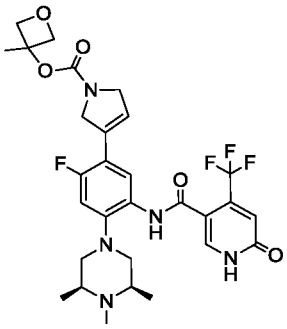
[00856] The procedure followed was similar to that of Example 472 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (35 mg, 0.069 mmol) and 3-methyloxetan-3-yl (4-nitrophenyl) carbonate (20.08 mg, 0.079 mmol) to give the title compound (29 mg, 64 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.85 - 7.81 (m, 1H), 7.70 - 7.61 (m, 1H), 6.88 - 6.82 (m, 1H), 6.81 - 6.76 (m, 1H), 5.94 - 5.85 (m, 1H), 4.72 - 4.67 (m, 2H), 4.42 - 4.37 (m, 2H), 4.10 - 3.93 (m, 2H), 3.65 - 3.49 (m, 2H), 2.95 - 2.89 (m, 2H), 2.49 - 2.39 (m, 6H), 2.28 - 2.24 (m, 3H), 1.66 - 1.62 (m, 3H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 622.5.

Example 489: (3-methyloxetan-3-yl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



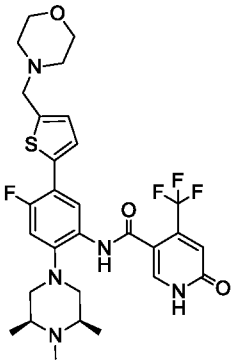
[00857] The procedure followed was similar to Example 472 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) 3-methyloxetan-3-yl (4-nitrophenyl) carbonate (17.96 mg, 0.071 mmol) to give the title compound (23 mg, 60% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.80 (m, 1H), 7.70 - 7.59 (m, 1H), 6.89 - 6.82 (m, 1H), 6.82 - 6.76 (m, 1H), 6.05 - 5.96 (m, 1H), 4.72 - 4.66 (m, 2H), 4.41 - 4.36 (m, 2H), 4.20 - 4.10 (m, 2H), 3.57 - 3.46 (m, 2H), 2.95 - 2.89 (m, 2H), 2.53 - 2.39 (m, 4H), 2.28 - 2.23 (m, 5H), 1.65 - 1.61 (m, 3H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 622.7.

Example 490: (3-methyloxetan-3-yl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -2,5-dihydropyrrole-l-carboxylate



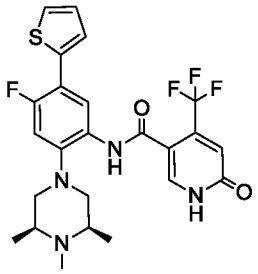
[00858] The procedure followed was similar to Example 472 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (34 mg, 0.069 mmol) and 3-methyloxetan-3-yl (4-nitrophenyl) carbonate (20.93 mg, 0.083 mmol) to give the title compound (29 mg, 66 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 - 7.82 (m, 1H), 7.75 - 7.65 (m, 1H), 6.93 - 6.87 (m, 1H), 6.83 - 6.78 (m, 1H), 6.28 - 6.21 (m, 1H), 4.75 - 4.69 (m, 2H), 4.51 - 4.36 (m, 4H), 4.32 - 4.19 (m, 2H), 2.98 - 2.90 (m, 2H), 2.53 - 2.45 (m, 2H), 2.45 - 2.36 (m, 2H), 2.29 - 2.24 (m, 3H), 1.68 - 1.61 (m, 3H), 1.07 - 1.02 (m, 6H); LCMS [M+H]+ 608.6

Example 491: N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-2-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00859] The title compound (62.5 mg, 54% yield) was prepared by a method similar to that of Example 39 using N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (62.27 mg, 0.103 mmol) and 5-((morpholino)methyl) -2-thiopheneboronic acid pinacol ester (47.7 mg, 0.154 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.95 (s, 1H), 7.30 (d, *J* = 3.3 Hz, 1H), 7.04 (d, *J* = 12.5 Hz, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 6.91 (s, 1H), 3.75 (s, 2H), 3.72 - 3.70 (m, 4H), 3.05 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.53 (s, 6H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l] $^+$ = 608.45.

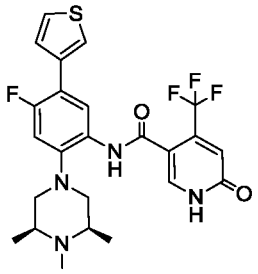
Example 492: N-[4-fluoro-2-[(3R, 5SJ-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-2-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00860] The title compound (50.7 mg, 32% yield) was prepared using a similar procedure to Example 39 using N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (60.4 mg, 0.100 mmol) and thiophene-2-boronic acid (19.2 mg, 0.150 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.96 (s, 1H), 7.45 (d, *J* = 4.8 Hz, 2H), 7.12 (t, *J* = 4.3 Hz, 1H), 7.05 (d, *J* = 12.5 Hz,

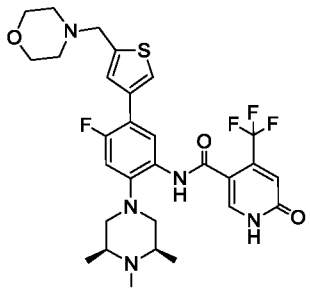
1H), 6.91 (s, 1H), 3.05 (d, *J* = 11.3 Hz, 2H), 2.61 (t, *J* = 11.1 Hz, 2H), 2.54 (d, *J* = 6.3 Hz, 2H), 2.37 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 6H); LCMS [M+l] $^{+}$ = 509.14.

Example 493: N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-3-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00861] The title compound (52.1 mg, 29% yield) was prepared by a similar procedure to that of Example 39 using N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (62 mg, 0.102 mmol) and 3-thienylboronic acid (19.65 mg, 0.154 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.68 - 7.65 (m, 1H), 7.49 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.04 (d, *J* = 12.4 Hz, 1H), 6.91 (s, 1H), 3.06 (d, *J* = 10.2 Hz, 2H), 2.65 - 2.57 (m, 4H), 2.40 (s, 3H), 1.17 (d, *J* = 5.7 Hz, 6H); LCMS [M+l] $^{+}$ = 509.29.

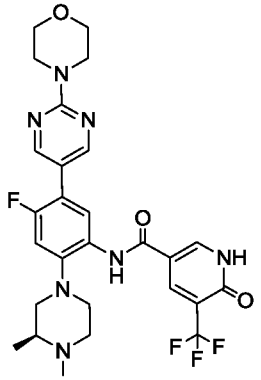
Example 494: N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-3-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00862] The title compound (61.6 mg, 23% yield) was prepared by a similar procedure to that described in Example 39 using N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (61.40 mg, 0.101 mmol) and 2-(morpholin-4-

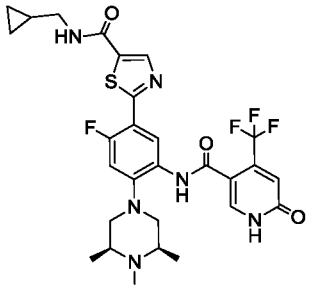
ylmethyl)thiophene-4-boronic acid, pinacol ester (47.0 mg, 0.152 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.59 (s, 1H), 7.32 (s, 1H), 7.03 (d, *J* = 12.5 Hz, 1H), 6.91 (s, 1H), 3.77 (s, 2H), 3.72 - 3.70 (m, 4H), 3.05 (d, *J* = 11.1 Hz, 2H), 2.64 - 2.59 (m, 2H), 2.54 (s, 6H), 2.38 (s, 3H), 1.16 (d, *J* = 5.9 Hz, 6H); LCMS HSS [M+l] $^+$ = 608.45.

Example 495: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-5-(Mfluoromethyl)-lH-pyridine-3-carboxamide



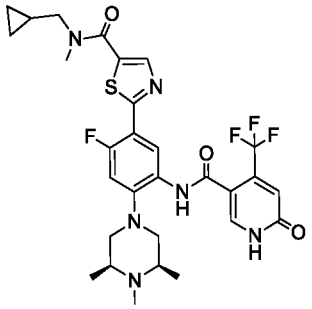
[00863] In a 5 mL microwave vial to a suspension of 6-oxo-5-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (114 mg, 0.553 mmol) in pyridine, anhydrous (671 µï, 8.29 mmol) was added slowly diethyl chlorophosphate (90 µï, 0.622 mmol) at RT in an atmosphere of nitrogen. The reaction mixture was stirred at rt for 2 h. The suspension turned into a solution and then into a suspension again. To this mixture (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-mo rpholinopyrimidin-5-yl)aniline (53.4 mg, 0.138 mmol) was added and the reaction was heated at 70 °C for 3 h. After completion, pyridine was removed in vacuo and the residue partitioned between dichloromethane (3 mL) and saturated sodium bicarbonate solution (3 mL). The suspension was stirred for 10 min. The organic layer was separated, and dried over anhydrous **Na_2S0_4.** The solvent was evaporated in vacuo yielding the crude product which was purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the title compound.

Example 496: N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenylj-l ,3-thiazole-5-carboxamide



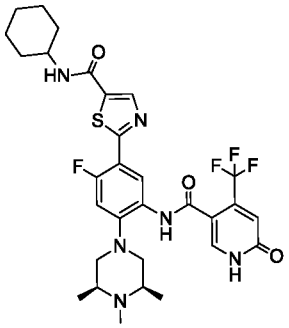
[00864] The title compound was prepared similar to the procedure described for the preparation of Example 482 using 2-bromo-5-thiazolecarboxylic acid in place of 2-bromo-4-thiazolecarboxylic acid in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (br s, 1H), 8.84 (t, *J*=5.6 Hz, 1H), 8.55 - 8.47 (m, 2H), 7.99 (s, 1H), 7.12 (d, *J*=13.2 Hz, 1H), 6.67 (br s, 1H), 3.17 - 3.10 (m, 5H), 2.39 - 2.30 (m, 3H), 2.19 (s, 3H), 1.01 (d, *J*=6.1 Hz, 6H), 0.49 - 0.43 (m, 2H), 0.24 (q, *J*=4.6 Hz, 2H); LCMS [M+H]+: 607.5.

Example 497: N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-5-carboxamide



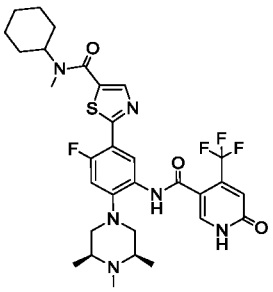
[00865] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using 1-cyclopropyl-N-methylmethanamine in place of aminomethyl cyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.53 - 9.43 (m, 1H), 8.53 (d, *J*=8.2 Hz, 1H), 8.39 - 8.18 (m, 1H), 7.98 (s, 1H), 7.12 (d, *J*=13.2 Hz, 1H), 6.65 (br s, 1H), 6.56 (s, 1H), 3.15 (br d, *J*=11.4 Hz, 5H), 2.41 - 2.33 (m, 3H), 2.21 (s, 3H), 1.11 - 1.06 (m, 1H), 1.03 (d, *J*=6.1 Hz, 6H), 0.55 - 0.49 (m, 2H), 0.32 - 0.22 (m, 2H); LCMS [M+H]+: 621.4.

Example 498: N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-5-carboxamide



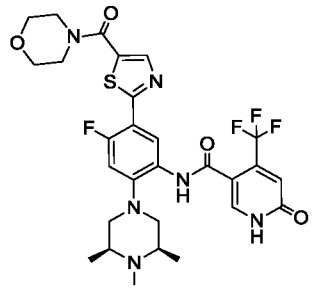
[00866] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using cyclohexylamine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.54 (br s, IH), 9.61 (s, IH), 8.52 - 8.41 (m, 3H), 7.95 (s, IH), 7.11 (d, *J*=13.2 Hz, IH), 6.79 (s, IH), 3.14 (br d, *J*=11.6 Hz, 2H), 2.39 - 2.31 (m, 2H), 2.19 (s, 3H), 1.85 (br s, 2H), 1.80 - 1.71 (m, 2H), 1.61 (br d, *J*=ll.l Hz, IH), 1.30 (br t, *J*=9.5 Hz, 4H), 1.01 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 635.5.

Example 499: N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-5-carboxamide



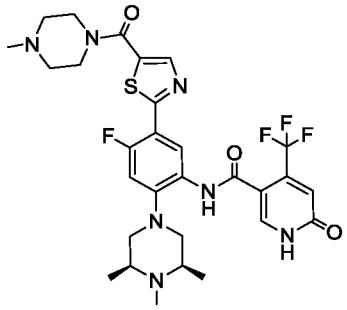
[00867] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using N-methylcyclohexylamine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.49 (br s, IH), 9.56 (s, IH), 8.41 (d, *J*=7.9 Hz, IH), 8.15 (br s, IH), 7.85 (s, IH), 7.04 (d, *J*=13.1 Hz, IH), 6.74 (s, IH), 3.09 (br d, *J*=l 1.6 Hz, 2H), 3.03 - 2.90 (m, 2H), 2.29 (br t, *J*=7.9 Hz, 3H), 2.13 (s, 3H), 1.76 - 1.68 (m, 2H), 1.62 (br s, 2H), 1.52 (br s, 3H), 1.29 - 1.18 (m, 2H), 1.10 - 1.03 (m, IH), 0.95 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 649.4.

Example 500: N-[4-fluoro-5-[5-(morpholine-4-carbonyl)-l, 3-thiazol-2-yl]-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



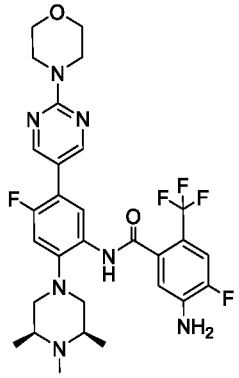
[00868] The title compound was prepared similar to the procedure described for the preparation of Example 482 using morpholine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.54 (br s, IH), 9.63 (s, IH), 8.46 (d, *J*=8.1 Hz, IH), 8.23 (d, *J*=2.2 Hz, IH), 7.92 (s, IH), 7.11 (d, *J*=13.1 Hz, IH), 6.80 (s, IH), 3.70 - 3.63 (m, 9H), 3.16 (br d, *J*=\ 1.6 Hz, 2H), 2.38 - 2.31 (m, 2H), 2.20 (s, 3H), 1.01 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 623.4.

Example 501: N-[4-fluoro-5-[5-(4-methylpiperazine-l -carbonyl)-l ,3-thiazol-2-yl] -2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

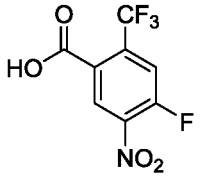


[00869] The title compound was prepared similar to the procedure described above for the preparation of Example 482 using 1-methylpiperazine in place of aminomethylcyclopropane in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.59 (br s, IH), 9.52 (br s, IH), 8.51 (d, *J*=8.1 Hz, IH), 8.21 (d, *J*=2.2Hz, IH), 7.97 (s, IH), 7.12 (d, *J*=13.0 Hz, IH), 6.69 (br d, *J*=1.0 Hz, IH), 3.67 (br s, 4H), 3.15 (br d, *J*=11.2 Hz, 2H), 2.40 - 2.33 (m, 7H), 2.22 (s, 3H), 2.21 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 636.5.

Example 502: 5-amino-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-2-(trifluoromethyl)benzamide

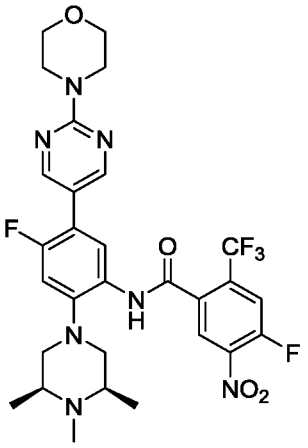


Step 1: 4-Fluoro-5-nitro-2-(trifluoromethyl)benzoic acid



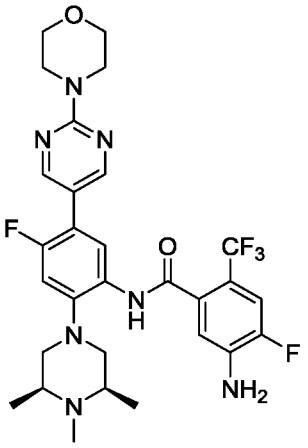
[00870] To a solution of 4-fluoro-5-nitro-2-(trifluoromethyl)benzoic acid (0.50 g, 2.4 mmol) in sulphuric acid (4 mL) at 0 °C was added fuming nitric acid (0.1 1 mL 2.6 mmol). The reaction was warmed to room temperature and stirred for 18 h. An additional equivalent of fuming nitric acid (0.11 mL, 2.6 mmol) was added to the reaction mixture and the reaction was warmed to 45 °C for 4 hours. After cooling to room temperature the mixture was added dropwise to water (25 mL) at 0 °C. The mixture was transferred to a separatory funnel and extracted with EtOAc. The combined organics were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded 4-fluoro-5-nitro-2-(trifluoromethyl)benzoic acid (0.12 g, 19 %). LCMS [M-H]-: 252.0.

Step 2: 4-Fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3, 4,5-trimethylpiperazin-l-yl)phenyl)-5-nitro-2-(trifluoromethyl)benzamide



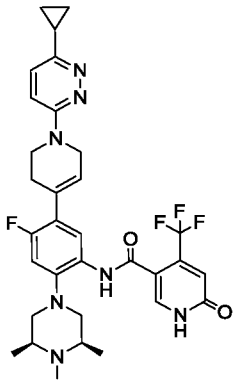
[00871] Thionyl chloride (0.18 mL, 2.5 mmol) was added to a vial containing 4-fluoro-5-nitro-2-(trifluoromethyl)benzoic acid (0.020 g, 0.075 mmol). The resulting suspension was heated at 80 °C for 30 minutes. The reaction mixture was concentrated to dryness and then quickly dried under reduced pressure to afford the crude acid chloride which was used immediately. A solution of 4-fluoro-5-(2-morpholinopyrirnidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.020 g, 0.050 mmol) and N,N-diisopropylethylamine (0.030 mL, 0.15 mmol) in DCM (1 mL) at room temperature was treated with a solution of acid chloride prepared above in DCM (1 mL). The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated directly onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford 4-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-nitro-2-(trifluoromethyl)benzamide (0.014 g, 45 %). 'HNMR (500**MHZ**, CHLOROFORM-d) δ = 8.76 (s, 1H), 8.58 (s, 2H), 8.53 (d, *J*=8.1 Hz, 1H), 8.36 (d, *J*=6.8 Hz, 1H), 7.78 (d, *J*=10.1 Hz, 1H), 7.04 (d, *J*=ll.l Hz, 1H), 3.90 - 3.87 (m, 4H), 3.82 - 3.79 (m, 4H), 2.84 (br d, *J*=l 1.1 Hz, 2H), 2.66 (br t, *J*=10.8 Hz, 2H), 1.26 (s, 3H), 1.14 (d, *J*=6.2 Hz, 6H).

Step 3: 5-amino-4-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-2-(trifluoromethyl)benzamide



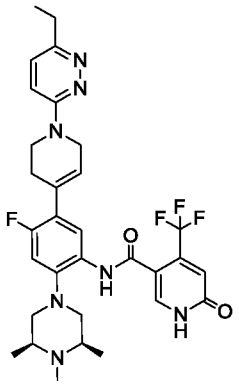
[00872] A mixture of 4-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,54rimethylpiperazin-l-yl)phenyl)-5-nitro-2-(trifluoromethyl)benzamide (0.014 g, 0.022 mmol) and tin chloride (0.012 g, 0.066 mmol) in EtOH (2 mL) was heated to 75 °C for 1 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purification by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded the title compound 5-amino-4-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-2-(trifluoromethyl)benzamide (0.009 g, 69 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (d, *J*=0.9 Hz, 2H), 8.06 (d, *J*=8.3 Hz, 1H), 7.37 (d, *J*=11.7 Hz, 1H), 7.10 (d, *J*=12.0 Hz, 1H), 7.01 (d, *J*=8.3 Hz, 1H), 3.87 - 3.81 (m, 4H), 3.79 - 3.74 (m, 4H), 3.00 (br d, *J*=11.4 Hz, 2H), 2.60 (t, *J*=11.2 Hz, 2H), 2.43 (dt, *J*=3.2, 6.6 Hz, 2H), 2.32 (s, 3H), 1.14 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+: 606.4.

Example 503: N-[5-[l-(6-cyclopropylpyridazin-3-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



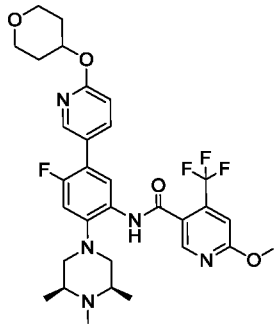
[00873] The procedure was similar to that of Example 270 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 3-bromo-6-cyclopropyl-pyridazine hydrobromide (23.17 mg, 0.083 mmol) to give the title compound (5 mg, 11 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.81 (m, 1H), 7.74 - 7.65 (m, 1H), 7.15 - 7.05 (m, 2H), 6.88 - 6.82 (m, 1H), 6.81 - 6.78 (m, 1H), 6.08 - 6.01 (m, 1H), 4.13 - 4.02 (m, 2H), 3.85 - 3.68 (m, 2H), 2.94 - 2.89 (m, 2H), 2.57 - 2.42 (m, 6H), 2.29 - 2.26 (m, 3H), 2.05 - 1.97 (m, 1H), 1.07 - 1.04 (m, 6H), 0.96 - 0.88 (m, 2H), 0.85 - 0.80 (m, 2H); LCMS [M+H]+ 626.7.

Example 504: N-[5-[l-(6-ethylpyridazin-3-yl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

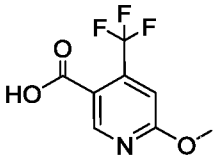


[00874] The procedure was similar to that of Example 372 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 3-bromo-6-ethyl-pyridazine hydrobromide (22.17 mg, 0.083 mmol) to give the title compound (4 mg, 9 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.84 - 7.81 (m, 1H), 7.74 - 7.67 (m, 1H), 7.30 - 7.24 (m, 1H), 7.19 - 7.13 (m, 1H), 6.89 - 6.83 (m, 1H), 6.82 - 6.80 (m, 1H), 6.09 - 6.02 (m, 1H), 4.13 - 4.10 (m, 2H), 3.84 - 3.74 (m, 2H), 2.95 - 2.91 (m, 2H), 2.75 - 2.70 (m, 2H), 2.57 - 2.46 (m, 6H), 2.28 - 2.27 (m, 3H), 1.20 - 1.17 (m, 3H), 1.07 - 1.05 (m, 6H); LCMS [M+H]+ 614.6.

Example 505: N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridim -3-carboxamide

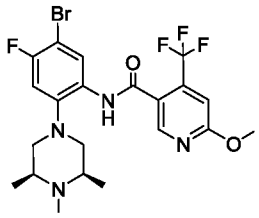


Step 1: 6-methoxy-4-(trifluoromethyl)nicotinic acid



[00875] A mixture of 6-chloro-4-(trifluoromethyl)nicotinic acid (4 g, 17.73 mmol) and sodium methoxide (95%, powder) (15.13 g, 266 mmol) in MeOH (40 mL) was heated at reflux under nitrogen in a RB flask. The reaction was complete after 5 h. The mixture was cooled to rt and quenched with satd. citric acid solution. The mixture was concentrated to remove most of the methanol and then extracted with EtOAc (1 x 200 ml and the 1 x 100ml). The combined org phase was dried over Na_2S0_4 and concentrated to afford the desired product as a white solid. (4.18 g, 95 % purity, quantitative yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 8.79 (s, 1H), 7.28 (s, 1H), 3.99 (s, 3H).

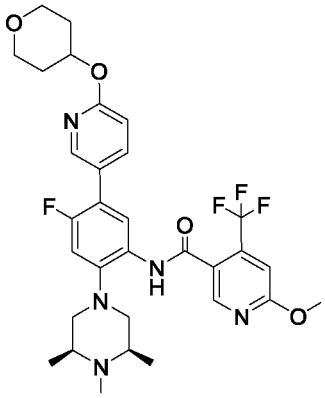
Step 2: N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methoxy-4-(trifluoromethyl)nicotinamide



[00876] Propylphosphonic anhydride solution (1.412 ml, 2.372 mmol) was added dropwise to a mixture of 6-methoxy-4-(trifluoromethyl)nicotinic acid (265 mg, 1.138 mmol) and pyridine (0.306 ml, 3.79 mmol) in dry THF (6 ml) under N_2 at RT. A dark wine red-coloured solution was obtained. After 1.25 h of stirring at RT, 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (300 mg, 0.949

mmol) was added as a solution in 1.5 ml THF and the reaction mixture was heated at 50 °C for 16 h. Complete disappearance of the aniline was observed along with the starting acid (20 % excess acid was used) and the desired product. The mixture was allowed to cool to RT, THF was removed on a Rotovap, the residue was taken up in DCM (25 ml) and water (25 ml). The org phase was separated and the aq phase was extracted with DCM (2 x 15 ml). The combined org phase was washed with NaOH (IN, 2 x 20 ml) solution to remove the excess starting material (acid), then with water (20 ml), and brine(20 ml), dried over Na_2SO_4 and concentrated to afford the desired product as light brown solid (250 mg) . LCMS shows the purity of the crude as 96 %. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.42 (s, 1H), 8.07 (d, *J*=7.5 Hz, 1H), 7.11 (s, 1H), 7.01 (d, *J*=10.0 Hz, 1H), 3.95 (s, 3H), 2.94 (d, *J*=10.5 Hz, 2H), 2.54 - 2.44 (m, 4H), 2.28 (s, 3H), 1.07 (d, *J*=5.9 Hz, 6H).

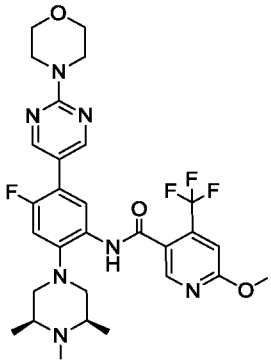
Step 3: N-(4-fluoro-5-(6-((tetrahydro-2H-pyran-4-yl)oxy)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-methoxy-4-(trifluoromethyl)nicotinamide



[00877] The procedure followed was similar to that of Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-methoxy-4-(trifluoromethyl)nicotinamide (40 mg, 0.077 mmol) and 2-(tetrahydropyran-4-yloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (35.3 mg, 0.116 mmol) to afford the title compound (29 mg, 58% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.48 - 8.40 (m, 1H), 8.23 - 8.15 (m, 1H), 7.91 - 7.83 (m, 1H), 7.81 - 7.74 (m, 1H), 7.15 - 7.08 (m, 1H), 7.03 - 6.95 (m, 1H), 6.82 - 6.74 (m, 1H), 5.23 - 5.10 (m, 1H), 4.00 - 3.94 (m, 3H), 3.92 - 3.84 (m, 2H), 3.58 - 3.50 (m, 2H), 3.03 - 2.95 (m, 2H),

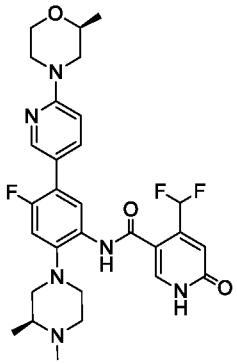
2.59 - 2.49 (m, 2H), 2.48 - 2.38 (m, 2H), 2.30 - 2.24 (m, 3H), 2.04 - 1.96 (m, 2H), 1.73 - 1.65 (m, 2H), 1.07 (d, *J*=6.2 Hz, 6H); LCMS [M+H]+ 618.7

Example 506: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1 -ylj'phenyl]'-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide



[00878] The procedure followed was similar to Example 505, Step 3 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methoxy-4-(trifluoromethyl)nicotinamide (40 mg, 0.077 mmol), 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (33.6 mg, 0.116 mmol) to give the title compound. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.48 - 8.41 (m, 3H), 7.91 - 7.83 (m, 1H), 7.14 - 7.08 (m, 1H), 7.00 - 6.93 (m, 1H), 4.00 - 3.92 (m, 3H), 3.76 - 3.71 (m, 4H), 3.69 - 3.63 (m, 4H), 2.98 - 2.91 (m, 2H), 2.54 - 2.47 (m, 2H), 2.44 - 2.34 (m, 2H), 2.27 - 2.22 (m, 3H), 1.05 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 604.4.

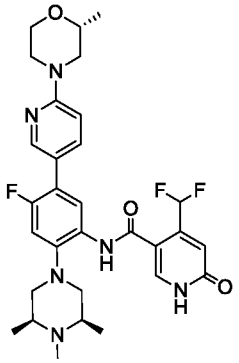
Example 507: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-6<>xo-lH-pyridim -3-carboxamide



[00879] The procedure followed was similar to that used for Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-

(2-(trimethylsilyl)ethoxy Nicotinamide (100.7 mg, 0.176 mmol) and (S)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)mo rpholine (112 mg, 0.368 mmol) to afford, after TFA deprotection of the silyloxy intermediate, the title compound (64.8 mg, 0.111 mmol, 63.3 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.02 (br. s, IH), 9.51 (s, IH), 8.27 (s, IH), 8.00 (s, IH), 7.66-7.72 (m, 2H), 7.34 (t, *J*=54.00 Hz, IH), 7.04 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.80 Hz, IH), 6.57 (s, IH), 4.18 (d, *J*=12.47 Hz, IH), 4.08 (d, *J*=12.84 Hz, IH), 3.92 (dd, *J*=2.51, 11.43 Hz, IH), 3.51-3.62 (m, 2H), 3.00 (dd, *J*=11.07, 19.13 Hz, 2H), 2.73-2.89 (m, 3H), 2.54 (s, IH), 2.42 (t, *J*=10.51 Hz, IH), 2.27-2.37 (m, IH), 2.17-2.24 (m, 4H), 1.17 (d, *J*=6.24 Hz, 3H), 0.97 (d, *J*=6.24 Hz, 3H); LCMS [M]+ 571.4.

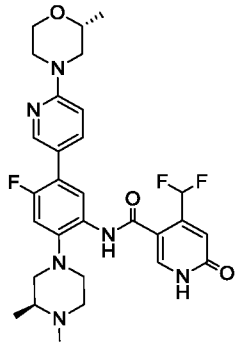
Example 508: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[00880] The procedure followed was similar to that for Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (100.4 mg, 0.171 mmol) and (R)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (107.3 mg, 0.353 mmol) to afford, after deprotection of the silyloxy intermediate, the title compound (55.7 mg, 54.7 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.07 (br. s, IH), 9.54 (s, IH), 8.26 (s, IH), 8.00 (s, IH), 7.65-7.70 (m, 2H), 7.35 (t, *J*=54.90 Hz, IH), 7.01 (d, *J*=12.59 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.58 (s, IH), 4.18 (d, *J*=12.72 Hz, IH), 4.08 (d, *J*=12.84 Hz, IH), 3.92 (dd, *J*=2.38, 11.43 Hz, IH), 3.51-3.60 (m, 2H), 3.01 (d, *J*=10.88 Hz, 2H), 2.84 (dt, *J*=3.42, 12.35 Hz, IH),

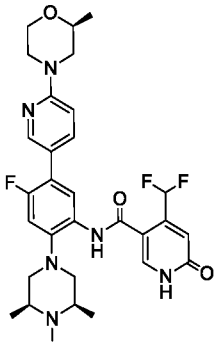
2.54 (s, IH), 2.45 (t, *J*=11.00 Hz, 2H), 2.28-2.37 (m, 2H), 2.19 (s, 3H), 1.17 (d, *J*=6.24 Hz, 3H), 1.00 (d, *J*=6.11 Hz, 6H); LCMS [M]+ 585.5.

Example 509: 4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-6<>xo-lH-pyridine-3-carboxamide



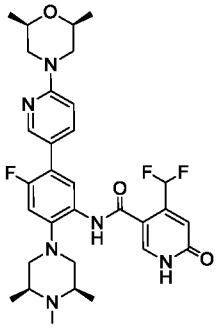
[00881] The procedure followed was similar to that described in Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(tamethylsilyl)ethoxy)mcotinamide (101.4 mg, 0.177 mmol, from Example 396) and (R)-2-me%l-4<5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)mo ϕ holine (109.6 mg, 0.360 mmol) to give, after deprotection of the silyloxy intermediate, the title compound (63.3 mg, 60.3 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 12.09 (br. s, IH), 9.52 (s, IH), 8.27 (s, IH), 8.00 (s, IH), 7.68 (d, *J*=8.68 Hz, 2H), 7.34 (t, *J*=56.50 Hz, IH), 7.04 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.58 (s, IH), 4.18 (d, *J*=12.47 Hz, IH), 4.08 (d, *J*=12.84 Hz, IH), 3.92 (dd, *J*=2.51, 11.55 Hz, IH), 3.51-3.61 (m, 2H), 3.01 (dd, *J*=11.00, 19.56 Hz, 2H), 2.72-2.88 (m, 3H), 2.52-2.54 (m, IH), 2.41 (t, *J*=10.51 Hz, IH), 2.28-2.37 (m, IH), 2.21 (s, 4H), 2.19-2.25 (m, 4H), 1.17 (d, *J*=6.11 Hz, 3H), 0.97 (d, *J*=6.24 Hz, 3H); LCMS [M]+ 571.5.

Example 510: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[00882] The procedure followed was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (104.6 mg, 0.178 mmol) and (S)-2-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (109.7 mg, 0.361 mmol) to afford, after deprotection of the silyloxy intermediate with TFA, the title compound (57.6 mg, 54.2 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 11.91 (br. s, IH), 9.54 (s, IH), 8.26 (s, IH), 7.99 (s, IH), 7.64-7.71 (m, 2H), 7.35 (t, *J*=54.30 Hz, IH), 7.01 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.58 (s, IH), 4.18 (d, *J*=12.59 Hz, IH), 4.08 (d, *J*=12.84 Hz, IH), 3.92 (dd, *J*=2.45, 11.49 Hz, IH), 3.51-3.62 (m, 2H), 3.01 (d, *J*=10.76 Hz, 2H), 2.84 (dt, *J*=3.55, 12.35 Hz, IH), 2.51-2.54 (m, IH), 2.45 (t, *J*=11.00 Hz, 2H), 2.27-2.38 (m, 2H), 2.19 (s, 3H), 1.17 (d, *J*=6.24 Hz, 3H), 1.00 (d, *J*=6.24 Hz, 6H); LCMS [M]+ 585.5.

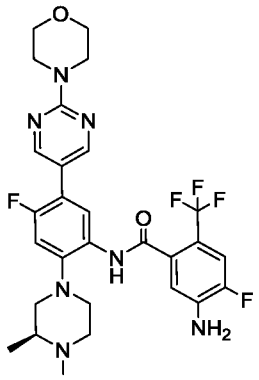
Example 511: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



[00883] The procedure followed was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (100.1 mg, 0.170 mmol) and (2S,6R)-2,6-

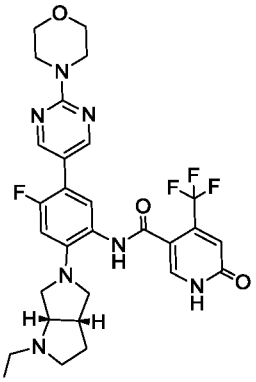
dimethyl-4-(5-(4,4,5,54etramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (109.7 mg, 0.345 mmol) to afford, after deprotection of the silyoxy intermediate, the title compound (53 mg, 51.0 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.14 (br. s, IH), 9.52 (s, IH), 8.25 (s, IH), 8.01 (s, IH), 7.68 (d, *J*=8.56 Hz, 2H), 7.35 (t, *J*=56.70 Hz, IH), 7.01 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.56 (s, IH), 4.19 (d, *J*=11.49 Hz, 2H), 3.61 (ddd, *J*=2.38, 6.30, 10.39 Hz, 2H), 3.01 (d, *J*=11.00 Hz, 2H), 2.40-2.48 (m, 4H), 2.32 (d, *J*=6.36 Hz, 2H), 2.19 (s, 3H), 1.16 (d, *J*=6.24 Hz, 6H), 1.00 (d, *J*=6.24 Hz, 6H); LCMS [M]+ 599.4.

Example 512: 5-amino-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



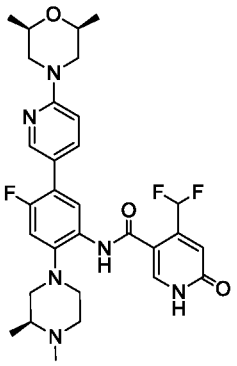
[00884] The title compound was prepared similar to the procedure described above for the preparation of Example 502 using (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline in place of 4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline in Step 2. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (d, *J*=1.0 Hz, 2H), 8.06 (d, *J*=8.3 Hz, IH), 7.37 (d, *J*=11.9 Hz, IH), 7.12 (d, *J*=12.0 Hz, IH), 7.01 (d, *J*=8.4 Hz, IH), 3.87 - 3.82 (m, 4H), 3.79 - 3.74 (m, 4H), 3.07 (br dd, *J*=2.2, 11.7 Hz, IH), 3.00 (br d, *J*=11.5 Hz, IH), 2.96 - 2.85 (m, 2H), 2.56 (t, *J*=10.8 Hz, IH), 2.45 (dt, *J*=2.9, 11.5 Hz, IH), 2.33 (s, 3H), 1.10 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 592.4.

Example 513: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3aR, 6aR)-l-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[2, 3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00885] The procedure followed was similar to that of Example 476 using N-(4-fluoro-2-(hexahydropyrrolo[3,4-b]pyrrol-5(lH)-yl)-5-(2-mo ϕ holinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3 -carboxamide TFA (70 mg, 0.064 mmol) and propionaldehyde (19.4 mg, 0.334 mmol) to afford the title compound (10.7 mg, 0.016 mmol, 25.6 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 12.58 (br. s., 1H), 9.63 (br. s., 1H), 8.51 (s, 2H), 8.02 (br. s., 1H), 7.53 (d, *J*=7.83 Hz, 1H), 6.76-6.88 (m, 2H), 3.72-3.78 (m, 5H), 3.65-3.70 (m, 5H), 3.19 (br. s., 1H), 3.11 (br. s., 1H), 2.92-3.07 (m, 3H), 2.74 (d, *J*=9.78 Hz, 1H), 2.43 (br. s., 1H), 2.36 (br. s., 1H), 2.19 (br. s., 2H), 1.98 (br. s., 1H), 1.61 (br. s., 1H), 1.35 (br. s., 1H), 1.23 (br. s., 1H), 0.81-0.96 (m, 1H), 0.77 (t, *J*=7.09 Hz, 3H); LCMS [M+H]+ 616.6.

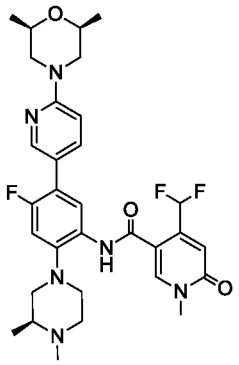
Example 514: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl] -6-oxo-1H-pyridine-3-carboxamide



[00886] The procedure followed was similar to that of Example 39 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (97 mg, 0.169 mmol) and (2S,6R)-2,6-dimethyl-

4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (112 mg, 0.352 mmol) to afford, after deprotection of the silyloxy intermediate with TFA, the title compound (43.2 mg, 0.069 mmol, 40.6 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.35 (bs, IH), 9.53 (s, IH), 8.26 (s, IH), 8.00 (s, IH), 7.67 (d, *J*=8.68 Hz, 2H), 7.34 (t, *J*=56.50 Hz, IH), 7.04 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.59 (s, IH), 4.19 (d, *J*=11.49 Hz, 2H), 3.61 (ddd, *J*=2.20, 6.30, 10.33 Hz, 2H), 3.00 (dd, *J*=11.07, 19.75 Hz, 2H), 2.71-2.85 (m, 2H), 2.38-2.47 (m, 3H), 2.28-2.37 (m, IH), 2.22-2.19 (m, IH), 2.21 (s, 3H), 1.16 (d, *J*=6.11 Hz, 6H), 0.97 (d, *J*=6.24 Hz, 3H); LCMS [M]+ 585.5.

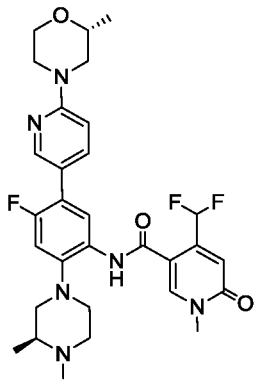
Example 515: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide



[00887] To a suspension of 4-(difluoromethyl)-N-(5-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo- l,6-dihydropyridine-3-carboxamide (22.6 mg, 0.039 mmol) and cesium carbonate (13.85 mg, 0.043 mmol) in DMF (3 ml) was added Mel (2.65 µï, 0.043 mmol) at room temperature and the reaction mixture was stirred for IhOO at room temperature. The reaction mixture was poured into water and the product was extracted by DCM. The organic phase was dried over MgSC>4 and after filtration and solvent removal the crude material was dissolved in MeOH and passed through a PoraPak Rxn CX (20cc-2g) cartridge in a catch and elute method. The cartridge was washed with MeOH, then the solution of product in MeOH was added onto the cartridge. The cartridge was rinsed with MeOH (2x20mL) and then with a solution of lOmL (N¾ in MeOH at 7N) in 40 mL of MeOH to release the free base of the title compound (22.6

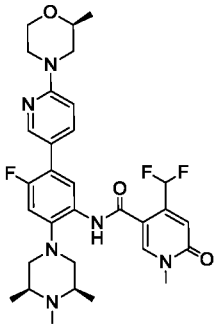
mg, 0.035 mmol, 90 % yield) as an off-white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.45 (s, IH), 8.36 (s, IH), 8.25 (s, IH), 7.67 (d, *J*=8.68 Hz, 2H), 7.33 (t, *J*=55.40 Hz, IH), 7.05 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.64 (s, IH), 4.19 (d, *J*=11.49 Hz, 2H), 3.61 (ddd, *J*=2.26, 6.33, 10.24 Hz, 2H), 3.52 (s, 3H), 2.97-3.08 (m, 2H), 2.73-2.86 (m, 2H), 2.38-2.47 (m, 3H), 2.30-2.38 (m, IH), 2.18-2.27 (m, 1H+3H), 1.17 (d, *J*=6.24 Hz, 6H), 0.97 (d, *J*=6.24 Hz, 3H); LCMS [M]+ 599.4.

Example 516: 4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l -yl]-5-[6-[(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide



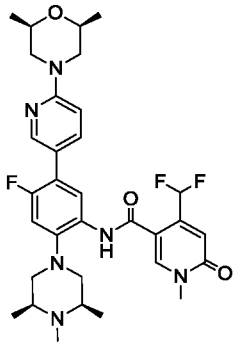
[00888] The procedure followed was similar to Example 515 using 4-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-((R)-2-methylmo rpholino)pyridin-3-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxarnide (39.7 mg, 0.070 mmol) to afford the title compound (39.2 mg, 0.064 mmol, 92 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.45 (s, IH), 8.36 (s, IH), 8.26 (s, IH), 7.67 (d, *J*=8.56 Hz, 2H), 7.33 (t, *J*=55.10 Hz, IH), 7.06 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.80 Hz, IH), 6.64 (s, IH), 4.18 (d, *J*=12.47 Hz, IH), 4.08 (d, *J*=13.20 Hz, IH), 3.92 (dd, *J*=2.63, 11.31 Hz, IH), 3.55 (d, *J*=2.57 Hz, 2H), 3.52 (s, 3H), 2.97-3.08 (m, 2H), 2.84 (br. s., 3H), 2.42 (br. s., IH), 2.36 (br. s., IH), 2.21 (br. s., 4H), 1.17 (d, *J*=6.24 Hz, 3H), 0.98 (d, *J*=5.99 Hz, 3H);LCMS [M]+ 585.5.

Example 517: 4-(Difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylj '-2-[(3S,5R)-3,4,5-trimethylpiperazin-l -yljphenyl]'-1-methyl-6-oxopyridine-3-carboxamide



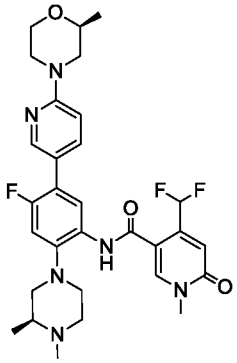
[00889] To a suspension of 4-(difluoromethyl)-N-(4-fluoro-5-(6-((S)-2-methylmo rpholino)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (35.2 mg, 0.060 mmol) and cesium carbonate (21.58 mg, 0.066 mmol) in DMF (6 mL) was added iodomethane (4.12 µï, 0.066 mmol) at room temperature and stirred for 1 hour. Then the reaction mixture was poured into water and the product was extracted by DCM. The organic phase was dried over MgSC>4 and after filtration and solvent removal the crude material was triturated with **Et_20 .** After removing the **Et_20** under vacuum, the desired 4-(difluoromethyl)-N-(4-fluoro-5-(6-((S)-2-methylmo rpholino)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl -6-oxo- 1,6-dihydropyridine-3 -carboxamide (35.5 mg, 0.056 mmol, 94 % yield) was obtained as a white powder. ^{1}H NMR (500MHz, DMSO-de) δ = 9.47 (s, 1H), 8.35 (s, 1H), 8.26 (s, 1H), 7.64-7.70 (m, 2H), 7.33 (t, *J*=56.50 Hz, 1H), 7.03 (d, *J*=12.59 Hz, 1H), 6.94 (d, *J*=8.93 Hz, 1H), 6.64 (s, 1H), 4.18 (d, *J*=12.72 Hz, 1H), 4.08 (d, *J*=12.84 Hz, 1H), 3.92 (dd, *J*=2.32, 11.37 Hz, 1H), 3.56 (dd, *J*=2.51, 11.07 Hz, 2H), 3.49-3.54 (m, 3H), 3.02 (d, *J*=11.00 Hz, 2H), 2.84 (dt, *J*=3.42, 12.29 Hz, 1H), 2.51-2.54 (m, 1H), 2.46 (s, 2H), 2.28-2.38 (m, 2H), 2.18 (s, 4H), 1.17 (d, *J*=6.11 Hz, 3H), 1.00 (d, *J*=6.11 Hz, 7H); LCMS [M]+ 599.4.

Example 518: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R, 6S)-2, 6-dimethylmorpholin-4-ylJpyridin-3-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[00890] The title compound (white solid, 26.4 mg, 42%) was prepared using (2S,6R)-2,6-dimethyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (47 mg, 0.15 mmol) and N-(5-bromo-4-fiuoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (51.8 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.31 (s, IH), 8.26 (s, IH), 7.93 (d, *J*=8.3 Hz, IH), 7.79 (br d, *J*=8.8 Hz, IH), 7.09 (d, *J*=12.0 Hz, IH), 6.95 (s, IH), 6.92 (d, *J*=8.7 Hz, IH), 4.16 (br d, *J*=12.1 Hz, 2H), 3.78 - 3.70 (m, 2H), 3.66 (s, 3H), 3.09 (br d, *J*=8.4 Hz, 2H), 2.73 - 2.51 (m, 6H), 2.44 (br s, 3H), 1.27 (d, *J*=6.2 Hz, 6H), 1.21 (br s, 6H); LCMS $[M + H]^{+}$ 631.6.

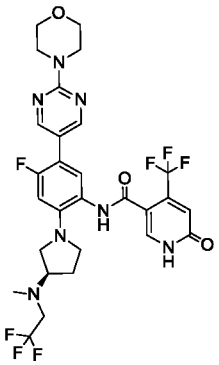
Example 519: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJ-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



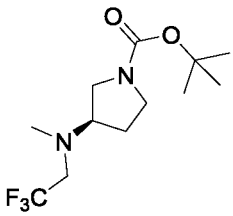
[00891] To a suspension of 4-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-((S)-2-methylmo rpholino)pyridin-3-yl)phenyl)-6-oxo- l,6-dihydropyridine-3-carboxamide (43.4 mg, 0.076 mmol) and cesium carbonate (27.3 mg, 0.084 mmol) in N,N-dimethylformamide (6 ml) was added Mel (5.21 μï, 0.084 mmol) at room temperature. The reaction mixture was stirred for 1

hour at room temperature. The reaction mixture was poured into water and the product was extracted by DCM. The organic phase was dried over MgSC>4 and after filtration and solvent removal the crude material was triturated with Et_20. After removing the Et_20 under vacuum, the desired 4-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-((S)-2-methylmo rpholino)pyridin-3-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (45.7 mg, 0.074 mmol, 98 % yield) was obtained as a white powder. ^1H NMR (500MHz, DMSO-de) δ = 9.45 (s, IH), 8.36 (s, IH), 8.26 (s, IH), 7.66-7.71 (m, IH), 7.67 (d, *J*=8.68 Hz, 2H), 7.33 (t, *J*=56.10 Hz, IH), 7.06 (d, *J*=12.35 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.64 (s, IH), 4.18 (d, *J*=12.84 Hz, IH), 4.08 (d, *J*=12.59 Hz, IH), 3.92 (dd, *J*=2.51, 11.55 Hz, IH), 3.56 (dd, *J*=2.32, 11.00 Hz, 2H), 3.49-3.53 (m, 3H), 2.96-3.09 (m, 2H), 2.74-2.88 (m, 3H), 2.41 (d, *J*=10.88 Hz, IH), 2.34 (br. s., IH), 2.20 (s, 4H), 1.17 (d, *J*=6.24 Hz, 3H), 0.97 (d, *J*=6.24 Hz, 3H); LCMS [M]+ 585.4.

Example 520: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-fmethyl(2,2,2-trifluoroethyl)aminoJpyrrolidin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



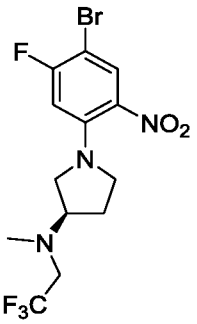
Step 1: tert-butyl (R)-3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidine-l-carboxylate



[00892] Trifiuoroacetic acid (0.30 mL, 3.7 mmol) was activated with HATU (1.4 g, 3.7 mmol) and N,N-diisopropylethylamine (0.65 mL, 3.7 mmol) in DMF (3 mL) at room temperature. After stirring for 10 minutes the solution of activated acid was

added to a vial containing a solution of (R)-3-(methylamino)pyrrolidine-l-carboxylic acid tert-butyl ester (0.50 g, 2.5 mmol) in DMF (3 mL) at room temperature. The reaction was allowed to stir at room temperature for 2 h. The solvent was removed in vacuo and the residue was partitioned between DCM and saturated aqueous NaHCCb. The layers were separated and the organics were dried over magnesium sulfate. After removing the inorganics by filtration the filtrate was concentrated to dryness and the residue was purified by flash chromatography [25-75% EtOAc/hexanes]. The resultant trifluoroacetamide was dissolved in THF (12 mL) and cooled to 0 °C. A solution of borane dimethyl sulfide complex (3.3 mL, 2 M THF) was added and the ice bath was removed. The reaction mixture was heated to 60 °C for 4 h. After cooling to room temperature the reaction was carefully quenched with a saturated aqueous $NaHCO_3$ solution and then diluted with DCM and water. The layers were separated and the aqueous layer was extracted with an additional portion of DCM. The combined organic layers were dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated onto celite. Flash chromatography [0-30% EtOAc/hexanes] afforded tert-butyl (R)-3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidine-l-carboxylate (0.54 g, 77 % yield). ^1H NMR (500MHz, DMSO-d6) δ = 3.46 (q, *J*=8.7 Hz, 1H), 3.39 - 3.31 (m, 2H), 3.27 - 3.09 (m, 4H), 3.03 - 2.87 (m, 1H), 2.36 (s, 3H), 1.98 (br s, 1H), 1.77 - 1.62 (m, 1H), 1.39 (s, 9H).

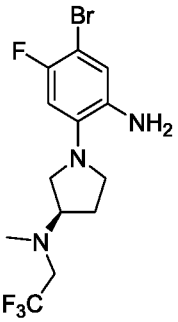
Step 2: (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine



[00893] A solution of tert-butyl (R)-3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidine-l-carboxylate (0.54 g, 1.93 mmol) in DCM (5 mL) was treated with TFA (3.0 mL) at room temperature. After stirring ovemight at room temperature the volatiles were removed under a stream of air. The TFA salt of the

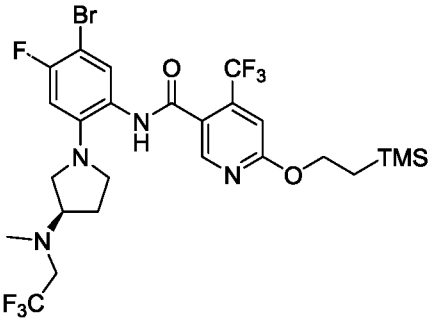
deprotected amine was suspended in toluene (3 mL) and potassium carbonate (0.40 g, 2.9 mmol) was added carefully in portions. A solution of l-bromo-2,4-difluoro-5-nitrobenzene (0.46 g, 1.93 mmol) in toluene (3 mL) was added dropwise and the reaction was warmed to 50 °C. After 3 h the reaction mixture was cooled to room temperature and partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with an additional portion of EtOAc. The combined extracts were dried over magnesium sulfate and after removal of the inorganics by filtration the filtrate was concentrated onto celite. Purification by flash chromatography [10-50% EtOAc/hexanes] afforded (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine (0.40 g, 52 %). LCMS [M+H]+: 400.2.

Step 3: (R)-l-(2-amino-4-bromo-5-fluorophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine



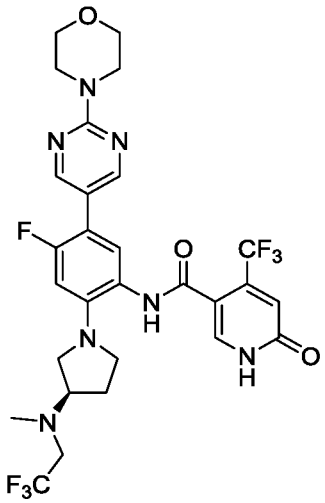
[00894] Tin chloride (0.57 g, 3.00 mmol) was added to a solution of (R)-l-(4-bromo-5-fluoro-2-nitrophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine (0.40 g, 1.000 mmol) in EtOH (8 mL) and the reaction was heated to 80 °C for 1 h. After cooling to room temperature the reaction mixture was concentrated directly onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford (R)-l -(2-amino-4-bromo-5-fluorophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine (0.34 g, 91 %). LCMS [M+H]+: 370.1.

Step 4: (R)-N-(5-bromo-4-fluoro-2-(3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidin-1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00895] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.19 g, 0.61 mmol) was activated with HATU (0.23 g, 0.61 mmol) and N,N-diisopropylethylamine (0.11 niL, 0.61 mmol) in DMF (3 mL) at room temperature. After agitating for 5 minutes the solution of activated acid was added dropwise to a stirring solution of (R)-l-(2-amino-4-bromo-5-fluorophenyl)-N-methyl-N-(2,2,2-trifluoroethyl)pyrrolidin-3-amine (0.15 g, 0.41 mmol) in DMF (3 mL) and the reaction warmed to 40 °C for 18 h. The reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-5% MeOH/DCM + 0.5% NH_4OH] to afford (R)-N-(5-bromo-4-fluoro-2-(3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.22 g, 82 %). LCMS [M+H]+: 659.2.

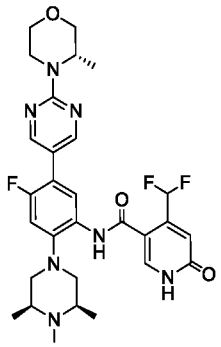
Step 5: (R)-N-(4-fluoro-2-(3-(methyl(2,2,2-trifluoroethyl)amino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00896] A vial was charged with 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (0.044 g, 0.15 mmol), (R)-N-(5-bromo-4-fluoro-2-(3-(methyl(2,2,2-

trifluoroethyl)amino)pyrrolidin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.050 g, 0.076 mmol), XPhos Pd G2 (0.0012 g, 1.5 μηιοΐ) and XPhos (0.0007 g, 1.5 μηιοΐ). The vial was sealed and evacuated and backfilled with nitrogen. 1,4-Dioxane (1.3 mL) and aqueous sodium carbonate, (0.15 mL, 0.27 mmol) were added via syringe and the vial evacuated and backfilled an additional time. The reaction was heated to 90 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford the silyl protected amide. The intermediate product was dissolved in DCM (2 mL) and treated with TFA (0.30 mL). After stirring for 1 h the volatiles were removed in vacuo and the product was isolated with a catch and release protocol using a PoraPak RXN CX ion exchange column to afford the title compound (R)-N-(4-fluoro-2-(3-(methyl(2,2,2-trifluoroethyl)amino)pyl rolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)-6- oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.020 g, 41 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.57 (br s, 1H), 9.79 (s, 1H), 8.50 (s, 2H), 7.96 (br s, 1H), 7.35 (d, *J*=8.8 Hz, 1H), 6.79 (s, 1H), 6.68 (d, *J*=13.8 Hz, 1H), 3.73 (br d, *J*=4.9 Hz, 4H), 3.68 (br d, *J*=4.8 Hz, 4H), 3.29 - 3.08 (m, 4H), 2.38 (s, 3H), 2.11 (br dd, *J*=5.5, 10.8 Hz, 1H), 1.79 - 1.67 (m, 1H); LCMS [M+H]+: 644.3.

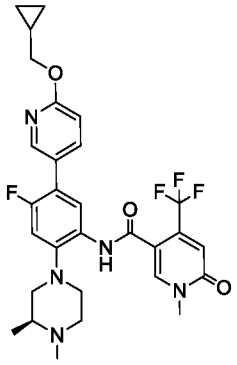
Example 521: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(3R)-3-methylmorpholin-4-ylJpyrimidin-5-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[00897] The title compound (light beige solid, 14.4 mg, 23%) was prepared from (S)-(2-(3-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-

(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.71 (br s, IH), 8.57 (s, 2H), 8.47 (br d, *J*=8.1 Hz, IH), 7.86 (br s, IH), 7.06 - 6.98 (m, 2H), 4.81 - 4.75 (m, IH), 4.42 (br d, *J*=13.4 Hz, IH), 4.03 (dd, *J*=3.4, 11.2 Hz, IH), 3.82 (d, *J*=11.4 Hz, IH), 3.75 (dd, *J*=2.7, 11.4 Hz, IH), 3.60 (dt, *J*=2.9, 11.8 Hz, IH), 3.34 (dt, *J*=3.8, 13.0 Hz, IH), 2.83 (br d, *J*=10.4 Hz, 2H), 2.75 - 2.61 (m, 2H), 2.41 - 2.27 (m, 5H), 1.36 (d, *J*=6.7 Hz, 3H), 1.16 (br d, *J*=5.6 Hz, 6H); LCMS $[M + H]^{+}$ 604.5.

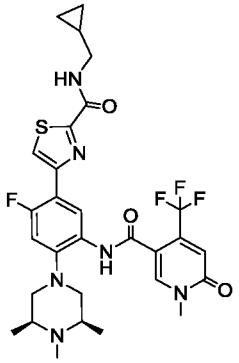
Example 522: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00898] A 30 mL vial was charged with a mixture of (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (37.1 mg, 0.135 mmol). Then 1,4-dioxane (5 ml) and a solution of potassium phosphate tribasic (25.2 mg, 0.119 mmol) in water (0.5 ml) were added via syringe and the vial was flushed with argon for 10 minutes. Then bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (6.3 1 mg, 8.91 μηιοΐ) was added and the reaction was stirred at 110 °C under microwave for 1.5 hours. The solvent was removed under vacuum and the crude material was concentrated onto celite and purified by Flash chromatography [0-30% MeOH/DCM] to afford the desired (S)-N-(5-(6-(cyclopropylmethoxy)pyridin-3-yl)-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (28.4 mg, 0.049 mmol, 82 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 9.46 (s, IH), 8.31 (s, IH), 8.25 (s, IH), 7.81 (d, *J*=9.78 Hz, IH), 7.76 (d, *J*=8.44 Hz, IH), 7.09 (d, *J*=12.35 Hz, IH), 6.94 (d, *J*=8.68 Hz,

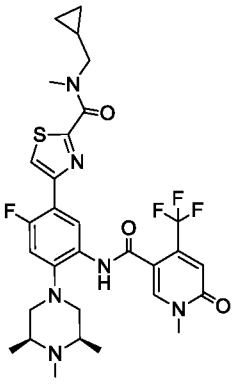
IH), 6.87 (s, IH), 4.14 (d, *J*=7.21 Hz, 2H), 3.52 (s, 3H), 2.98-3.09 (m, 2H), 2.83 (br. s., IH), 2.72-2.79 (m, IH), 2.42 (t, *J*=10.45 Hz, IH), 2.31-2.38 (m, IH), 2.18-2.29 (m, 4H), 1.23 (s, 2H), 0.98 (d, *J*=6.24 Hz, 3H), 0.56 (dd, *J*=1.59, 8.07 Hz, 2H), 0.34 (d, *J*=4.89 Hz, 2H); LCMS [M+H]+ 574.4.

Example 523: N-(cyclopropylmethyl)-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl] -l,3-thiazole-2-carboxamide



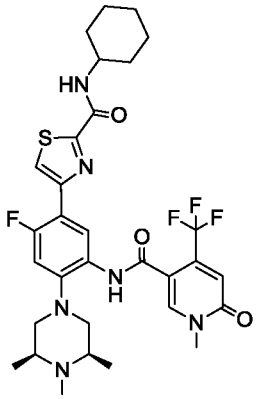
[00899] The title compound was prepared using l-methyl-6-oxo-4-(trifluorometriyl)-l,6-dihydropyridine-3-carboxylic acid and 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)thiazole-2-carboxamide according to a procedure similar to Example 34. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.55 (s, IH), 8.86 (t, *J*=6.1 Hz, IH), 8.40 (s, IH), 8.23 (d, *J*=8.3 Hz, IH), 8.15 (d, *J*=2.1 Hz, IH), 7.07 (d, *J*=13.1 Hz, IH), 6.89 (s, IH), 3.55 (s, 3H), 3.17 (t, *J*=6.5 Hz, 2H), 3.08 (br d, *J*=11.0 Hz, 2H), 2.38 - 2.30 (m, 2H), 2.18 (s, 3H), 1.12 - 1.05 (m, IH), 1.00 (d, *J*=6.1 Hz, 6H), 0.48 - 0.40 (m, 2H), 0.31 - 0.22 (m, 2H); LCMS [M+H]+: 621.1.

Example 524: N-(cyclopropylmethyl)-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide



[00900] The title compound was prepared using procedures similar to Example 482 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid and 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)-N-methylthiazole-2-carboxamide. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 - 9.37 (m, IH), 8.32 - 8.20 (m, 2H), 8.07 (s, IH), 7.05 - 6.97 (m, IH), 6.81 (s, IH), 3.89 (br d, *J*=6.8 Hz, IH), 3.52 (s, IH), 3.46 (s, 3H), 3.33 (br d, *J*=7.0 Hz, IH), 3.05 (s, 2H), 3.00 (br d, *J*=11.0 Hz, 2H), 2.33 - 2.27 (m, 2H), 2.12 (s, 3H), 1.19 - 1.12 (m, IH), 0.95 (br d, *J*=5.9 Hz, 6H), 0.48 - 0.34 (m, 2H), 0.28 - 0.16 (m, 2H); LCMS [M+H]+: 635.1.

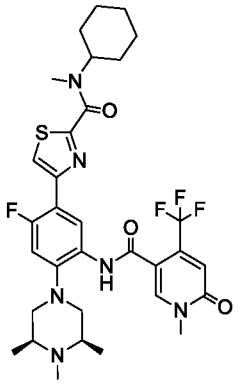
Example 525: N-cyclohexyl-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl] -l,3-thiazole-2-carboxamide



[00901] The title compound was prepared by procedures similar to Example 482 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid and 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-

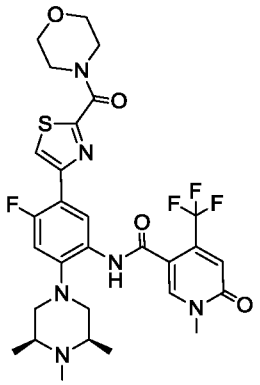
cyclohexylthiazole-2-carboxamide. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.55 (s, IH), 8.48 (d, *J*=8.3 Hz, IH), 8.39 (s, IH), 8.20 (d, *J*=8.4 Hz, IH), 8.14 (d, *J*=2.1 Hz, IH), 7.06 (d, *J*=13.1 Hz, IH), 6.89 (s, IH), 3.55 (s, 3H), 3.08 (br d, *J*=11.2 Hz, 2H), 2.39 - 2.30 (m, 2H), 2.18 (s, 3H), 1.87 - 1.78 (m, 2H), 1.73 (br d, *J*=13.2 Hz, 2H), 1.64 - 1.56 (m, IH), 1.45 (dq, *J*=3.1, 12.0 Hz, 2H), 1.36 - 1.23 (m, 2H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 649.2.

Example 526: N-cyclohexyl-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide



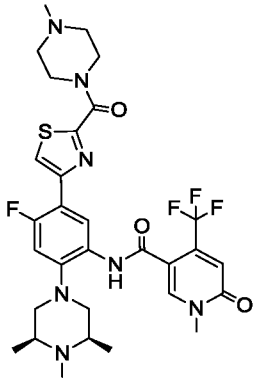
[00902] The title compound was prepared according to a procedure similar to that of Example 482 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid and 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-cyclohexyl-N-methylthiazole-2-carboxamide. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.49 (br s, IH), 8.39 - 8.29 (m, 2H), 8.13 (s, IH), 7.15 - 7.04 (m, IH), 6.88 (s, IH), 3.53 (s, 3H), 3.09 (br d, *J*=10.6 Hz, 2H), 2.37 (br t, *J*=6.9 Hz, 2H), 2.19 (s, 3H), 1.78 (br d, *J*=10.9 Hz, 2H), 1.70 - 1.55 (m, 4H), 1.38 (br d, *J*=9.8 Hz, 3H), 1.02 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 663.4.

Example 527: N-[4-fluoro-5-[2-(morpholine-4-carbonyl)-l, 3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00903] The title compound was prepared according to a procedure similar to that described above for the preparation of Example 482 using 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid and (4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-2-yl)(morpholino)methanone. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (s, IH), 8.39 (d, *J*=8.3 Hz, IH), 8.25 (s, IH), 8.16 (d, *J*=2.0 Hz, IH), 7.08 (d, *J*=13.0 Hz, IH), 6.89 (s, IH), 4.36 (br s, 2H), 3.70 (br s, 6H), 3.53 (s, 3H), 3.09 (br d, *J*=11.0 Hz, 2H), 2.43 - 2.34 (m, 3H), 2.20 (s, 3H), 1.03 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 637.3.

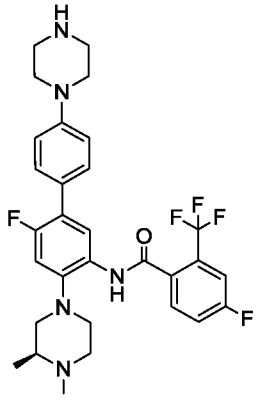
Example 528: N-[4-fluoro-5-[2-(4-methylpiperazine-l -carbonyl)-l ,3-thiazol-4-yl]-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00904] The title compound was prepared according to a procedure similar to that described above for the preparation of Example 482 using 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid and (4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-2-yl)(4-methylpiperazin-l-

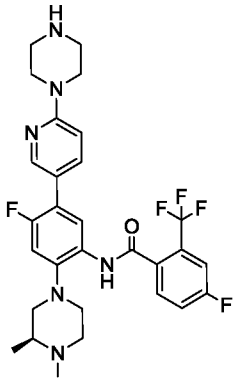
yl)methanone. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.49 (s, IH), 8.41 (d, *J*=8.3 Hz, IH), 8.23 (s, IH), 8.14 (d, *J*=2.0 Hz, IH), 7.07 (d, *J*=13.0 Hz, IH), 6.89 (s, IH), 4.29 (br s, 2H), 3.68 (br s, 2H), 3.52 (s, 3H), 3.08 (br d, *J*=ll.l Hz, 2H), 2.42 (br s, 5H), 2.20 (s, 3H), 2.20 (s, 3H), 1.03 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 650.3.

Example 529: 4-fluoro-N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



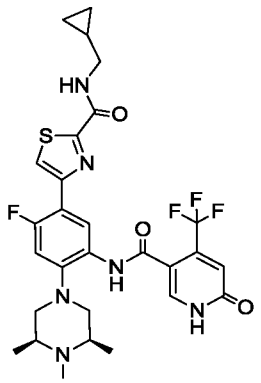
[00905] To a solution of tert-butyl (S)-4-(4'-(3,4-dimethylpiperazin-l-yl)-2'-fluoro-5'-(4-fluoro-2-(trifluoromethyl)berizarnido)-[1,1'-biphenyl]-4-yl)piperazine-l -carboxylate (68.4 mg, 0.102 mmol, prepared by similar methods to Example 400) in DCM (3 ml) was added trifluoroacetic acid (3 ml, 39.2 mmol). The reaction mixture was stirred at 24 °C for 30 minutes. Workup and purification gave the title compound (58.1 mg, 0.096 mmol, 95 % yield) as a white powder. ¾ NMR (500MHz, DMSO-d6) δ = 9.60 (s, IH), 7.75-7.83 (m, 3H), 7.69-7.74 (m, IH), 7.44 (d, *J*=8.80 Hz, IH), 7.36 (d, *J*=7.95 Hz, 2H), 7.00-7.07 (m, 3H), 6.88-6.97 (m, IH), 3.09-3.14 (m, 4H), 3.09-3.14 (m, 4H), 2.98-3.08 (m, 4H), 2.84-2.89 (m, 6H), 2.74-2.81 (m, IH), 2.43 (t, *J*=10.51 Hz, IH), 2.27-2.34 (m, IH), 2.19 (s, 4H), 0.98 (d, *J*=6.24 Hz, 3H); LCMS [M+H]+ 574.4.

Example 530: 4-fluoro-N-[4-fluoro-5-(6-piperazin-l-ylpyridin-3-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00906] To a solution of tert-butyl (S)-4-(5-(4-(3,4-dimethylpiperazin-l-yl)-2-fluoro-5-(4-fluoro-2-(trifluoromethyl)benzamido)phenyl)pyridin-2-yl)piperazine-l-carboxylate (69.9 mg, 0.104 mmol, prepared by similar methods as those in Example 400) in DCM (3 ml) was added TFA (3 ml, 39.2 mmol). The reaction mixture was stirred at 24 °C for 30 min. Standard workup and purification gave the title compound (47.7 mg, 0.081 mmol, 79 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.63 (s, 1H), 8.25 (s, 1H), 7.75-7.83 (m, 3H), 7.72 (dt, *J*=1.96, 8.30 Hz, 1H), 7.65 (d, *J*=8.80 Hz, 1H), 7.07 (d, *J*=12.35 Hz, 1H), 6.90 (d, *J*=8.93 Hz, 1H), 3.43-3.48 (m, 4H), 3.02 (dd, *J*=10.94, 18.28 Hz, 2H), 2.72-2.86 (m, 7H), 2.43 (t, *J*=10.51 Hz, 1H), 2.27-2.34 (m, 1H), 2.19 (s, 4H), 0.98 (d, *J*=6.24 Hz, 3H); LCMS [M+H]+ 575.4.

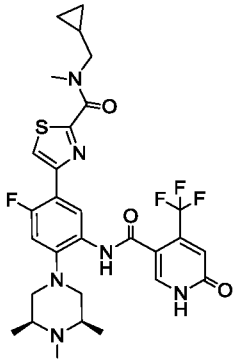
Example 531: N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l -yljphenylj-l ,3-thiazole-2-carboxamide



[00907] The title compound was prepared in a manner similar to Example 482 from 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid and 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-

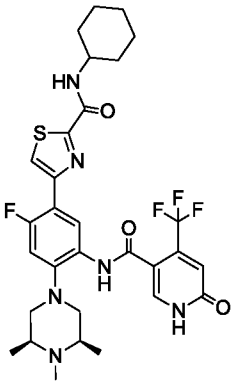
(cyclopropylmethyl)thiazole-2-carboxamide. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.54 (s, IH), 8.86 (t, *J*=6.0 Hz, IH), 8.20 (d, *J*=8.6 Hz, IH), 8.14 (d, *J*=2.1 Hz, IH), 8.01 (s, IH), 7.06 (d, *J*=13.1 Hz, IH), 6.75 (s, IH), 3.17 (t, *J*=6.5 Hz, 3H), 3.08 (br d, *J*=ll.l Hz, 2H), 2.37 - 2.27 (m, 3H), 2.19 (s, 3H), 1.24 (s, IH), 1.01 (d, *J*=6.1 Hz, 6H), 0.47 - 0.42 (m, 2H), 0.29 - 0.24 (m, 2H); LCMS [M+H]+: 607.0.

Example 532: N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide



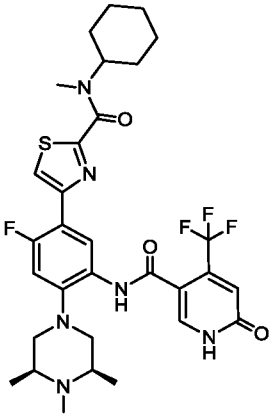
[00908] The title compound was prepared according to a procedure similar to Example 482 using 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-(cyclopropylmethyl)-N-methylthiazole-2-carboxamide and 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.43 - 9.32 (m, IH), 8.32 - 8.23 (m, IH), 8.06 (d, *J*=1.8 Hz, IH), 7.86 (br s, IH), 7.04 - 6.93 (m, IH), 6.62 (br s, IH), 3.90 (d, *J*=7.0 Hz, IH), 3.53 (s, IH), 3.34 (br d, *J*=6.8 Hz, IH), 3.05 (s, 2H), 3.00 (br d, *J*=10.1 Hz, 2H), 2.31 - 2.25 (m, 2H), 2.13 (s, 3H), 1.17 (s, IH), 0.95 (d, *J*=6.1 Hz, 6H), 0.46 - 0.35 (m, 2H), 0.27 - 0.17 (m, 2H); LCMS [M+H]+: 621.6.

Example 533: N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide



[00909] The title compound was prepared according to a procedure similar to Example 482 from 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-cyclohexylthiazole-2-carboxamide and 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.41 (br s, IH), 8.41 (d, *J*=8.6 Hz, IH), 8.12 (d, *J*=8.4 Hz, IH), 8.05 (d, *J*=2.1 Hz, IH), 7.96 (s, IH), 6.97 (d, *J*=13.1 Hz, IH), 6.61 (br s, IH), 3.70 (dtd, *J*=3.7, 7.7, 15.1 Hz, IH), 3.00 (br d, *J*=10.9 Hz, 3H), 2.29 - 2.21 (m, 2H), 2.12 (s, 3H), 1.79 - 1.72 (m, 2H), 1.66 (br d, *J*=13.0 Hz, 2H), 1.58 - 1.50 (m, IH), 1.44 - 1.33 (m, 2H), 1.29 - 1.15 (m, 4H), 1.10 - 1.03 (m, IH), 0.93 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 635.2.

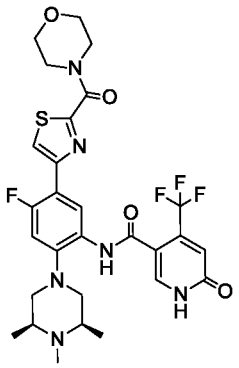
Example 534: N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide



[00910] The title compound was prepared according to a procedure similar to Example 482 from 4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-N-cyclohexyl-N-methylthiazole-2-carboxamide and 4-(trifluoromethyl)-6-

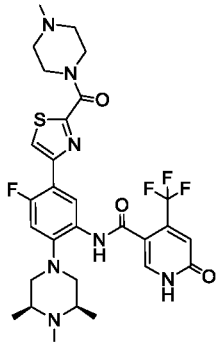
(2-(trimethylsilyl)ethoxy)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.52 (s, IH), 8.34 - 8.25 (m, IH), 8.13 (s, IH), 7.95 - 7.86 (m, IH), 7.12 - 7.02 (m, IH), 6.76 (s, IH), 5.23 - 5.09 (m, IH), 4.40 - 4.29 (m, IH), 3.39 (s, IH), 3.08 (br d, *J*=10.9 Hz, 2H), 2.94 (s, 2H), 2.36 (br dd, *J*=3.4, 6.7 Hz, 2H), 2.20 (s, 3H), 1.79 (br d, *J*=10.9 Hz, 2H), 1.73 - 1.54 (m, 5H), 1.46 - 1.29 (m, 3H), 1.24 (s, IH), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 649.4.

Example 535: N-[4-fluoro-5-[2-(morpholine-4-carbonyl)-l, 3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



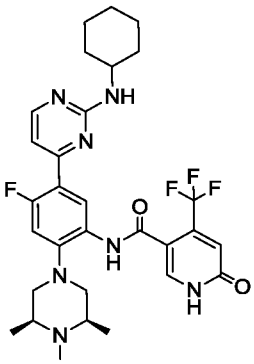
[00911] The title compound was prepared according to a procedure similar to the preparation of Example 482 from (4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)thiazol-2-yl)(morpholino)methanone and 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.65 - 12.42 (m, IH), 9.55 (s, IH), 8.36 (d, *J*=8.4 Hz, IH), 8.15 (d, *J*=2.1 Hz, IH), 7.86 (s, IH), 7.06 (d, *J*=13.1 Hz, IH), 6.79 (s, IH), 4.39 (br s, 2H), 3.71 (br s, 6H), 3.09 (br d, *J*=10.9 Hz, 2H), 2.41 - 2.33 (m, 2H), 2.21 (s, 3H), 1.03 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 623.5.

Example 536: N-[4-fluoro-5-[2-(4-methylpiperazine-l -carbonyl)-l ,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00912] The title compound was prepared by a procedure similar to the preparation of Example 482 from (4-(5-amino-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)thiazol-2-yl)(4-methylpiperazin- 1-yl)methanone and 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (br s, IH), 8.40 (br d, *J*=8.3 Hz, IH), 8.14 (d, *J=l.6* Hz, IH), 7.87 (s, IH), 7.07 (d, *J*=13.0 Hz, IH), 6.73 (br s, IH), 4.32 (br s, 2H), 3.69 (br s, 2H), 3.08 (br d, *J*=11.0 Hz, 2H), 2.43 (br s, 4H), 2.38 (br d, *J*=6.6 Hz, 2H), 2.22 (br s, 6H), 1.04 (d, *J*=6.0 Hz, 7H); LCMS [M+H]+: 636.5.

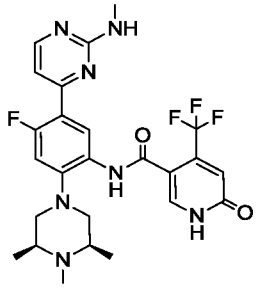
Example 537: N-[5-[2-(cyclohexylamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[00913] In N,N-Dimethylformamide (520 μï) was dissolved N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (106 mg, 0.130 mmol, preparation described in Example 384). To the solution was added (4-bromopyrimidin-2-yl)cyclohexylamine (33.3 mg, 0.130 mmol), LiCl (16.53 mg, 0.390 mmol) and bis(triphenylphosphine)palladium(II) dichloride (5.02 mg, 7.15 μηιοï) at room temperature and then it was microwaved at the temperature of 120 °C

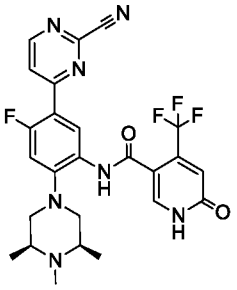
for 3 hours. The reaction mixture was quenched with water and then extracted with DCM. The organic layer, thus separated, was concentrated and purified by column chromatography. Purification was performed via Biotage column, (100-0%, CH2CI2: 10%» MeOH in CH_2C1_2 + NH_4Ac; in 10 min and isocratic for 5min [new isolera 2.3] using KP-SIL lOg column. Collected 20% of the $CH2C1_2$) to yield the pure product that was lyophilized for 1 day. There were several impurities present so it was decided to purify via prep-HPLC after the deprotection. The product was dissolved in 2 mL of DCM and trifluoroacetic acid (995 μï, 12.99 mmol) was added. The purple solution was stirred for 1 h and the solvent was evaporated. The product was purified by prep HPLC to give the title compound (4.3 mg, 6% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.56 (s, 1H), 8.24 (d, *J* = 5.3 Hz, 1H), 7.91 (s, 1H), 7.06 - 6.99 (m, 2H), 6.92 (s, 1H), 3.86 (s, 1H), 3.15 (s, 1H), 2.68 - 2.54 (m, 4H), 2.40 (s, 3H), 2.04 (d, *J* = 9.9 Hz, 2H), 1.78 (d, *J* = 13.6 Hz, 2H), 1.66 (d, *J* = 13.0 Hz, 1H), 1.46 (dd, *J* = 25.1, 12.5 Hz, 2H), 1.34 - 1.24 (m, 3H), 1.18 (d, *J* = 5.6 Hz, 6H); LCMS [M+l] $^+$ = 602.7.

Example 538: N-[4-fluoro-5-[2-(methylamino)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carb oxamide



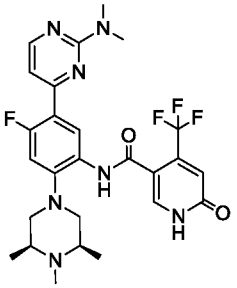
[00914] The title compound was prepared similar to the sequence described above for the preparation of Example 537 using 4-bromo-N-methylpyrimidin-2-amine and N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide. ^{1}H NMR (500 MHz, MeOD) δ 8.53 (s, 1H), 8.27 (d, *J* = 5.2 Hz, 1H), 7.94 (s, 1H), 7.06 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.03 (d, *J* = 13.1 Hz, 1H), 6.92 (s, 1H), 3.19 (s, 2H), 2.98 (s, 3H), 2.69 (s, 2H), 2.45 (s, 2H), 1.20 (s, 6H); LCMS [M+l] $^+$ = 534.6.

Example 539: N-[5-(2-cyanopyrimidin-4-yl)-4-fluoro-2-[(3R, 5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



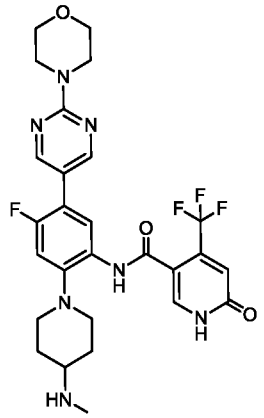
[00915] The title compound was prepared similar to the sequence described above for the preparation of Example 537 using 4-bromopyrimidine-2-carbonitrile and N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide. ^{1}H NMR (500 MHz, DMSO) δ 9.72 (s, 1H), 9.00 (d, *J* = 5.5 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 5.0 Hz, 1H), 7.08 (d, *J* = 13.9 Hz, 1H), 6.82 (s, 1H), 3.23 (d, *J* = 10.9 Hz, 2H), 2.55 (d, *J* = 11.1 Hz, 2H), 2.34 (s, 2H), 2.19 (s, 4H), 1.01 (d, *J* = 5.9 Hz, 6H); ^{19}F NMR (471 MHz, DMSO) δ -61.26 (s), -114.60 (s); LCMS HSS [M+l] $^{+}$ = 530.5.

Example 540: N-[5-[2-(dimethylamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide

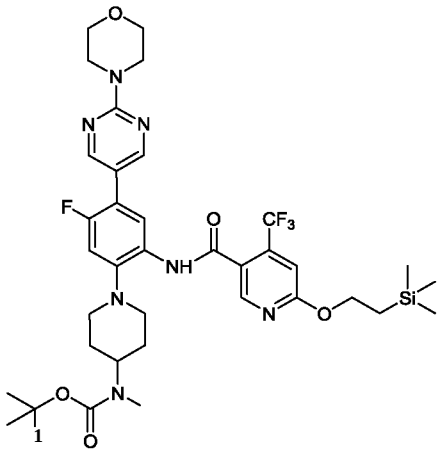


[00916] The title compound was prepared similar to the sequence described above for the preparation of Example 537 using 4-bromo-N,N-dimethylpyrimidin-2-amine and N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide. ^{1}H NMR (500 MHz, MeOD) δ 8.60 (d, *J* = 8.1 Hz, 1H), 8.32 (d, *J* = 5.3 Hz, 1H), 7.93 (s, 1H), 7.05 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.00 (d, *J* = 13.2 Hz, 1H), 6.91 (s, 1H), 3.23 (s, 6H), 3.16 (d, *J* = 11.2 Hz, 2H), 2.63 (t, *J* = 11.2 Hz, 2H), 2.56 (d, *J* = 6.2 Hz, 2H), 2.37 (s, 3H), 1.17 (d, *J* = 6.2 Hz, 6H); LCMS [M+l] $^{+}$ = 590.6.

Example 541: N-[4-fluoro-2-[4-(methylamino)piperidin-l-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



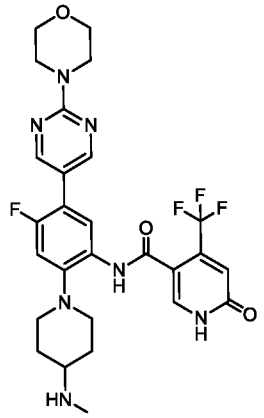
Step 1: tert-butyl (l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)piperidin-4-y^^ (methyl)carbamate



[00917] To a solution of tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)piperidin-4-yl)(methyl)carbamate , (0.623 g, 1.280 mmol, prepared from a 3 step procedure similar to Examples hereinabove starting from tert-butyl methyl(piperidin-4-yl)carbamate and l-bromo-2,4-difluoro-5-nitrobenzene), 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.512 g, 1.664 mmol) in ethyl acetate (EtOAc) (15 ml) was added 4-methylmorpholine (0.422 ml, 3.84 mmol) at 0 °C. The reaction mixture was stirred for 15 minutes before adding propylphosphonic anhydride solution (2.287 ml, 3.84 mmol) dropwise. The reaction mixture was further stirred at 0 °C for 1 hour and at room temperature for an

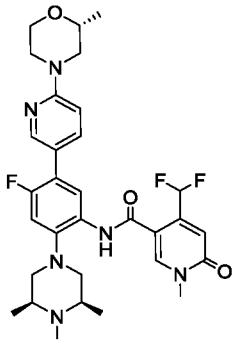
extra 5 hours. A standard workup and purification with silica gel chromatography afforded the title compound (1.08 g, 84% yield). LCMS [M+H]+ = 776.5.

Step 2: N-[4-fluoro-2-[4-(methylamino)piperidin-l-ylJ-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



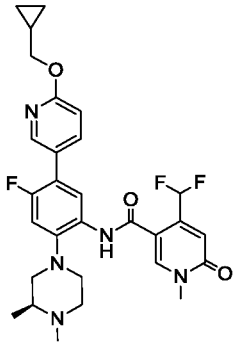
[00918] To a solution of tert-butyl (l-(5-fluoro-4-(2-mo rpholinopyrimidin-5-yl)-2-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)phenyl)piperidin-4-yl)(methyl)carbamate (1.0756 g, 1.081 mmol) in DCM (3 mL) was added TFA (3 ml, 39.2 mmol). The reaction mixture was stirred at 24 °C for 30 minutes. The TFA and solvent were removed under vacuum and the product was purified by Flash chromatography [0-30% MeOH/DCM] to afford the TFA salt of N-(4-fluoro-2-(4-(methylamino)piperidin-l-yl)-5-(2-mo ϕ holinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-a^hydropyridine-3-carboxarnide. The product was dissolved in MeOH and passed through a PoraPak Rxn CX (20cc-2g) cartridge in a catch and elute method. The cartridge was washed with MeOH, then the solution of product in MeOH was added onto the cartridge. The cartridge was rinsed with MeOH (2x20mL) and then with a solution of lOmL (NH_3 in MeOH at 7N) in 40 mL of MeOH to release the free base of the title compound (228.9 mg, 0.338 mmol, 31.3 % yield) as a white powder. ^1H NMR (500MHz, DMSO-d6) δ = 9.43 (s, 1H), 8.52 (d, *J*=0.86 Hz, 2H), 7.95 (s, 1H), 7.81 (d, *J*=8.56 Hz, 1H), 7.09 (d, *J*=12.35 Hz, 1H), 6.73 (s, 1H), 3.74-3.78 (m, 4H), 3.65-3.70 (m, 4H), 3.11 (d, *J*=11.74 Hz, 2H), 2.66 (t, *J*=11.19 Hz, 2H), 2.42-2.48 (m, 1H), 2.31 (s, 3H), 1.88 (d, *J*=14.55 Hz, 2H), 1.44 (d, *J*=10.15 Hz, 2H); LCMS [M+H]+ 576.5.

Example 542: 4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmorpholin-4-ylJpyridin-3-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



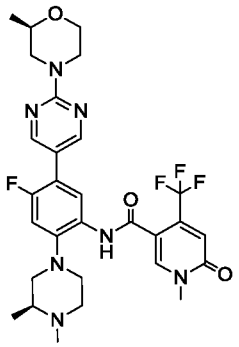
[00919] To a suspension of 4-(difluoromethyl)-N-(4-fluoro-5-(6 **-((R)**-2-methylmo rpholino)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (41.8 mg, 0.071 mmol) and cesium carbonate (25.6 mg, 0.079 mmol) in N,N-dimethylformamide (4 ml) was added iodomethane (4.90 µï, 0.079 mmol) at room temperature and the reaction mixture was stirred for 2 hours. Then the reaction mixture was poured into water and the product was extracted by DCM. The organic phase was dried over MgSC>4. After filtration and evaporation of the solvent, the product was dissolved in MeOH and passed through a PoraPak Rxn CX (20cc-2g) cartridge in a catch and elute method. The cartridge was washed with MeOH, then the solution of product in MeOH was added onto the cartridge. The cartridge was rinsed with MeOH (2x20mL) and then with a solution of lOmL (NH_3 in MeOH at 7N) in 40 mL of MeOH to release the free base of 4-(difluoromethyl)-N-(4-fluoro-5-(6-((R)-2-methylmorpholino)pyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (36.2 mg, 80 % yield) as an off-white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 (s, IH), 8.35 (s, IH), 8.26 (s, IH), 7.64-7.70 (m, 2H), 7.33 (t, *J*=54.50 Hz, IH), 7.03 (d, *J*=12.47 Hz, IH), 6.94 (d, *J*=8.93 Hz, IH), 6.64 (s, IH), 4.18 (d, *J*=12.47 Hz, IH), 4.08 (d, *J*=12.84 Hz, IH), 3.92 (dd, *J*=2.45, 11.49 Hz, IH), 3.56 (dd, *J*=2.51, 11.07 Hz, 2H), 3.52 (s, 3H), 3.02 (d, *J*=10.88 Hz, 2H), 2.84 (dt, *J*=3.42, 12.35 Hz, IH), 2.35 (d, *J*=6.24 Hz, 2H), 2.19 (s, 3H), 1.17 (d, *J*=6.24 Hz, 4H), 1.00 (d, *J*=6.11 Hz, 6H); LCMS [M]+ 599.6.

Example 543: N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3 -carboxamide



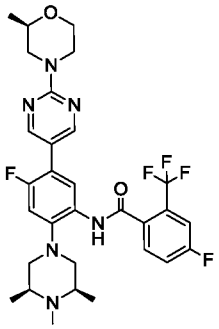
[00920] The procedure followed was similar to Example 217 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-(cyclopropylmethoxy)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine (37.1 mg, 0.135 mmol) to afford the title compound (28.4 mg, 0.049 mmol, 82 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 (s, IH), 8.31 (s, IH), 8.25 (s, IH), 7.81 (d, *J*=9.78 Hz, IH), 7.76 (d, *J*=8.44 Hz, IH), 7.09 (d, *J*=12.35 Hz, IH), 6.94 (d, *J*=8.68 Hz, IH), 6.87 (s, IH), 4.14 (d, *J*=7.21 Hz, 2H), 3.52 (s, 3H), 2.98-3.09 (m, 2H), 2.83 (br. s., IH), 2.72-2.79 (m, IH), 2.42 (t, *J*=10.45 Hz, IH), 2.31-2.38 (m, IH), 2.18-2.29 (m, 4H), 1.23 (s, 2H), 0.98 (d, *J*=6.24 Hz, 3H), 0.56 (dd, *J*=1.59, 8.07 Hz, 2H), 0.34 (d, *J*=4.89 Hz, 2H); LCMS [M+H]+ 574.4.

Example 544: N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



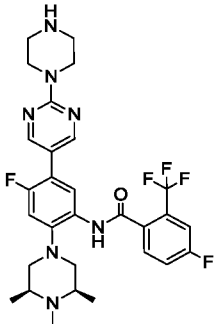
[00921] The title compound (off white solid, 16.4 mg, 35%) was prepared by a procedure similar to Example 100 using crude (R)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.15 mmol x 2) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (38 mg, 0.075 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.27 (s, IH), 7.91 (d, *J*=8.2 Hz, IH), 7.12 (d, *J*=12.1 Hz, IH), 6.95 (s, IH), 4.65 - 4.54 (m, 2H), 3.99 (dd, *J*=2.5, 11.6 Hz, IH), 3.67 (s, 3H), 3.65 - 3.59 (m, 2H), 3.17 - 3.03 (m, 3H), 3.02 - 2.87 (m, 2H), 2.73 (dd, *J*=10.5, 13.3 Hz, IH), 2.59 (br t, *J*=10.6 Hz, 2H), 2.47 (br s, IH), 2.41 (br s, 3H), 1.25 (d, *J*=6.2 Hz, 3H), 1.15 (br d, *J*=6.1 Hz, 3H); LCMS [M + H]$^{+}$ 604.4.

Example 545: 4-fluoro-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



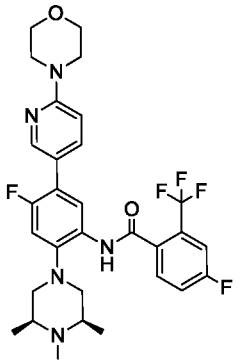
[00922] The title compound (formic acid salt, off white solid, 44.0 mg, 67%) was prepared by a procedure similar to Example 31 using crude (R)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.44 (br s, IH), 8.06 (d, *J*=8.2 Hz, IH), 7.81 (dd, *J*=5.3, 8.4 Hz, IH), 7.67 (dd, *J*=2.2, 9.0 Hz, IH), 7.58 (dt, *J*=2.3, 8.3 Hz, IH), 7.20 (d, *J*=11.7 Hz, IH), 4.66 - 4.55 (m, 2H), 3.99 (dd, *J*=3.1, 11.5 Hz, IH), 3.68 - 3.59 (m, 2H), 3.30 - 3.19 (m, 4H), 3.18 - 3.05 (m, IH), 2.97 - 2.86 (m, 2H), 2.82 - 2.77 (m, 3H), 2.74 (dd, *J*=10.5, 13.1 Hz, IH), 1.37 (dd, *J*=1.5, 6.1 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^{+}$ 605.4.

Example 546: 4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



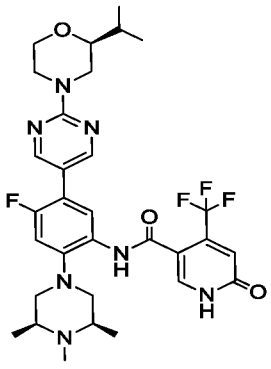
[00923] Intermediate tert-butyl 4-(5-(2-fluoro-5-(4-fluoro-2-(trifluoromethyl)benzamido)-4-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)pyrimidin-2-yl)piperazine-l-carboxylate (dark brown solid) was prepared by a procedure similar to Example 400 using 2-(4-Boc-piperazino)pyrimidine-5-boronic acid pinacol ester (78 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). LCMS $[M + H]^+$ 690.4. The solid was redissolved in DCM (5 mL) and treated with TFA (0.31 mL). The resulting mixture was stirred at rt overnight. After removal of the solvents, the residue was purified by prep-HPLC and Biotage Isolute SCX-2 column to give the title compound as a beige solid (49.0 mg, 81% over 2 steps). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.02 (d, *J*=8.2 Hz, IH), 7.78 (dd, *J*=5.3, 8.4 Hz, IH), 7.66 (dd, *J*=2.3, 9.0 Hz, IH), 7.57 (dt, *J*=2.2, 8.2 Hz, IH), 7.11 (d, *J*=12.0 Hz, IH), 3.88 (br s, 4H), 3.06 (br d, *J*=11.2 Hz, 2H), 2.93 (br s, 4H), 2.62 (br t, *J*=11.2 Hz, 2H), 2.51 - 2.41 (m, 2H), 2.34 (s, 3H), 1.16 (d, *J*=6.2 Hz, 6H); LCMS $[M + H]^+$ 590.4.

Example 547: 4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



[00924] The title compound (formic acid salt, pale beige solid, 57.1 mg, 88%) was prepared by a procedure similar to Example 400 using 4-[5-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-mo rpholine (58 mg, 0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.42 (br s, IH), 8.35 (s, IH), 8.07 (d, *J*=8.2 Hz, IH), 7.85 - 7.77 (m, 2H), 7.67 (br d, *J*=8.8 Hz, IH), 7.58 (br t, *J*=7.9 Hz, IH), 7.20 (d, *J*=11.9 Hz, IH), 6.94 (br d, *J*=8.9 Hz, IH), 3.87 - 3.78 (m, 4H), 3.56 (br s, 4H), 3.42 (br s, 2H), 3.30 (br d, *J*=12.8 Hz, 2H), 3.00 (br d, *J*=10.5 Hz, 2H), 2.89 (s, 3H), 1.42 (br d, *J*=6.2 Hz, 6H); LCMS $[M + H]^{+}$ 590.4.

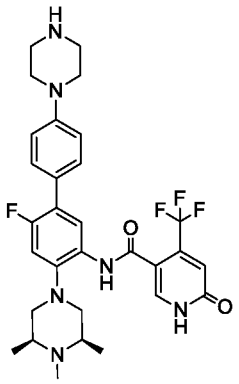
Example 548: N-[4-fluoro-5-[2-[(2R)-2-propan-2-ylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00925] The title compound (beige solid, 30.8 mg, 49%) was prepared by a procedure similar to Example 29 using crude (S)-(2-(2-isopropylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-

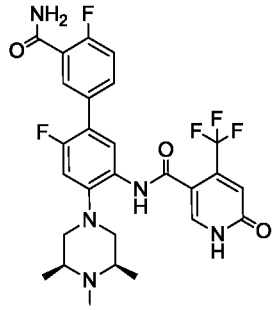
trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50.5 mg, 0.1 mmol). ¾ NMR (500MHz, CHLOROFORM-d) δ = 8.69 (br s, IH), 8.56 (s, 2H), 8.45 (br d, *J*=7.9 Hz, IH), 7.86 (s, IH), 7.06 - 6.97 (m, 2H), 4.67 (br d, *J*=13.0 Hz, IH), 4.56 (br d, *J*=13.2 Hz, IH), 4.03 (dd, *J*=2.5, 11.4 Hz, IH), 3.62 (dt, *J*=2.6, 11.6 Hz, IH), 3.22 - 3.04 (m, 2H), 2.89 - 2.76 (m, 3H), 2.73 - 2.58 (m, 2H), 2.41 - 2.25 (m, 5H), 1.81 (qd, *J*=6.8, 13.5 Hz, IH), 1.14 (br d, *J*=5.7 Hz, 6H), 1.04 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H); LCMS $[M + H]^+$ 632.6.

Example 549: N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



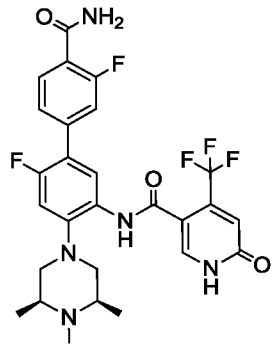
[00926] The procedure followed was similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (207 mg, 0.342 mmol) and tert-butyl 4-[4-(4,4,5, 5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl]tetrahydro-l(2H)-pyrazinecarboxylate (211 mg, 0.543 mmol) to afford the intermediate tert-butyl 4-(2'-fluoro-5'-(4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)- [1,1'-biphenyl] -4-yl)piperazine- 1-carboxylate which was deprotected using TFA and DCM according to procedures hereinabove to provide the title compound (18.2 mg, 66.3 % yield) as a white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.44 (s, IH), 7.92 (s, IH), 7.75 (d, *J*=8.56 Hz, IH), 7.35 (d, *J*=7.83 Hz, 2H), 6.96-7.03 (m, 3H), 6.78 (s, IH), 3.08-3.14 (m, 4H), 3.00 (d, *J*=10.88 Hz, 2H), 2.83-2.89 (m, 4H), 2.45 (t, *J*=10.94 Hz, 2H), 2.30-2.38 (m, 2H), 2.19 (s, 3H), 1.01 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 587.4.

Example 550: N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00927] The title compound was prepared using a procedure similar to that used in Example 100 using 3-carbamoyl-4-fluorophenylboronic acid to afford the title compound (TFA salt) as a white solid (43 mg, 0.060 mmol, 98 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.85 (s, IH), 7.85 - 7.82 (m, IH), 7.80 (d, *J*=8.2 Hz, IH), 7.60 - 7.50 (m, IH), 7.18 (dd, *J*=8.7, 10.6 Hz, IH), 7.02 (d, *J*=11.7 Hz, IH), 6.79 - 6.74 (m, IH), 3.39 - 3.30 (m, 2H), 3.24 (br d, *J*=13.1 Hz, 2H), 2.84 (s, 3H), 2.81 -2.73 (m, 2H), 1.29 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^+$ 564.

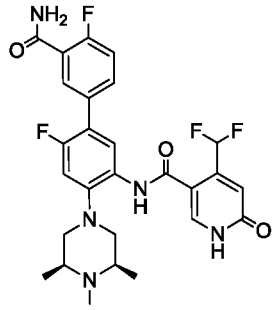
Example 551: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[00928] The procedure followed was similar to Example 100 using *N*-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (62 mg, 0.102 mmol) and 4-carbamoyl-3-fluorophenylboronic acid, 96% (28.1 mg, 0.154 mmol) afforded, after deprotection of the intermediate, the title compound as a white solid (53 mg, 99 % yield for last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.92 (s, IH), 7.90 (d, *J*=8.1 Hz, IH), 7.81 (t, *J*=7.9 Hz, IH), 7.39 (d, *J*=8.1 Hz, IH), 7.34 (d, *J*=12.2 Hz, IH), 7.09 (d, *J*=11.9

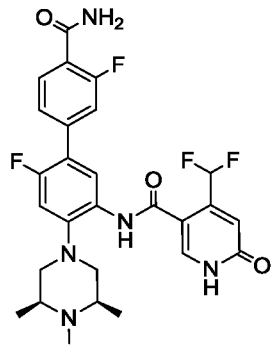
Hz, 1H), 6.85 - 6.82 (m, 1H), 3.45 - 3.37 (m, 2H), 3.31 (br d, *J*=13.1 Hz, 2H), 2.89 (s, 3H), 2.88 - 2.79 (m, 2H), 1.35 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 564.

Example 552: N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpipercmn-l-yl]phmyl]-4-(diflwromethy^)-6-oxo-1H-pyridine-3-carboxamide



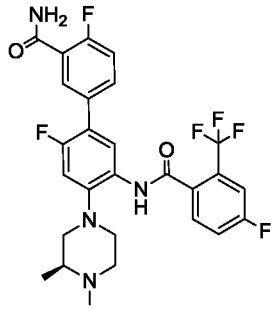
[00929] A procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (60 mg, 0.102 mmol, preparation shown in Example 397) and 3-carbamoyl-4-fluorophenylboronic acid, 97% (28.0 mg, 0.153 mmol) gave, after deprotection of the silyloxy intermediate, the title compound (TFA salt) as a white solid (61 mg, 0.075 mmol, 95 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.96 (s, 1H), 7.89 (br d, *J*=6.0 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.32 - 7.08 (m, 2H), 7.05 (d, *J*=11.7 Hz, 1H), 6.72 - 6.67 (m, 1H), 3.42 - 3.34 (m, 2H), 3.31 (br d, *J*=13.3 Hz, 2H), 2.88 (s, 3H), 2.86 - 2.78 (m, 2H), 1.34 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 546.

Example 553: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl] -4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide



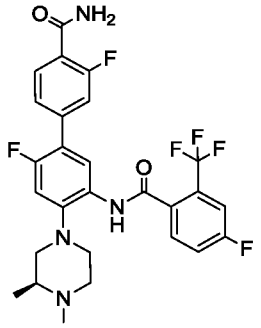
[00930] The title compound was prepared by a procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (60 mg, 0.102 mmol) and 4-carbamoyl-3-fluorophenylboronic acid, 96% (28.0 mg, 0.153 mmol). Deprotection with TFA gave the product (TFA salt) as an off- white solid (66.8 mg, 0.082 mmol, 95 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 (s, 1H), 7.82 (t, *J*=8.0 Hz, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 7.40 (d, *J*=8.2 Hz, 1H), 7.37 - 7.11 (m, 2H), 7.08 (d, *J*=12.0 Hz, 1H), 6.72 (s, 1H), 3.45 - 3.37 (m, 2H), 3.34 (br d, *J*=13.3 Hz, 2H), 2.91 (s, 3H), 2.89 - 2.83 (m, 2H), 1.36 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 546.

Example 554: 2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



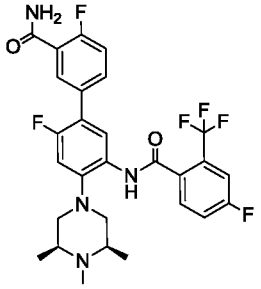
[00931] A procedure similar to Example 400 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (62 mg, 0.126 mmol) and 3-carbamoyl-4-fluorophenylboronic acid, 97% (34.6 mg, 0.189 mmol) gave the title compound which was isolated as a very light yellow foamy powder (45.7 mg, 0.079 mmol, 62.6 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.07 (d, *J*=8.2 Hz, 1H), 8.02 (br d, *J*=6.1 Hz, 1H), 7.79 (dd, *J*=5.4, 8.4 Hz, 1H), 7.77 - 7.71 (m, 1H), 7.66 (dd, *J*=2.3, 9.0 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.34 (dd, *J*=8.7, 10.6 Hz, 1H), 7.13 (d, *J*=12.0 Hz, 1H), 3.14 (br dd, *J*=1.9, 11.4 Hz, 1H), 3.10 - 3.04 (m, 1H), 3.00 - 2.95 (m, 1H), 2.92 (br d, *J*=13.8 Hz, 1H), 2.59 (t, *J*=10.9 Hz, 1H), 2.49 (dt, *J*=2.6, 11.2 Hz, 1H), 2.35 (s, 3H), 1.13 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 551.

Example 555: 2-fluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[00932] A procedure similar to Example 400 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (62 mg, 0.126 mmol) and 4-carbamoyl-3-fluorophenylboronic acid, 96% (34.6 mg, 0.189 mmol) provided the title compound as an off-white foamy powder (41 mg, 0.071 mmol, 56.2% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.09 (d, *J*=8.2 Hz, IH), 7.93 (t, *J*=8.0 Hz, IH), 7.82 - 7.76 (m, IH), 7.66 (dd, *J*=2.2, 9.0 Hz, IH), 7.57 (dt, *J*=2.3, 8.3 Hz, IH), 7.52 (br d, *J*=8.2 Hz, IH), 7.47 (br d, *J*=12.3 Hz, IH), 7.14 (d, *J*=12.2 Hz, IH), 3.16 (br dd, *J*=1.7, 11.4 Hz, IH), 3.11 (br d, *J*=11.6 Hz, IH), 3.01 - 2.96 (m, IH), 2.95 - 2.90 (m, IH), 2.59 (t, *J*=10.9 Hz, IH), 2.49 (dt, *J*=2.7, 11.2 Hz, IH), 2.37 (br d, *J*=2.9 Hz, IH), 2.35 (s, 3H), 1.14 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 551.

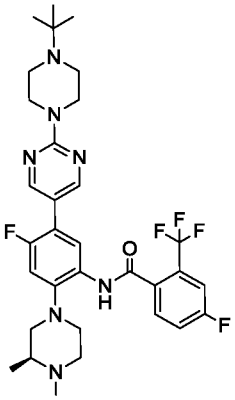
Example 556: 2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-ylJphenylJbenzamide



[00933] A procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (31 mg, 0.061 mmol) and 3-carbamoyl -4-fluorophenylboronic acid, 97% (16.80 mg, 0.092 mmol) provided the title compound which was isolated as a white fluffy powder (25.9 mg, 0.044 mmol, 71.2 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.94 (d, *J*=8.2 Hz, IH), 7.91 - 7.88 (m, IH), 7.69 - 7.60 (m, 2H), 7.54 (dd, *J*=2.3, 9.0 Hz, IH), 7.45 (dt, *J*=2.4, 8.3 Hz, IH), 7.23 (dd, *J*=8.6, 10.7 Hz, IH), 7.02 - 6.94 (m, IH),

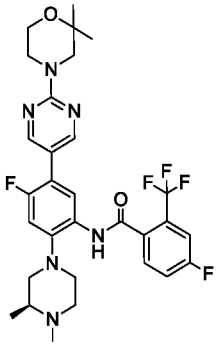
2.97 (br d, *J*=11.4 Hz, 2H), 2.52 (t, *J*=11.2 Hz, 2H), 2.39 - 2.30 (m, 2H), 2.22 (s, 3H), 1.05 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 565.

Example 557: N-[5-[2-(4-tert-butylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl] phenyl] -4-fluoro-2-(trifluoromethyl)benzamide



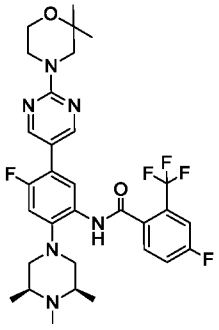
[00934] To a mixture of 2-chloropyrimidine-5-boronic acid (633 mg, 4 mmol) and 1-tert-butylpiperazine (0.64 mL, 4.4 mmol) in EtOH (8 mL) was added triethylamine (0.84 mL, 6 mmol). The resulting mixture was stirred at 75 °C for 1 h. Solvents were removed and the residue was dried under high vacuum to give crude (2-(4-(tert-bu†yl)piperazin-l-yl)pyrimidin-5-yl)boronic acid as a light beige solid (1.361 g, 77% purity assuming full conversion). LCMS $[M+ H]^+$ 265.32. The title compound (di-formic acid salt, light brown solid, 56.7 mg, 78%) was prepared using a procedure similar to Example 400 using crude (2-(4-(tert-butyl)piperazin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.64 (s, 2H), 8.43 (br s, 2H), 8.07 (d, *J*=8.2 Hz, IH), 7.82 (dd, *J*=5.3, 8.4 Hz, IH), 7.67 (dd, *J*=2.0, 9.0 Hz, IH), 7.58 (dt, *J*=2.1, 8.2 Hz, IH), 7.22 (d, *J*=11.7 Hz, IH), 4.21 (br s, 4H), 3.48 - 3.36 (m, 5H), 3.26 (br t, *J*=9.0 Hz, 2H), 3.21 - 3.03 (m, 3H), 2.96 - 2.84 (m, IH), 2.81 - 2.73 (m, 3H), 1.47 (s, 9H), 1.34 (br d, *J*=6.5 Hz, 3H); LCMS $[M+ H]^+$ 632.4.

Example 558: N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl] phenyl] -4-fluoro-2-(trifluoromethyl)benzamide



[00935] The title compound (formic acid salt, off white solid, 35.1 mg, 54%) was prepared according to a procedure similar to Example 400 using crude (2-(2,2-dimethylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ¾ NMR (500MHz, METHANOL-d4) δ = 8.53 (s, 2H), 8.42 (br s, IH), 8.03 (br d, *J*=8.2 Hz, IH), 7.80 (dd, *J*=5.3, 8.4 Hz, IH), 7.67 - 7.62 (m, IH), 7.56 (br t, *J*=8.2 Hz, IH), 7.18 (d, *J*=l 1.9 Hz, IH), 3.82 (br dd, *J*=4.2, 15.8 Hz, 4H), 3.71 (s, 2H), 3.48 - 3.38 (m, IH), 3.28 - 3.22 (m, 2H), 3.21 - 3.05 (m, 3H), 2.90 (br s, IH), 2.80 (br s, 3H), 1.38 - 1.30 (m, 3H), 1.24 (s, 6H); LCMS $[M + H]^+$ 605.3.

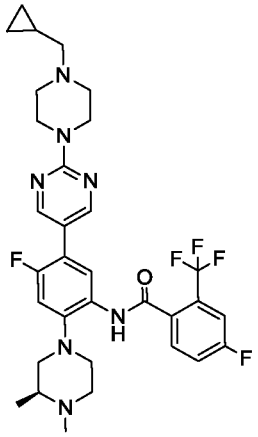
Example 559: N-[5-[2-(2, 2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide



[00936] The title compound (formic acid salt, beige solid, 26.4 mg, 40%) was prepared by a procedure similar to Example 400 using crude (2-(2,2-dimethylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and (N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifiuoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.54 (s, 2H), 8.36 (br s, IH), 8.04 (d, *J*=8.2 Hz, IH), 7.80 (dd, *J*=5.3, 8.5 Hz, IH), 7.66 (dd, *J*=2.1, 9.0 Hz, IH), 7.57 (dt, *J*=2.2, 8.3 Hz, IH), 7.19 (d,

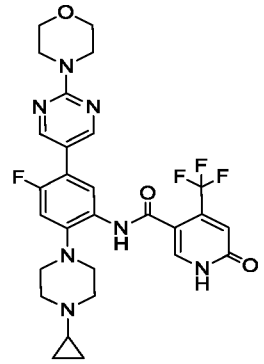
J=11.9 Hz, IH), 3.88 - 3.77 (m, 4H), 3.72 (s, 2H), 3.30 - 3.24 (m, 4H), 2.97 - 2.85 (m, 2H), 2.81 (br s, 3H), 1.37 (br d, *J*=6.2 Hz, 6H), 1.25 (s, 6H); LCMS $[M + H]^+$ 619.4.

Example 560: N-[5-[2-[4-(cyclopropylmethyl)piperazin-l -yl]pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-fluoro-2-(Mfluoromethyl)benzamide



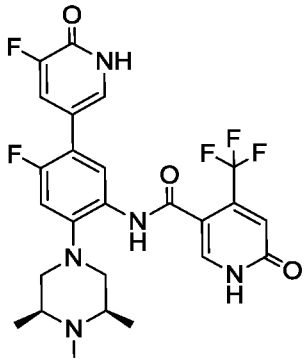
[00937] To a mixture of 2-chloropyrimidine-5-boronic acid (633 mg, 4 mmol) and 1-(cyclopropylmethyl)piperazine (0.62 mL, 4.4 mmol) in EtOH (8 mL) was added triethylamine (0.84 mL, 6 mmol). The resulting mixture was stirred at 75 °C for 1 h. Solvents were removed and the residue was dried under high vacuum to give crude (2-(4-(cyclopropylmethyl)piperazin-l-yl)pyrimidin-5-yl)boronic acid as a yellow solid (1.458g, 72% purity assuming full conversion). LCMS $[M + H]^+$ 263.4. The title compound (di-formic acid salt, beige solid, 45.9 mg, 63%) was prepared by a procedure similar to Example 40 using crude (2-(4-(cyclopropylmethyl)piperazin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.62 (s, 2H), 8.46 (br s, 2H), 8.05 (d, *J*=8.1 Hz, IH), 7.81 (dd, *J*=5.4, 8.2 Hz, IH), 7.65 (d, *J*=8.6 Hz, IH), 7.57 (t, *J*=8.2 Hz, IH), 7.21 (d, *J*=11.7 Hz, IH), 4.19 (br s, 4H), 3.56 - 3.44 (m, IH), 3.41 - 3.34 (m, 4H), 3.30 - 3.25 (m, 3H), 3.23 - 3.14 (m, 2H), 3.04 (br d, *J*=6.6 Hz, 3H), 2.97 (br d, *J*=10.5 Hz, IH), 2.83 (br s, 3H), 1.43 - 1.32 (m, 3H), 1.16 (br s, IH), 0.81 - 0.73 (m, 2H), 0.47 - 0.40 (m, 2H); LCMS $[M + H]^+$ 630.4.

Example 561: N-[2-(4-cyclopropylpiperazin-l-yl)-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00938] Through a sequence similar to Example 541 using 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (65.3 mg, 0.212 mmol) and 2-(4-cyclopropylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (65. 1 mg, 0.163 mmol) and deprotection of the N-(2-(4-cyclopropylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide intermediate, the title compound TFA salt (24.0 mg, 95 % yield in last step) was isolated as a light brown powder. ^{1}H NMR (500 MHz, DMSO-d6) δ = 9.65 (s, 1 H), 8.54 (s, 2 H), 7.99 (br s, 1 H), 7.88 (d, J=8.31 Hz, 1 H), 7.21 (d, J=11.98 Hz, 1 H), 6.84 (s, 1 H), 3.78 - 3.74 (m, 4 H), 3.70 - 3.66 (m, 4 H), 3.57 (br s, 2 H), 3.34 (br s, 4 H), 2.99 (br s, 2 H), 2.89 (br s, 1 H), 0.99 (br s, 2 H), 0.85 (br d, J=5.01 Hz, 2 H); LCMS [M+H]+ 588.4.

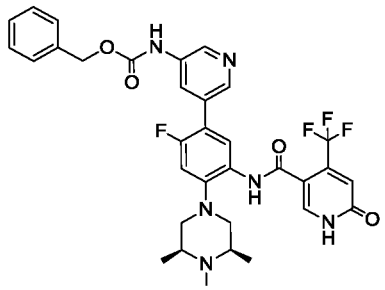
Example 562: N-[4-fluoro-5-(5-fluoro-6-oxo-lH-pyridin-3-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



[00939] A procedure similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and (5-fluoro-6-oxo-l,6-

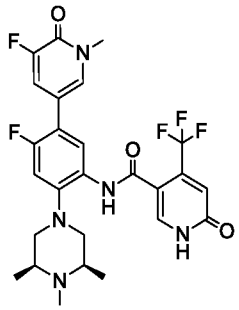
dihydropyridin-3-yl)boronic acid gave the title compound (19 mg, 74% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.03 - 7.94 (m, 1H), 7.91 - 7.84 (m, 1H), 7.75 - 7.65 (m, 1H), 7.55 - 7.49 (m, 1H), 7.15 - 7.06 (m, 1H), 6.99 - 6.91 (m, 1H), 3.15 - 3.04 (m, 2H), 2.73 - 2.60 (m, 4H), 2.50 - 2.40 (m, 3H), 1.25 - 1.16 (m, 6H); LCMS [M+H]+ 538.5

Example 563: benzyl N-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazm-l-ylJphenylJpyridm-3-ylJcarba mate



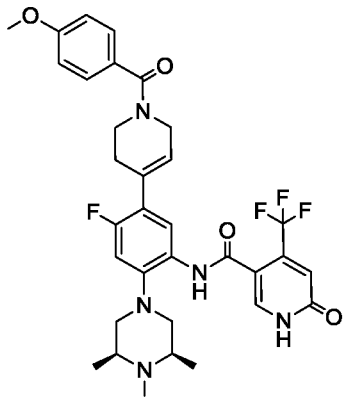
[00940] The sequence followed was similar to Example 39 starting with N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (70 mg, 0.116 mmol) and 5-(benzyloxycarbonylamino)pyridine-3-boronic acid, pinacol ester (61.4 mg, 0.173 mmol) to give the title compound (14 mg, 61 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.83 - 8.57 (m, 1H), 8.53 - 8.32 (m, 1H), 8.29 - 8.11 (m, 1H), 8.08 - 7.87 (m, 2H), 7.51 - 7.31 (m, 5H), 7.20 - 7.04 (m, 1H), 7.02 - 6.85 (m, 1H), 5.35 - 5.17 (m, 2H), 3.19 - 3.00 (m, 2H), 2.84 - 2.51 (m, 4H), 2.50 - 2.26 (m, 3H), 1.31 - 1.04 (m, 6H); LCMS [M+H]+ 653.4.

Example 564: N-[4-fluoro-5-(5-fluoro-l-methyl-6-oxopyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridme-3-carbom mide



[00941] N-(4-Fluoro-5 -(5-fluoro- 1-methyl-6-oxo- 1,6-dihydropyridin-3 -yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide, obtained as the intermediate in the preparation of Example 562, was treated with cesium carbonate (18.90 mg, 0.058 mmol) and iodomethane (5.42 µï, 0.087 mmol) in DMF (1.5ml) at RT. Purification of N-(4-fluoro-5-(5-fluoro-l-methyl-6-oxo-l,6-dihydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide and deprotection using standard conditions provided the title compound (9 mg, 44 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, 1H), 7.87 (d, *J*=8.3 Hz, 1H), 7.77 (s, 1H), 7.62 (br d, *J*=10.6 Hz, 1H), 7.10 (d, *J*=12.1 Hz, 1H), 6.92 (s, 1H), 3.74 - 3.66 (m, 3H), 3.19 - 3.12 (m, 2H), 2.92 (br s, 2H), 2.77 - 2.70 (m, 2H), 2.59 (br s, 3H), 1.29 - 1.23 (m, 6H); LCMS [M+H]+ 552.5.

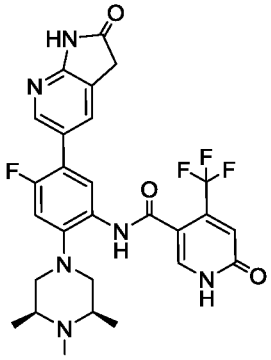
Example 565: N-[4-fluoro-5-[1-(4-methoxybenzoyl)-3, 6-dihydro-2H-pyridin-4-yl] -2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00942] The procedure followed was similar to Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 4-methoxybenzoyl chloride, 99% (8.55 µï, 0.062 mmol) to give the title compound as a white powder (23 mg, 58 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.91 - 7.78 (m, 1H), 7.76 - 7.59 (m, 1H), 7.42 - 7.27 (m, 2H), 6.96 - 6.89 (m, 2H), 6.89 - 6.84 (m, 1H), 6.83 - 6.79 (m, 1H), 6.12 - 5.64 (m, 1H), 4.32 - 3.99 (m,

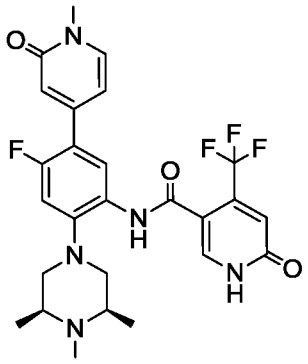
2H), 3.98 - 3.67 (m, 4H), 3.66 - 3.52 (m, 1H), 3.00 - 2.87 (m, 2H), 2.65 - 2.42 (m, 6H), 2.37 - 2.27 (m, 3H), 1.08 (br d, *J*=4.9 Hz, 6H); LCMS [M+H]+ 642.5

Example 566: N-[4-fluoro-5-(2-oxo-l, 3-dihydropyrrolo[2, 3-b]pyridin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



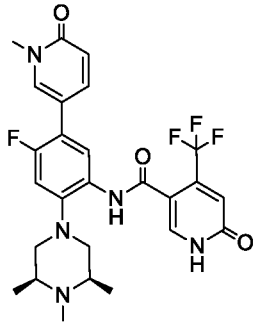
[00943] A sequence similar to Example 39 using 5-(4,4,5, 5-tetramethyl- 1,3,2-dioxaborolan-2-yl)-lh-pyrrolo[2,3-b]pyridin-2(3h)-one (0.034 g, 0.129 mmol) and N-(5-bromo-4-fluoro-2-((3R,5S)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.05216 g, 0.086 mmol) gave the title compound (16 mg, 32% yield). ^{1}H NMR (500 MHz, DMSO) δ 11.92 (s, 1H), 10.33 (s, 1H), 8.97 (s, 1H), 8.72 (s, 1H), 8.57 (d, *J* = 8.5 Hz, 1H), 8.48 (s, 1H), 8.38 (t, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 12.4 Hz, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 4.44 (s, 2H), 3.84 (d, *J* = 10.8 Hz, 2H), 3.77 (s, 2H), 3.17 (s, 3H), 3.00 (s, 3H), 1.95 (d, *J* = 13.2 Hz, 8H), 1.82 (d, *J* = 6.1 Hz, 6H); ^{19}F NMR (471 MHz, DMSO) δ -61.35 (s), -119.83 (s); LCMS HSS [M+l]+ = 559.32. **Major rotamer reported**

Example 567: N-[4-fluoro-5-(l-methyl-2-oxopyridin-4-yl)-2-[(3R, 5S)-3, 4, 5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^oxamide



[00944] A procedure similar to Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg, 0.066 mmol) and l-methyl-2-oxo-l,2-dihydropyridin-4-ylboronic acid pinacol ester (23.29 mg, 0.099 mmol) gave the title compound (28 mg, 90% yield for last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.97 (d, *J*=6.0 Hz, 2H), 7.73 (d, *J*=7.1 Hz, IH), 7.09 (d, *J*=12.5 Hz, IH), 6.93 (s, IH), 6.77 (s, IH), 6.64 (br d, *J*=7.0 Hz, IH), 3.62 (s, 3H), 3.14 (br d, *J*=ll.l Hz, 2H), 2.70 - 2.63 (m, 2H), 2.62 - 2.54 (m, 2H), 2.40 (s, 3H), 1.21 - 1.17 (m, 6H); LCMS [M+H]+ 534.2.

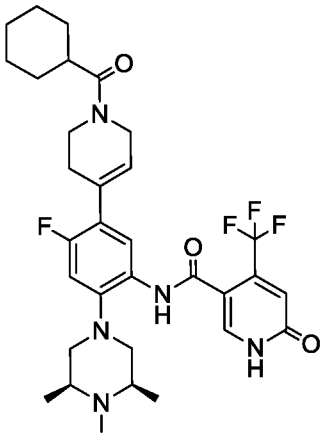
Example 568: N-[4-fluoro-5-(l-methyl-6-oxopyridin-3-yl)-2-[(3R, 5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



[00945] The title compound (30 mg, 97% for final step) was prepared through a procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg, 0.066 mmol) and 1-methyl- lH-pyridin-2-one-5-boronic acid, pinacol ester (23.3 mg, 0.099 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.94 (s, IH), 7.89 (d, *J*=8.4 Hz, IH), 7.79 (br d,

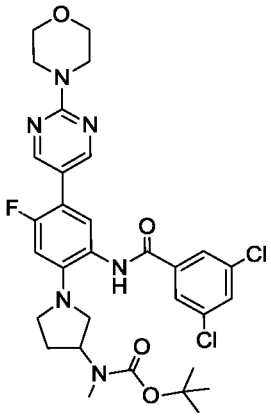
J=9*A* Hz, IH), 7.09 (d, *J*=12.1 Hz, IH), 6.93 (s, IH), 6.65 (d, *J*=9.3 Hz, IH), 3.67 (s, 3H), 3.07 (br d, *J*=11.0 Hz, 2H), 2.67 - 2.54 (m, 4H), 2.40 (s, 3H), 1.21 - 1.16 (m, 6H)LCMS [M+H]+ 534.5.

Example 569: N-[5-[l-(cyclohexanecarbonyl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



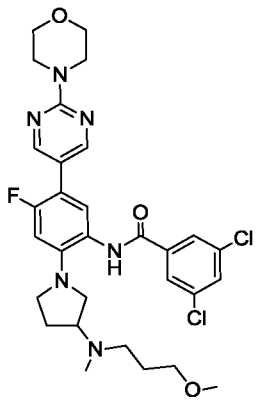
[00946] A procedure similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and cyclohexanecarbonyl chloride (7.03 µï, 0.052 mmol) gave the title compound. (23 mg, 72 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 - 7.92 (m, IH), 7.82 - 7.74 (m, IH), 6.99 - 6.94 (m, IH), 6.93 - 6.89 (m, IH), 6.09 - 5.99 (m, IH), 4.33 - 4.18 (m, 2H), 3.84 - 3.78 (m, 2H), 3.07 - 3.00 (m, 2H), 2.80 - 2.66 (m, IH), 2.63 - 2.50 (m, 6H), 2.39 - 2.37 (m, 3H), 1.85 - 1.74 (m, 5H), 1.54 - 1.36 (m, 5H), 1.18 - 1.15 (m, 6H), -0.71 - -0.73 (m, IH); LCMS [M+H]+ 618.5.

Example 570: tert-butyl N-[l-[2-[(3,5-dichlorobenzoyl)amino]-5-fluoro-4-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]pyrrolidin-3-yl]-N-methylcarbamate



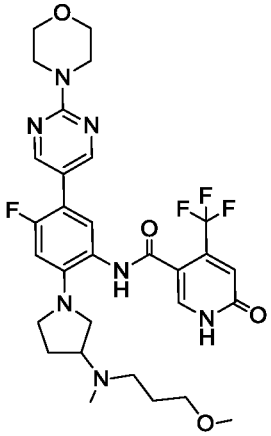
[00947] To a solution of tert-butyl (l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (211 mg, 0.446 mmol, prepared using a sequence similar to Example 541) and triethylamine (0.187 ml, 1.339 mmol) in DCM (40 ml) was added 3,5-dichlorobenzoyl chloride (94 mg, 0.446 mmol). Then the reaction mixture was stirred at room temperature for 2 hours. Then the crude material was dry loaded and purified by chromatography [0-10% DCM/MeOH] to afford the desired tert-butyl (l-(2-(3,5-dichlorobenzamido)-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)pyrrolidin-3-yl)(methyl)carbamate (288 mg, 0.424 mmol, 95 % yield) as a yellow solid. ^{1}H NMR (500MHz, DMSO-d6) δ = 10.16 (s, 1H), 8.52 (s, 2H), 7.95-8.02 (m, 2H), 7.88 (s, 1H), 7.34 (d, *J*=8.80 Hz, 1H), 6.72 (d, *J*=13.94 Hz, 1H), 5.75 (s, 1H), 4.55 (br. s., 1H), 3.71-3.75 (m, 5H), 3.65-3.68 (m, 4H), 3.35-3.41 (m, 2H), 3.25-3.30 (m, 2H), 2.69 (s, 3H), 1.92-2.07 (m, 2H), 1.35 (s, 9H); LCMS [M+H]+ 645.2.

Example 571: 3,5-dichloro-N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide



[00948] To a solution of 3,5-dichloro-N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)benzamide (35 mg, 0.064 mmol, prepared by procedures described hereinabove) and 3-methoxypropanal (11 mg, 0.125 mmol) in 1,2-dichloroethane (3 ml) was added acetic acid (23 mg, 0.383 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Then sodium triacetoxyborohydride (50 mg, 0.236 mmol) was added and the reaction mixture was stirred at room temperature for lh30min. Then a saturated solution of $NaHCO_3$ (3 mL) was added and the product was extracted using DCM (3x20mL). The organic phase was dried over MgSC>4 and after filtration and solvents removal, the crude material was dry loaded and purified by Flash chromatography [0-10% MeOH/DCM] to afford the 3,5-dichloro-N-(4-fluoro-2-(3-((3-methoxypropyl)(methyl)alnino)pyl rolidin-l-yl)-5-(2-mo rpholinopyrilnidin-5-yl)phenyl)benzamide (20.1 mg, 0.031 mmol, 48.2 % yield) as a yellow powder. ¾ NMR (500MHz, DMSO-d6) δ = 10.16 (s, 1H), 8.51 (s, 2H), 7.99 (d, *J*=1.71 Hz, 2H), 7.89 (s, 1H), 7.30 (d, *J*=8.80 Hz, 1H), 6.65 (d, *J*=14.06 Hz, 1H), 3.71-3.75 (m, 4H), 3.65-3.69 (m, 4H), 3.41 (t, *J*=8.19 Hz, 1H), 3.34-3.37 (m, 1H), 3.27-3.30 (m, 1H), 3.16-3.25 (m, 3H), 3.15 (s, 3H), 2.84-2.91 (m, 1H), 2.19-2.37 (m, 2H), 2.10 (s, 3H), 2.03-2.08 (m, 1H), 1.60-1.70 (m, 1H), 1.55 (quin, *J*=6.82 Hz, 2H); LCMS [M+H]+ 617.3.

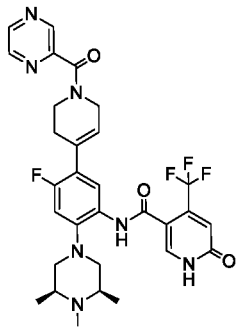
Example 572: N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l -yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00949] To a solution of N-(4-fluoro-2-(3-(methylamino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (42 mg, 0.075 mmol) and 3-methoxypropanal (20 mg, 0.227 mmol) in

1,2-dichloroethane (DCE) (3 ml) was added acetic acid (33 mg, 0.550 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Then sodium triacetoxyborohydride (57.1 mg, 0.269 mmol) was added and the reaction mixture was stirred at room temperature for an additional 20 minutes. Then a saturated solution of NaHCCb (3 mL) was added and the product was extracted with DCM (3x20mL). The organic phase was dried over MgSC>4 and after filtration and solvents removal, the crude material was dry loaded and purified by Flash chromatography [0-30% MeOH/DCM] to afford the N-(4-fluoro-2-(3-((3-methoxypropyl)(methyl)amino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide TFA salt (17.6 mg, 0.022 mmol, 29.9 % yield) as an off-white powder. ^{1}H NMR (500MHz, DMSO-d6) δ = 11.99 (br. s., 2H), 9.80 (s, *J*=7.01, 7.01 Hz, 1H), 8.50 (s, 2H), 7.97 (s, 1H), 7.31 (d, *J*=8.68 Hz, 1H), 6.79 (s, *J*=18.52, 18.52 Hz, 1H), 6.65 (d, *J*=14.06 Hz, 1H), 3.71-3.76 (m, 4H), 3.65-3.70 (m, 4H), 3.38 (br. s., 2H), 3.20-3.29 (m, 4H), 3.17 (s, 3H), 2.85-2.95 (m, 1H), 2.29-2.43 (m, 2H), 2.14 (s, 3H), 2.07 (d, *J*=3.91 Hz, 1H), 1.65-1.74 (m, 1H), 1.61 (t, *J*=6.72 Hz, 2H); LCMS [M+H]+ 634.4.

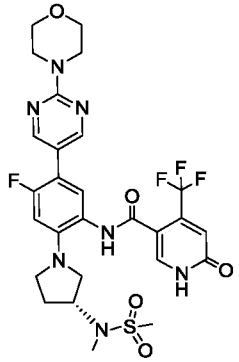
Example 573: N-[4-fluoro-5-[l-(pyrazine-2-carbonyl)-3, 6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00950] The procedure followed was similar to that of Example 253 using N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and pyrazine-2-carbonyl chloride (7.37 mg, 0.052 mmol) to afford the title compound (11 mg, 35 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.96 - 8.89 (m, 1H), 8.76 - 8.72 (m, 1H), 8.71 - 8.68 (m, 1H), 7.99 - 7.91 (m, 1H), 7.85 -

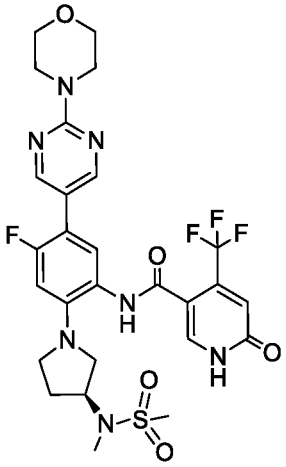
7.76 (m, 1H), 7.01 - 6.95 (m, 1H), 6.94 - 6.91 (m, 1H), 6.16 - 5.92 (m, 1H), 4.45 - 4.41 (m, 1H), 4.33 - 4.30 (m, 1H), 4.10 - 4.10 (m, 1H), 4.06 - 4.02 (m, 1H), 3.77 (t, *J*=5.6 Hz, 1H), 3.07 - 3.01 (m, 2H), 2.71 - 2.65 (m, 2H), 2.63 - 2.53 (m, 4H), 2.40 - 2.37 (m, 3H), 1.19 - 1.16 (m, 6H); LCMS [M+H]+ 614.4.

Example 574: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



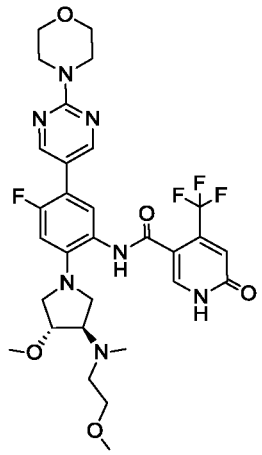
[00951] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using (R)-N-methyl-N-(pyrrolidin-3-yl)methanesulfonamide in place of (R)-N-ethyl-N-methylpyrrolidin-3 -amine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.80 (s, 1H), 8.51 (s, 2H), 7.98 (br s, 1H), 7.38 (br d, *J*=8.6 Hz, 1H), 6.79 (s, 1H), 6.74 (br d, *J*=13.6 Hz, 1H), 4.45 - 4.34 (m, 1H), 3.73 (br d, *J*=4.2 Hz, 4H), 3.68 (br d, *J*=3.9 Hz, 4H), 3.39 (br d, *J*=5.0 Hz, 4H), 2.92 (s, 3H), 2.75 (s, 3H), 2.12 (br d, *J*=6.8 Hz, 1H), 2.07 - 1.97 (m, 1H); LCMS [M+H]+: 640.4.

Example 575: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3S)-3-[methyl(methylsulfonyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

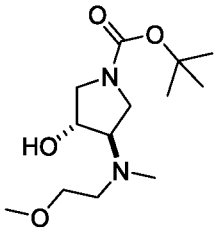


[00952] The title compound was prepared similar to the procedure described above for the preparation of Example 417 using (S)-N-methyl-N-(pyrrolidin-3-yl)methanesulfonamide in place of (R)-N-ethyl-N-methylpyrrolidin-3-amine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.73 (s, 1H), 8.44 (s, 2H), 7.92 (br s, 1H), 7.31 (d, *J*=8.7 Hz, 1H), 6.75 - 6.61 (m, 2H), 4.33 (br t, *J*=7.9 Hz, 1H), 3.67 (br d, *J*=4.9 Hz, 4H), 3.62 - 3.59 (m, 4H), 3.36 - 3.29 (m, 4H), 2.85 (s, 3H), 2.68 (s, 3H), 2.12 - 2.02 (m, 1H), 1.99 - 1.90 (m, 1H); LCMS [M+H]+: 640.5.

Example 576: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4R)-3-methoxy-4-[2-methoxyethyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

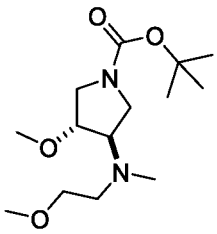


Step 1: tert-butyl trans-3-hydroxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate



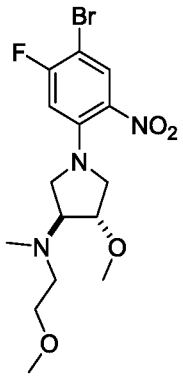
[00953] A solution of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.84 mL, 5.4 mmol) and N-(2-methoxyethyl)methylamine (0.59 mL, 10.8 mmol) in a sealed microwave vial was stirred at 60 °C for 48 h. Flash column chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] afforded tert-butyl trans-3-hydroxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate (1.48 g, 100 %). ^1H NMR (500MHz, DMSO-d6) δ = 5.08 (br d, *J*=2.9 Hz, 1H), 4.09 (br s, 1H), 3.48 - 3.36 (m, 4H), 3.23 (s, 3H), 3.12 (dt, *J*=5.7, 11.6 Hz, 1H), 3.05 - 2.94 (m, 1H), 2.85 (br dd, *J*=6.1, 14.5 Hz, 1H), 2.71 - 2.63 (m, 1H), 2.57 - 2.53 (m, 1H), 2.22 (s, 3H), 1.39 (s, 9H).

Step 2: tert-butyl trans-3-methoxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate



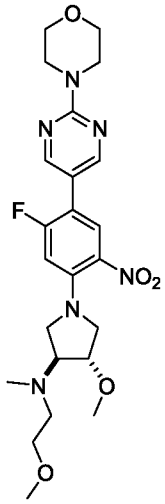
[00954] To a solution of tert-butyl trans-3-hydroxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate (0.26 g, 0.95 mmol) in THF (10 mL) at 0 °C was added sodium hydride (60%, 0.055 g, 1.42 mmol) and the reaction mixture was allowed to stir at 0 °C for 10 min. Iodomethane (0.08 mL, 1.23 mmol) was added and the resulting mixture was allowed to stir at room temperature for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous brine and dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated to dryness to afford tert-butyl trans-3-methoxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate (0.089 g, 32 %) that was used in the next step without further purification.

Step 3: trans-l-(4-bromo-5-fluoro-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-5'-amine



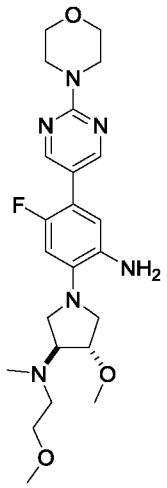
[00955] To a solution of tert-butyl trans-3-methoxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidine-l-carboxylate (0.14 g, 0.48 mmol) in DCM (5 mL) was added TFA (0.19 mL, 2.4 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in toluene (1 mL). The solution of deprotected amine was added dropwise to a rapidly stirring mixture of l-bromo-2,4-difluoro-5-nitrobenzene (0.120 g, 0.48 mmol), potassium carbonate (0.033 g, 0.24 mmol) and N,N-diisopropylethylamine (0.085 mL, 0.48 mmol) in toluene (2 mL) at room temperature. After stirring for 20 minutes at room temperature the reaction mixture was heated to 45 °C for 18 h. The reaction mixture was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with an additional portion of ethyl acetate. The combined organic extracts were dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated to dryness and the residue was purified by flash chromatography [1-10% MeOH/DCM + 0.5% NH_4OH] to afford trans- l-(4-bromo-5-fluoro-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (0.034 g, 17%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.01 (d, *J*=7.3 Hz, 1H), 6.94 (d, *J*=11.9 Hz, 1H), 4.05 (q, *J*=4.8 Hz, 1H), 3.54 (dd, *J*=5.9, 10.8 Hz, 1H), 3.52 - 3.47 (m, 2H), 3.44 - 3.39 (m, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 3.29 - 3.23 (m, 2H), 3.11 (dd, *J*=4.5, 10.9 Hz, 1H), 2.82 - 2.74 (m, 1H), 2.73 - 2.65 (m, 1H), 2.35 (s, 3H).

Step 4: trans-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine



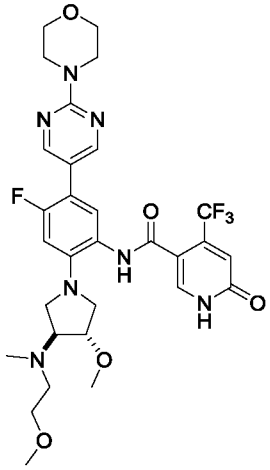
[00956] A microwave vial was charged with 2-(4-morpholino)pyrimidine-5-boronic acid pinacol ester (0.037 g, 0.13 mmol), potassium phosphate (0.053 g, 0.25 mmol) and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.006 g, 8.4 μηοΐ). The vial was sealed with a septum and then evacuated and backfilled with nitrogen. A solution of trans-l-(4-bromo-5-fluoro-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (0.034 g, 0.084 mmol) in 1,4-dioxane (4.4 mL) was added via syringe followed by water (0.5 mL). The reaction was irradiated to a temperature of 110 °C for 40 min. The reaction mixture was partitioned between water and DCM. The layers were separated and the aqueous layer was extracted with an additional portion of DCM. The combined organic extracts were dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated to dryness and the residue was purified by flash chromatography [0.5-7.5% MeOH/DCM + 0.5% NH_4OH] to afford trans- 1-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3 -amine (0.043 g, 100 %). LCMS [M+H]+: 491.5.

Step 5: trans-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine



[00957] A mixture of trans-l-(5-fluoro-4-(2-morpholinopyrimidin-5-yl)-2-nitrophenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (0.040 g, 0.082 mmol) and tin(II) chloride (0.046 g, 0.25 mmol) in EtOH (5 mL) was heated to 70 °C for 18 h. The reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford trans-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (0.023 g, 61 %). LCMS [M+H]+: 461.5.

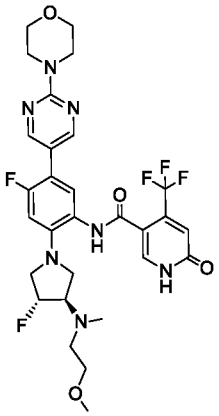
Step 6: N-(4-fluoro-2-(trans-3-methoxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidin-l-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[00958] 4<Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.022 g, 0.072 mmol) and propylphosphonic anhydride solution (0.15 mL, 0.48 mmol) were added to a suspension of trans-l-(2-amino-5-fluoro-4-(2-mo rpholinopyrirnidin-5-

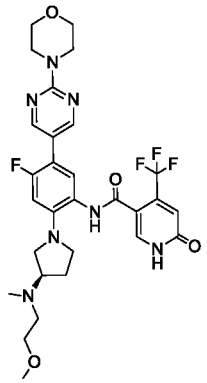
yl)phenyl)-4-methoxy-N-(2-methoxyethyl)-N-methylpyrrolidin-3 -amine (0.022 g, 0.048 mmol) in THF (0.8 mL) at room temperature. A solution of 4-methylmorpholine (0.013 mL, 0.12 mmol) in THF (0.2 mL) was added dropwise and the reaction was allowed to stir at room temperature for 4 h. The reaction mixture was partitioned between water and DCM. The layers were separated and the aqueous layer was extracted with an additional portion of DCM. The combined organic layers were washed with water, 1 N aqueous NaOH, a saturated brine solution and then dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated to dryness and the residue was purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (2 mL) and treated with TFA (0.2 mL) at room temperature. After stirring for 1 h the volatiles were removed in vacuo and the title compound was isolated using a catch and release protocol with a PoraPak Rxn CX ion exchange column to afford the title compound N-(4-fluoro-2-((3S,4S)-3-methoxy-4-((2-methoxyethyl)(methyl)amino)pyrrolidin-l-yl)-5-(2-mo rpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (6.0 mg, 21 % yield). ^1H NMR (500MHz, DMSO-d6) δ = 9.80 (s, 1H), 8.51 (s, 2H), 7.97 (br s, 1H), 7.36 (br d, *J*=8.8 Hz, 1H), 6.81 (s, 1H), 6.75 (d, *J*=13.8 Hz, 1H), 3.87 (q, *J*=4.7 Hz, 1H), 3.77 - 3.71 (m, 4H), 3.70 - 3.64 (m, 4H), 3.50 (dd, *J*=6.2, 10.5 Hz, 1H), 3.44 (br dd, *J*=7.4, 10.0 Hz, 1H), 3.38 (br t, *J*=6.0 Hz, 2H), 3.26 (s, 3H), 3.21 (s, 3H), 3.10 - 3.04 (m, 1H), 2.68 - 2.61 (m, 1H), 2.58 - 2.53 (m, 1H), 2.23 (s, 3H); LCMS [M+H]+: 650.6.

Example 577: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4R)-3-fluoro-4-[2-methoxyethyl(methyl)aminoJpyrrolidin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00959] The title compound was prepared similar to the procedure described above for the preparation of Example 307 using N-(2-methoxyethyl)methylamine in place of dimethylamine in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.83 (s, 1H), 8.53 (s, 2H), 8.00 (br s, 1H), 7.41 (br d, *J*=8.9 Hz, 1H), 6.85 - 6.77 (m, 2H), 5.34 - 5.14 (m, 1H), 3.76 - 3.73 (m, 5H), 3.70 - 3.67 (m, 5H), 3.63 - 3.58 (m, 2H), 3.53 (br d, *J*=4.2 Hz, 1H), 3.43 - 3.39 (m, 3H), 3.28 - 3.25 (m, 2H), 3.22 (s, 3H), 3.16 (br dd, *J=6.9,* 9.7 Hz, 2H), 2.26 (s, 3H); LCMS [M+H]+: 638.5.

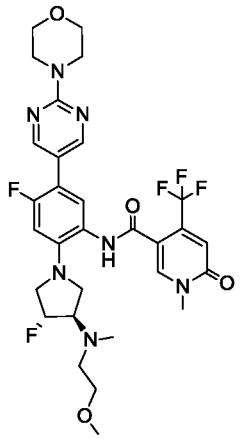
Example 578: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[2-methoxyethyl(methyl)aminoJpyrrolidin-l-yl]phenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00960] (R)-l-(2-Amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (50 mg, 0.116 mmol, prepared by a route similar to that described in Example 541) was dissolved in N,N-dimethylformamide (DMF) (1 ml) and treated with a solution of activated acid [4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (53.5 mg, 0.174 mmol), HATU (66.2 mg, 0.174

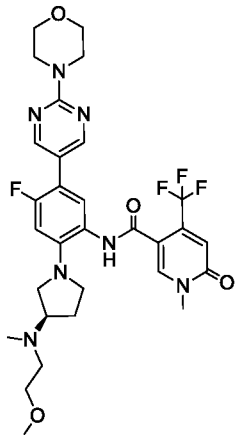
mmol) and N,N-diisopropylethylamine (0.030 ml, 0.174 mmol) in N,N-dimethylformamide (DMF) (0.5 ml)] at room temperature. After stirring for 30 minutes at room temperature, the standard workup and purification provided the title compound (0.065 mmol, 55.6 % yield) as a yellow solid. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.77 (s, IH), 8.51 (s, 2H), 8.00 - 7.94 (m, IH), 7.31 (d, *J*=8.6 Hz, IH), 6.76 (br s, IH), 6.67 (d, *J*=13.9 Hz, IH), 3.75 - 3.72 (m, 4H), 3.70 - 3.66 (m, 4H), 3.40 - 3.37 (m, 4H), 3.27 - 3.22 (m, 2H), 3.21 (s, 3H), 3.03 - 2.94 (m, IH), 2.20 (s, 3H), 2.11 - 2.06 (m, 2H), 1.70 (quin, *J*=10.0 Hz, IH); LCMS [M+H]+: 620.6.

Example 579: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R, 4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino]pyrrolidin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



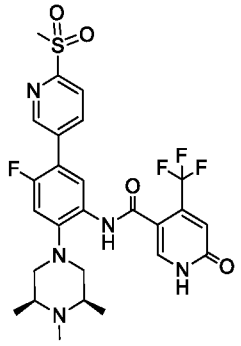
[00961] The title compound (47 mg, 57% yield) was from *cis* (3R,4S)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-4-fluoro-N-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (50 mg, 0.111 mmol) and [l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (37.0 mg, 0.167 mmol) using procedures similar to those described hereinabove. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.84 (s, IH), 8.52 (s, 2H), 8.36 (s, IH), 7.39 (d, *J*=8.8 Hz, IH), 6.91 - 6.81 (m, 2H), 5.32 - 5.12 (m, IH), 3.77 - 3.74 (m, 4H), 3.70 - 3.67 (m, 4H), 3.64 - 3.57 (m, 2H), 3.56 - 3.52 (m, 4H), 3.43 - 3.39 (m, 2H), 3.28 - 3.24 (m, IH), 3.22 (s, 3H), 3.15 (dd, *J*=6.7, 10.0 Hz, IH), 2.64 (br t, *J*=5.9 Hz, IH), 2.59 (br t, *J*=5.9 Hz, IH), 2.26 (s, 3H); LCMS [M+H]+: 652.5.

Example 580: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl) -2-[(3R)-3-[2-methoxyethyl(methyl)amino]pyrrolidin-l -yljphenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



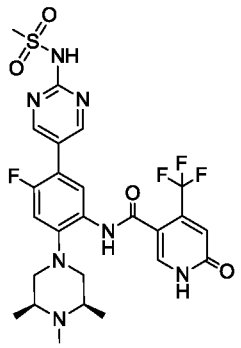
[00962] The title compound (46 mg, 53% yield) was prepared from (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-(2-methoxyethyl)-N-methylpyrrolidin-3 -amine (50 mg, 0.116 mmol) and [l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (38.5 mg, 0.174 mmol) according to procedures similar to those described hereinabove. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.79 (s, 1H), 8.50 (s, 2H), 8.33 (s, 1H), 7.30 (d, *J*=8.7 Hz, 1H), 6.87 (s, 1H), 6.70 (d, *J*=13.8 Hz, 1H), 3.76 - 3.73 (m, 4H), 3.70 - 3.67 (m, 4H), 3.55 (s, 3H), 3.40 - 3.37 (m, 5H), 3.24 (br d, *J*=7.2 Hz, 1H), 3.20 (s, 3H), 3.02 - 2.95 (m, 1H), 2.20 (s, 3H), 2.12 - 2.05 (m, 1H), 1.70 (quin, *J*=9.8 Hz, 1H); LCMS [M+H]+: 634.6.

Example 581: N-[4-fluoro-5-(5-methylsulfonylpyridin-3-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



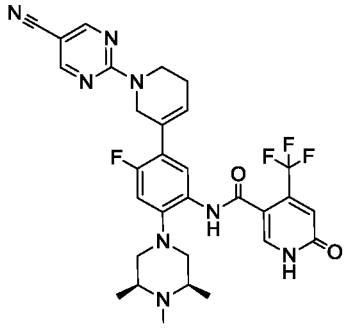
[00963] The title compound was prepared by methods similar to those described in Example 39 using 2-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.64 (s, IH), 8.92 (s, IH), 8.26 (dd, *J=1.2,* 8.3 Hz, IH), 8.15 (d, *J*=8.2 Hz, IH), 7.93 (s, IH), 7.87 (d, *J*=8.4 Hz, IH), 7.12 (d, *J*=12.6 Hz, IH), 6.81 (s, IH), 3.11 (br d, *J*=11.0 Hz, 2H), 2.37 (br s, 2H), 2.21 (br s, 3H), 1.02 (d, *J=6.1* Hz, 6H); LCMS [M+H]+: 582.1.

Example 582: N-[4-fluoro-5-[2-(methanesulfonamido)pyrimidin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



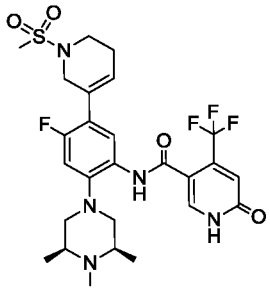
[00964] The title compound was prepared in a manner similar to the preparation of Example 39, from 2-(methylsulfonylamino)pyrirnidine-5-boronic acid pinacol ester. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.69 - 12.34 (m, IH), 9.54 (s, IH), 8.69 (s, 2H), 7.85 (br s, IH), 7.75 (br d, *J*=8.2 Hz, IH), 7.04 (br d, *J*=12.2 Hz, IH), 6.75 (s, IH), 3.33 (s, 3H), 3.03 (br d, *J*=7.6 Hz, 2H), 2.25 - 2.17 (m, 2H), 1.17 (br s, 2H), 0.98 (br s, 6H); LCMS [M+H]+: 598.4.

Example 583: N-[5-[l-(5-cyanopyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00965] The procedure used was similar to that of Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and 2-Bromo-5-cyanopyrimidine (13.05 mg, 0.071 mmol) to give the title compound (27 mg, 71 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.59 - 8.44 (m, 2H), 7.88 - 7.81 (m, 1H), 7.72 - 7.63 (m, 1H), 6.92 - 6.84 (m, 1H), 6.83 - 6.79 (m, 1H), 6.14 - 5.97 (m, 1H), 4.59 - 4.53 (m, 2H), 4.03 - 3.98 (m, 2H), 2.96 - 2.89 (m, 2H), 2.52 - 2.41 (m, 4H), 2.34 - 2.29 (m, 2H), 2.28 - 2.25 (m, 3H), 1.07 - 1.04 (m, 6H); LCMS [M+H]+ 611.5.

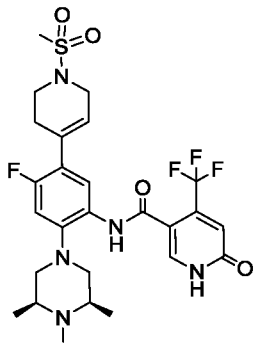
Example 584: N-[4-fluoro-5-(l-methylsulfonyl-3, 6-dihydro-2H-pyridin-5-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00966] To a solution of N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and N,N-diisopropylethylamine (0.017 ml, 0.099 mmol) in DCM (3 ml) at RT was added methanesulfonyl chloride (4.00 µï, 0.052 mmol). The mixture was stirred at room temperature for 5 min and quenched with MeOH, concentrated onto celite. It was purified on Isco column (4 g), eluting with DCM containing 0-6 % MeOH and 0-0.6 % NH40H. The desired

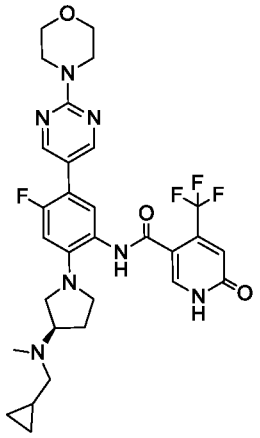
fractions were combined and concentrated to afford the title compound as a white powder (15 mg, 49 %). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.81 (m, 1H), 7.68 - 7.62 (m, 1H), 6.90 - 6.84 (m, 1H), 6.83 - 6.78 (m, 1H), 6.05 - 5.97 (m, 1H), 3.98 - 3.95 (m, 2H), 3.35 (t, *J*=5.9 Hz, 2H), 2.97 - 2.89 (m, 2H), 2.84 - 2.80 (m, 3H), 2.51 - 2.46 (m, 2H), 2.45 - 2.39 (m, 2H), 2.38 - 2.32 (m, 2H), 2.29 - 2.25 (m, 3H), 1.05 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 686.7.

Example 585: N-[4-fluoro-5-(l-methylsulfonyl-3, 6-dihydro-2H-pyridin-4-yl)-2-f(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



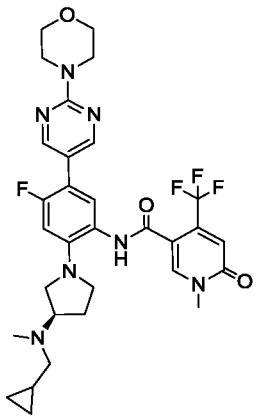
[00967] The procedure was similar to that used in Example 584 from N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (34 mg, 0.067 mmol) to give the title compound (17.5 mg, 42 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.99 - 7.93 (m, 1H), 7.83 - 7.75 (m, 1H), 7.00 - 6.95 (m, 1H), 6.94 - 6.90 (m, 1H), 6.09 - 6.01 (m, 1H), 4.00 - 3.94 (m, 2H), 3.53 - 3.48 (m, 2H), 3.06 - 3.01 (m, 2H), 2.95 - 2.92 (m, 3H), 2.67 - 2.62 (m, 2H), 2.62 - 2.57 (m, 2H), 2.56 - 2.50 (m, 2H), 2.41 - 2.36 (m, 3H), 1.19 - 1.16 (m, 6H); LCMS [M+H]+ 686.7.

Example 586: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



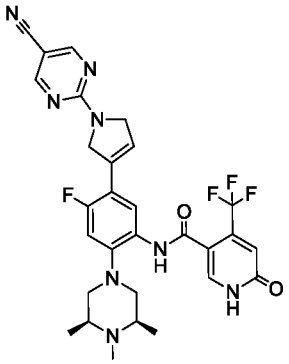
[00968] The title compound (17 mg, 59% yield) was prepared according to procedures similar to Examples hereinabove from (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-(cyclopropylmethyl)-N-methylpyrrolidin-3-amine (20 mg, 0.047 mmol) and [4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (21.62 mg, 0.070 mmol) and deprotection of the intermediate using TFA. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.48 (br s, IH), 9.79 (s, IH), 8.50 (s, 2H), 7.96 (br s, IH), 7.31 (br d, *J*=8.7 Hz, IH), 6.80 (s, IH), 6.66 (d, *J*=13.8 Hz, IH), 3.75 - 3.71 (m, 4H), 3.68 - 3.65 (m, 4H), 3.38 - 3.35 (m, 3H), 3.27 - 3.22 (m, 2H), 2.98 - 2.90 (m, IH), 2.25 (s, 3H), 2.23 - 2.19 (m, 2H), 2.10 - 2.04 (m, IH), 1.75 - 1.64 (m, IH), 0.99 (br d, *J*=5.7 Hz, 2H), 0.85 - 0.78 (m, IH), 0.43 (br d, *J*=7.9 Hz, 2H), 0.02 (br d, *J*=4.5 Hz, 2H); LCMS [M+H]+: 616.5.

Example 587: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)aminoJpyrrolidin-l-ylJphenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



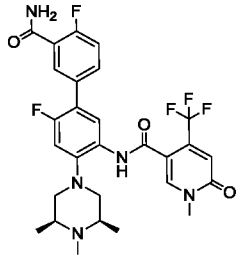
[00969] The title compound was prepared from (R)-l-(2-amino-5-fluoro-4-(2-morpholinopyrimidin-5-yl)phenyl)-N-(cyclopropylmethyl)-N-methylpyrrolidin-3-amine (20 mg, 0.047 mmol) and l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (15.55 mg, 0.070 mmol) followed by deprotection by procedures similar to those described hereinabove. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.78 (s, 1H), 8.49 (s, 2H), 8.34 (s, 1H), 7.29 (d, *J*=8.7 Hz, 1H), 6.86 (s, 1H), 6.69 (d, *J*=13.8 Hz, 1H), 3.75 - 3.72 (m, 4H), 3.69 - 3.65 (m, 4H), 3.54 (s, 3H), 3.41 - 3.34 (m, 5H), 3.29 - 3.21 (m, 2H), 2.98 - 2.89 (m, 1H), 2.24 (s, 3H), 2.21 (br d, *J*=6.4 Hz, 2H), 2.11 - 2.04 (m, 1H), 1.74 - 1.65 (m, 1H), 0.84 - 0.76 (m, 1H), 0.43 (br d, *J*=7.8 Hz, 2H), 0.02 (br d, *J*=4.5 Hz, 2H); LCMS [M+H]+: 630.6.

Example 588: N-[5-[l-(5-cyanopyrimidin-2-yl)-2, 5-dihydropyrrol-3-yl]-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



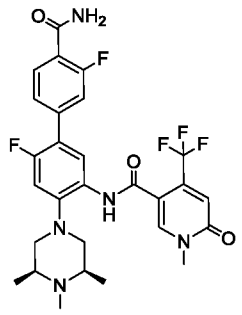
[00970] A procedure similar to that of Example 270 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (20 mg, 0.041 mmol) and 2-bromo-5-cyanopyrimidine (8.95 mg, 0.049 mmol) gave the title compound (10 mg, 39 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.53 - 9.42 (m, 1H), 8.90 - 8.79 (m, 2H), 8.03 - 7.92 (m, 1H), 7.81 - 7.70 (m, 1H), 7.07 - 6.97 (m, 1H), 6.82 - 6.72 (m, 1H), 6.49 - 6.40 (m, 1H), 4.75 - 4.67 (m, 2H), 4.58 - 4.51 (m, 2H), 3.08 - 3.01 (m, 2H), 2.47 - 2.41 (m, 2H), 2.36 - 2.28 (m, 2H), 2.19 (s, 3H), 1.03 - 0.98 (m, 6H); LCMS [M+H]+ 597.6.

Example 589: N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3, 4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[00971] The procedure was similar to that of Example 400 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50 mg, 0.096 mmol, from Example 226, Step 1) and 3-carbamoyl-4-fiuorophenylboronic acid, 97% (26.4 mg, 0.144 mmol). The title compound was isolated as a white fluffy powder (27 mg, 0.044 mmol, 46.1 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.14 (s, IH), 7.88 (br d, *J*=5.9 Hz, IH), 7.83 (d, *J*=8.3 Hz, IH), 7.65 - 7.54 (m, IH), 7.21 (dd, *J*=8.7, 10.6 Hz, IH), 6.97 (d, *J*=12.0 Hz, IH), 6.85 - 6.80 (m, IH), 3.54 (s, 3H), 2.95 (br d, *J*=11.4 Hz, 2H), 2.56 - 2.45 (m, 2H), 2.44 - 2.35 (m, 2H), 2.24 (s, 3H), 1.05 (d, *J*=6.2 Hz, 6H); LCMS $[M+H]^+$ 578.

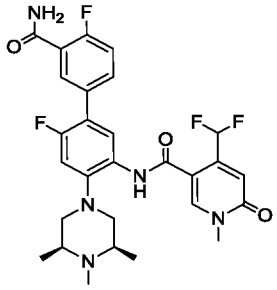
Example 590: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6<>xo-4-(trifluoromethyl)pyridine-3-carboxamide



[00972] The sequence used was similar to Example 400 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (50 mg, 0.096 mmol) and 4-carbamoyl-3-fluorophenylboronic acid, 96% (26.4 mg, 0.144 mmol). The title compound was isolated as a white fluffy powder (26 mg, 0.043 mmol, 44.4 % yield). 'HNMR (500**MHZ**, METHANOL-d4) δ = 8.14 (s, IH), 7.87 (d, *J*=8.3 Hz, IH), 7.80 (t, *J*=8.0 Hz, IH), 7.39 (d, *J*=8.2 Hz, IH), 7.34 (d, *J*=12.5 Hz, IH), 6.99 (d, *J*=12.2 Hz,

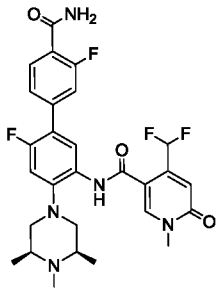
1H), 6.86 - 6.81 (m, 1H), 3.54 (s, 3H), 2.98 (br d, *J*=11.4 Hz, 2H), 2.52 (t, *J*=11.2 Hz, 2H), 2.46 - 2.34 (m, 2H), 2.24 (s, 3H), 1.05 (d, *J*=6.2 Hz, 6H); LCMS $[M+H]^+$ 578.

Example 591: N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-me thyl-6-oxopyridine-3-carboxamide



[00973] The procedure was similar to Example 400 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-l-methyl-6-oxo- l,6-dihydropyridine-3-carboxamide (50 mg, 0.100 mmol, preparation described in Example 461) and 3-carbamoyl-4-fluorophenylboronic acid, 97% (27.4 mg, 0.150 mmol). The title compound was isolated as an off-white fluffy powder (15.9 mg, 0.027 mmol, 27.1 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.20 (s, 1H), 7.91 - 7.85 (m, 1H), 7.71 (d, *J*=8.3 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.32 - 7.05 (m, 2H), 6.98 (d, *J*=12.1 Hz, 1H), 6.74 - 6.68 (m, 1H), 3.54 (s, 3H), 3.05 (br d, *J*=10.6 Hz, 2H), 2.68 - 2.52 (m, 4H), 2.37 (s, 3H), 1.11 (d, *J*=5.7 Hz, 6H); LCMS $[M+H]^+$ 560.

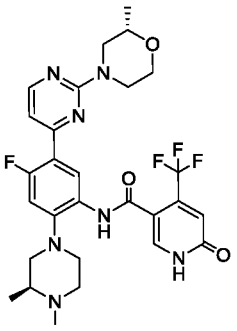
Example 592: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6 -oxopyridine-3-carboxamide



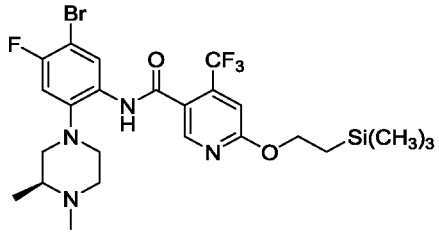
[00974] The title compound (11.9 mg, 20.3 % yield). was prepared by a procedure similar to Example 400 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (50 mg, 0.100 mmol) and 4-carbamoyl-3-

fluorophenylboronic acid, 96% (27.4 mg, 0.150 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.27 (s, 1H), 8.22 (s, 1H), 7.81 (t, *J*=7.9 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.31 - 7.08 (m, 1H), 7.03 (d, *J*=12.2 Hz, 1H), 6.75 - 6.68 (m, 1H), 3.55 (s, 3H), 3.17 (br d, *J*=12.3 Hz, 2H), 2.73 - 2.65 (m, 2H), 2.57 (s, 3H), 1.20 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 560.

Example 593: N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-6 -oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide



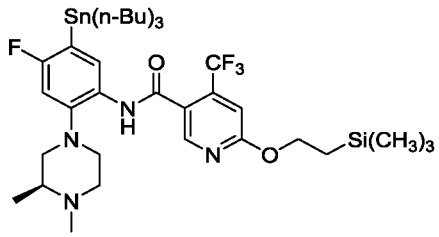
Step 1: (S)-N-(5-bromo-2-(3,4^imethylpipera^n-l-yl)-4-fluorophenyl)-4-(trifluorom ethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00975] To a stirred solution of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (5g, 16.28mmol, leq, preparation described in Example 39) in DMF (50mL) was added DIPEA (6mL, 32.57mmol, 2eq), HATU (44.9g, 12.37mmol, 2eq) and then (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (4.6 g, 16.28 mmol, leq) was added at 0°C under argon atm, and after that stirred for 16h. TLC analysis indicated formation of nonpolar spots. The reaction mixture was diluted with ice water (200mL) and extracted with EtOAc (2X500mL). The organic layer was washed with brine and dried over Na_2S0_4 and concentrated under reduced pressure to give crude product. The crude product was purified by

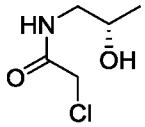
column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent to give (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (4g, 41.6%) as a pale yellow solid. TLC: 5% MeOH in DCM; R_f: 0.5

Step 2: (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00976] A stirred solution of (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (4 g, 6.77mmol, leq) in toluene (40mL) was degassed with argon for 15mins, then hexabutylditin (6.89mL, 13.5mmol, 2eq) was added, followed by Pd2(dppf)2Cl2 (0.55g, 0.67mmol, O.leq) and after that the reaction mixture was heated to reflux under argon atmosphere for 16h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; the filtrate was evaporated under reduced pressure. The crude compound was purified by column chromatography (neutral alumina) using 0-30% EtOAc in pet ether as an eluent to afford (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (2.8g, 51%) as a pale yellow liquid. LCMS: [M+H]+ 803.16.

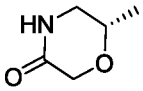
Step 3: (S)-2-chloro-N-(2-hydroxypropyl)acetamide



[00977] A solution of (S)-l-aminopropan-2-ol (25g, 332.8mmol, leq) in THF (500mL) was cooled to -10°C and a solution of K_2C0_3 (137.98g, 998.5mmol, 3eq) was added in H_20 (250mL, 10V) followed by chloro acetyl chloride (28.25mL, 366.2mmol, l.leq). The reaction mixture was stirred at the same temperature for lh. The reaction was monitored by TLC, and TLC analysis indicated formation of nonpolar spot. The reaction mixture was diluted with ethyl acetate (300mL) and

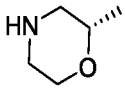
layers were separated. The aqueous layer was extracted with ethyl acetate (2x200mL), the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford (S)-2-chloro-N-(2-hydroxypropyl)acetamide (29g, 57.66% yield) as colourless oil. LCMS: [M+H]+ 152.31.

Step 4: (S)-6-methylmorpholin-3-one



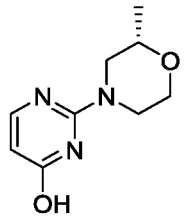
[00978] A solution of (S)-2-chloro-N-(2-hydroxypropyl)acetamide (29 g, 192.05 mmol, leq) in DCM (580 mL) was cooled to 0°C and a solution of f-BuOK (86.18g, 768.2mmol, 4eq) in IPA (580mL, 20V) was added. The reaction mixture was stirred at the same temperature for lh. The reaction was monitored by TLC, and TLC analysis indicated formation of nonpolar spot. The reaction mixture was neutralised (pH 7) with 2N HC1, and concentrated under reduced pressure. 5% methanol in DCM (250mL) was added to the residue, and the mixture stirred for 30 min. It was filtered through celite, washed with 5% methanol: DCM, filtrate was concentrated under reduced pressure to give crude product which was filtered through a column of neutral alumina with 5% methanol in DCM as an eluent to afford (S)-6-methylmorpholin-3-one (14 g, 63.4% yield) as a white solid. LCMS: [M+H]+ 116.34.

Step 5: (S)-2-methylmorpholine



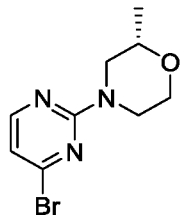
[00979] A solution of (S)-6-methylmorpholin-3-one (14 g, 121.7 mmol, 1 eq) in THF (280mL, 20V) was cooled to 0°C and LAH (13.8g, 365.2mmol, 3eq) was added slowly portion wise under argon atmosphere. Then, the reaction mixture was allowed to RT for 16h. The reaction was monitored by TLC, and TLC analysis indicated formation of polar spot. The reaction mixture was quenched with H_20 (14mL), 2N NaOH (28 mL) followed by H_20 (7mL) and the resulting precipitate was stirred at room temperature for lh. The mixture was filtered through celite, washed with ethyl acetate and the filtrate was concentrated under reduced pressure to afford (S)-2-methylmorpholine (lOg, 81.3% yield) as white solid. LCMS (ELSD): [M+H]+ 102.24.

Step 6: (S)-2-(2-methylmorpholino)pyrimidin-4-ol



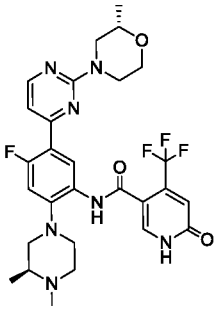
[00980] To a suspension of (S)-2-methylmorpholine (5g, 49.29 mmol, 2eq) was added 2-(methylthio)pyrimidin-4-ol (3.5 g, 24.64 mmol, 1 eq) at RT, and the resulting suspension was heated at 150°C for 2 h. The reaction was monitored by TLC, and TLC analysis indicated formation of spot. The reaction mixture was concentrated under reduced pressure to give crude compound. The crude compound was purified by column chromatography (silica gel 100-200 mesh) using 5% methanol: ethyl acetate as an eluent to give (S)-2-(2-methylmo rpholino)pyrimidin-4-ol (2.5g, 52% yield) as pale yellow liquid. LCMS: [M+H]+ 196.03.

Step 7: (S)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine



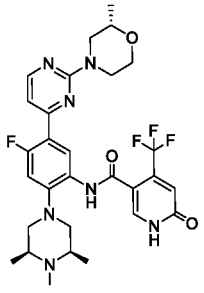
[00981] To a suspension of (8)-2-(2-methylmorpηo1ιηo)pyrimidiη-4-o1 (5g, 25.64mmol, leq) in ACN (50mL) was added $POBr_3$ (9.5g, 33.3mmol, 1.3eq) at RT and heated to 80°C for 3h. The reaction was monitored by TLC, and TLC analysis indicated formation of nonpolar spot. Then, the reaction mixture was diluted with ethyl acetate (200mL) and washed with $\mathbf{H_20}$ (2X100mL). The combined organic layer was dried over $\mathbf{Na_2S0_4}$ and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (silica gel 100-200 mesh) using 2% methanol: ethyl acetate as an eluent afforded (S)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine (3g, 45.59% yield) as pale yellow solid. LCMS: [M+H]+ 258.14.

Step 8: N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-ylj pyrimidin-4-yl) 'phenyl]'-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00982] The procedure followed was similar to Example 384 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (108 mg, 0.135 mmol). The solution was added with (S)-4-(4-bromopyrimidin-2-yl)-2-methylmo rpholine (38.3 mg, 0.148 mmol) to give the title compound (16.6 mg, 21% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.61 (d, *J* = 8.1 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 7.92 (s, 1H), 7.12 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.02 (d, *J* = 13.2 Hz, 1H), 6.92 (s, 1H), 4.65 (d, *J* = 13.1 Hz, 1H), 4.58 (d, *J* = 12.5 Hz, 1H), 3.96 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.64 (td, *J* = 11.9, 2.5 Hz, 2H), 3.22 (d, *J* = 10.9 Hz, 1H), 3.14 (s, 1H), 3.05 (td, *J* = 13.4, 3.5 Hz, 1H), 2.96 (t, *J* = 10.1 Hz, 2H), 2.70 (dd, *J* = 13.1, 10.5 Hz, 1H), 2.60 (t, *J* = 10.8 Hz, 2H), 2.47 (s, 1H), 2.40 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H); ^{19}F NMR (471 MHz, MeOD) δ -63.79, -115.96; LCMS [M+l] $^{+}$ = 590.35.

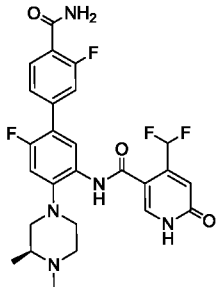
Example 594: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-f(3S, 5R)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00983] The procedure followed was similar to Example 384 using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (102 mg, 0.125 mmol, preparation described in Example 384, Step 1) and (S)-4-(4-bromopyrimidin-2-yl)-2-

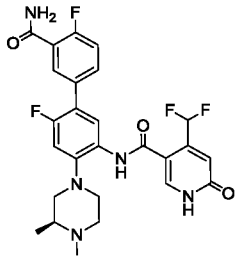
methylmorpholine (35.5 mg, 0.138 mmol) to give the title compound (29.4 mg, 37% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.60 (d, *J* = 8.1 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 7.90 (s, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.00 (d, *J* = 13.2 Hz, 1H), 6.92 (s, 1H), 4.65 (d, *J* = 12.9 Hz, 1H), 4.58 (d, *J* = 13.0 Hz, 1H), 3.96 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.67 - 3.58 (m, 2H), 3.16 (d, *J* = 10.9 Hz, 2H), 3.04 (td, *J* = 13.2, 3.2 Hz, 1H), 2.70 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.67 - 2.62 (m, 2H), 2.59 (s, 2H), 2.40 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 5.8 Hz, 6H); LCMS [M+l] $^+$ = 604.34.

Example 595: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide



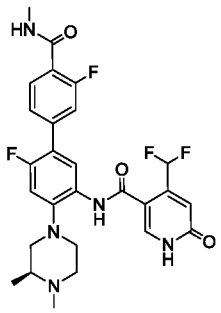
[00984] A procedure similar to Example 100 using 4-carbamoyl-3-fluorophenylboronic acid, 96% (23.92 mg, 0.131 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.087 mmol) gave the title compound (TFA salt) as a white powder (42 mg, 100 % yield for last step). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, 1H), 7.81 (t, *J*=8.0 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.32 - 7.09 (m, 1H), 7.07 (br d, *J*=12.1 Hz, 1H), 6.73 - 6.66 (m, 1H), 3.53 (br d, *J*=12.2 Hz, 1H), 3.37 - 3.28 (m, 3H), 3.05 - 2.98 (m, 1H), 2.88 (s, 3H), 2.83 - 2.73 (m, 1H), 1.31 (br d, *J*=6.4Hz, 3H); LCMS [M+H]$^+$ 532.

Example 596: N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide



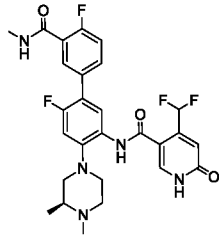
[00985] A procedure similar to Example 100 using 3-carbamoyl-4-fluorophenylboronic acid, 97% (15.95 mg, 0.087 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.087 mmol) gave the title compound (TFA salt) as a white powder (50 mg, 0100 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, 1H), 7.92 - 7.87 (m, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.66 - 7.60 (m, 1H), 7.31 - 7.08 (m, 2H), 7.06 (d, *J*=11.9 Hz, 1H), 6.70 (s, 1H), 3.53 (br d, *J*=12.2 Hz, 1H), 3.31 (br d, *J*=11.9 Hz, 3H), 3.05 - 2.98 (m, 1H), 2.88 (s, 3H), 2.82 - 2.72 (m, 1H), 1.31 (br d, *J*=6.2 Hz, 3H); LCMS $[M+H]^{+}$ 532.

Example 597: 4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-lH-pyridine-3-carboxamide



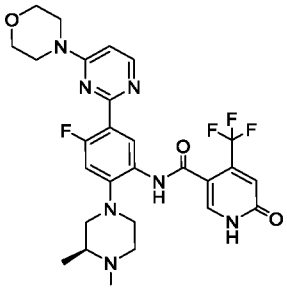
[00986] A procedure similar to Example 100 using 3-fluoro-4-(methylcarbamoyl)phenylboronic acid (25.8 mg, 0.131 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.087 mmol) gave the title compound (TFA salt) as a white powder (59 mg, 0.072 mmol, 97 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.09 (s, 1H), 7.87 - 7.82 (m, 2H), 7.50 (d, *J*=8.1 Hz, 1H), 7.46 - 7.20 (m, 2H), 7.18 (d, *J*=12.0 Hz, 1H), 6.84 - 6.80 (m, 1H), 3.65 (br d, *J*=12.2 Hz, 1H), 3.43 (br d, *J*=12.0 Hz, 3H), 3.20 - 3.10 (m, 1H), 2.99 (s, 3H), 2.97 (s, 3H), 2.95 - 2.88 (m, 1H), 1.43 (d, *J*=6.2 Hz, 3H); LCMS $[M+H]^{+}$ 546.

Example 598: 4-(difluoromethyl)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-lH-pyridine-3-carboxamide

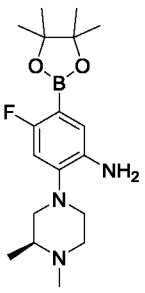


[00987] A procedure similar to Example 100 using N-methyl-5-borono-2-fluorobenzamide (25.8 mg, 0.131 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(ta methylsilyl)ethoxy)nicotinamide (50 mg, 0.087 mmol) gave the title compound (TFA salt) as a white powder (53 mg, 100 % yield for last step). ¾ NMR (500MHz, METHANOL-d4) δ = 7.97 (s, IH), 7.82 (br d, *J*=6.6 Hz, IH), 7.70 (d, *J*=8.2 Hz, IH), 7.61 (br dd, *J*=3.4, 7.6 Hz, IH), 7.32 -7.08 (m, 2H), 7.06 (br d, *J*=11.7 Hz, IH), 6.72 - 6.67 (m, IH), 3.53 (br d, *J*=12.3 Hz, IH), 3.30 (br d, *J*=12.0 Hz, 3H), 3.09 - 2.96 (m, IH), 2.87 (s, 3H), 2.85 (s, 3H), 2.82 - 2.73 (m, IH), 1.31 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 546.

Example 599: N-[4-fluoro-5-(4-morpholin-4-ylpyrimidin-2-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3 -carboxamide

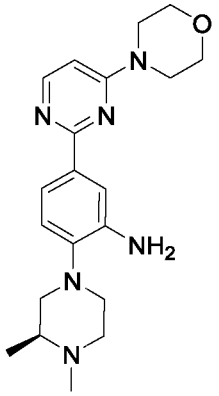


Step 1: (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4, 4,5,5-tetramethyl-l, 3,2-dioxaborolan-2-yl)aniline



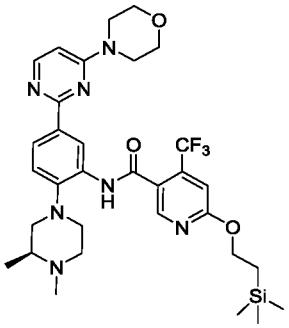
[00988] A suspension of potassium acetate (0.601 g, 6.12 mmol), bis(pinacolato)diboron (0.745 g, 2.040 mmol) in dioxane (12 ml) was degassed with N_2 for 10 min, then treated with PdCb(dppf) (0.050 g, 0.061 mmol). The reaction was sparged with N_2 for an additional 10 min. The mixture was heated to 80°C overnight, then allowed to cool to rt. The reaction was quenched with H_20 and diluted with EtOAc. Layers were separated. The aqueous phase was extracted with EtOAc (3X). The combined organic phases were washed with $\mathbf{H_20}$ (3X), dried over $Na_{2SC>4,}$ filtered, and concentrated to afford a black residue. The crude material was dissolved in a minimal amount of CH_2C1_2 and chromatographed. Purification of the crude material by silica gel chromatography gave (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)aniline (0.656 g, 80 % yield) as a brown residue.

Step 2: (S)-2-(3,4^imethylpiperazm-l-yl)-5-(4-morpholinopyrimidin-2-yl)aniline



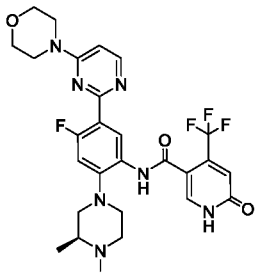
[00989] To a microwave vial charg ed with (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)aniline (0.143, 0.410 mmol), 4-(2-bromopyrimidin-4-yl)morpholine (0.150 g ,0.615 mmol), $\mathbf{K_3P0_4}$ (0.174 g, 0.819 mmol) was added dioxane (2 ml) and water (2 ml) and the vial was flushed with nitrogen. Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.0087 g, 0.030 mmol) was added, the vial was sealed, and the mixture heated in a microwave reactor to 110°C for 30 minutes. The crude mixture was concentrated onto celite and purified using reverse phase silca gel column chromatography (Water: AcCN gradient 0-100%). The product was dried under vacuum to give the title compound as a brown solid (0.097 g, 61 %); LCMS $[M + H]^+$ 387

Step 3: (S)-N-(2-(3,4^imethylpiperazin-l-yl)-5-(4-morpholinopyrimidin-2-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[00990] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid, (72mg, 0.233 mmol), HATU (89 mg, 0.233 mmol) and DIEA (0.081ml , 0.466 mmol) were combined in DMF (3.0 mL). After 30 min, (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4-morpholinopyrimidin-2-yl)aniline (45 mg, 0.116 mmol) was added and the reaction was heated to 60°C overnight. The reaction was concentrated onto celite then purified by reverse phase silica gel chromatography using a gradient of Water/AcCN from 0 to 100% to provide the desired product along with an impurity (70 mg, 89%) as a light brown oil; LCMS $[M + H]^+$ 676.

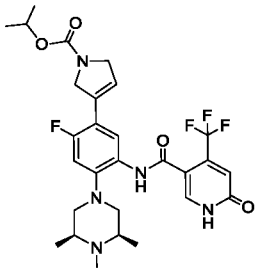
Step 4: N-[4-fluoro-5-(4-morpholin-4-ylpyrimidin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



[00991] To a vial of (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4-morpholinopyrimidin-2-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (70 mg, 0.104 mmol, 1 equiv.) was added TFA/CH2CI2 (2 ml of a 1:1 mixture). The reaction mixture was stirred at 22°C for 1h (Judged complete by LCMS). The solvent was removed in vacuo and the residue was triturated with ether to afford 51 mg title compound (RF=0.98 min) as a beige solid along with an impurity (RF 1.12 min). The material was then further purified by preparatory HPLC (0.1% Formic Acid in water/AcCN as eluent) to afford 18 mg (27% yield) of the title product as a beige solid. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.39 (br d, J=7.9 Hz, 2H), 8.27 (d, J=6.2 Hz, 1H), 8.06 - 7.94 (m, 1H), 7.08

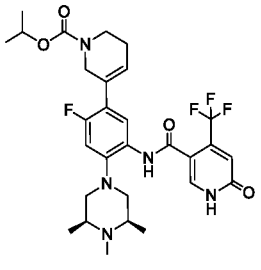
(d, *J*=12.2 Hz, 1H), 6.95 (s, 1H), 6.73 (d, *J*=6.4 Hz, 1H), 3.83 - 3.72 (m, 8H), 3.31 - 3.19 (m, 3H), 3.07 (s, 1H), 2.90 (br d, *J*=9.7 Hz, 2H), 2.77 (br d, *J*=11.6 Hz, 1H), 2.65 (s, 3H), 1.28 (d, *J*=6.4 Hz, 3H); LCMS [M+ H]$^+$ 576

Example 600: Propan-2-yl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]pheny l]-2,5-dihydropyrrole-1-carboxylate



[00992] The procedure followed was similar to Example 372 using N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and isopropyl chloroformate (0.061 ml, 0.061 mmol) to give the title compound (24 mg, 65 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.90 - 7.80 (m, 1H), 7.76 - 7.63 (m, 1H), 6.94 - 6.86 (m, 1H), 6.85 - 6.73 (m, 1H), 6.29 - 6.16 (m, 1H), 4.87 - 4.81 (m, 1H), 4.47 - 4.37 (m, 2H), 4.26 - 4.20 (m, 2H), 2.99 - 2.90 (m, 2H), 2.53 - 2.45 (m, 2H), 2.45 - 2.38 (m, 2H), 2.28 - 2.22 (m, 3H), 1.23 - 1.18 (m, 6H), 1.04 (br d, *J*=5.9 Hz, 6H); LCMS [M+H]+ 580.2

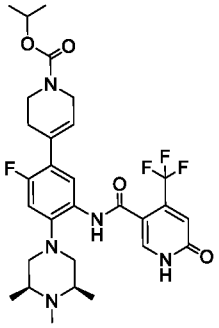
Example 601: propan-2-yl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonylJaminoJ-4-[(3R,5S)-3,4,5-trimethylpiperazm-l-ylJphenylJ-3,6-dihydro-2H-pyridine-1 -carboxylate



[00993] The procedure followed was similar to Example 372 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-

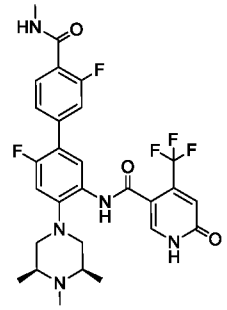
yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and isopropyl chloroformate (0.059 ml, 0.059 mmol) to give the title compound (27 mg, 73 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.80 (m, 1H), 7.69 - 7.60 (m, 1H), 6.89 - 6.83 (m, 1H), 6.82 - 6.77 (m, 1H), 6.03 - 5.96 (m, 1H), 4.86 - 4.80 (m, 1H), 4.18 - 4.10 (m, 2H), 3.56 - 3.47 (m, 2H), 2.91 (br d, *J*=ll.l Hz, 2H), 2.52 - 2.45 (m, 2H), 2.44 - 2.37 (m, 2H), 2.27 - 2.21 (m, 5H), 1.17 (br d, *J*=6.1 Hz, 6H), 1.05 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+ 594.6.

Example 602: propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]pheny l]-3,6-dihydro-2H-pyridine- 1-carboxylate



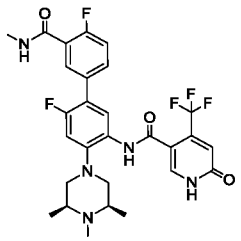
[00994] The procedure was similar to Example 372 using N-(4-fluoro-5-(1,2,3, 6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30 mg, 0.059 mmol) and isopropyl chloroformate (0.059 ml, 0.059 mmol) to give the title compound (28 mg, 76 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.80 (m, 1H), 7.70 - 7.61 (m, 1H), 6.87 - 6.81 (m, 1H), 6.80 - 6.76 (m, 1H), 5.95 - 5.82 (m, 1H), 4.85 - 4.80 (m, 1H), 4.03 - 3.97 (m, 2H), 3.58 - 3.53 (m, 2H), 2.93 - 2.87 (m, 2H), 2.50 - 2.44 (m, 2H), 2.42 - 2.36 (m, 4H), 2.27 - 2.23 (m, 3H), 1.20 - 1.17 (m, 6H), 1.04 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 594.2

Example 603: N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-4-(trifluoromethyl)-lH^yridine-3-carbom mide



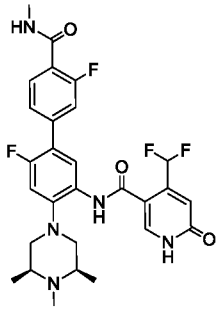
[00995] A procedure similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (54 mg, 0.089 mmol) and 3-fluoro-4-(methylcarbamoyl)phenylboronic acid (26.3 mg, 0.134 mmol) gave the title compound (TFA salt) as a white fluffy powder (58.8 mg, 0.069 mmol, 89 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.91 (s, IH), 7.88 (d, *J*=8.2 Hz, IH), 7.73 (t, *J*=7.9 Hz, IH), 7.37 (d, *J*=8.2 Hz, IH), 7.32 (d, *J*=12.1 Hz, IH), 7.07 (d, *J*=11.9 Hz, IH), 6.84 - 6.79 (m, IH), 3.46 - 3.35 (m, 2H), 3.29 (br d, *J*=13.1 Hz, 2H), 2.88 (s, 2H), 2.87 - 2.80 (m, 5H), 1.34 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^{+}$ 578.

Example 604: N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



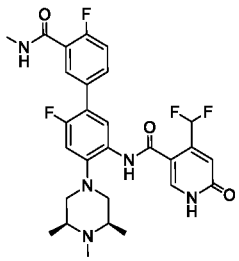
[00996] The procedure followed was similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.083 mmol) and N-methyl-5-borono-2-fluorobenzamide (24.40 mg, 0.124 mmol) to give the title compound (TFA salt) as an off-white fluffy powder (53.7 mg, 0.074 mmol, 99 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.93 (s, IH), 7.87 (d, *J*=8.2 Hz, IH), 7.84 (dd, *J*=l.l, 6.7 Hz, IH), 7.65 - 7.57 (m, IH), 7.24 (dd, *J*=8.7, 10.5 Hz, IH), 7.09 (d, *J*=11.7 Hz, IH), 6.87 - 6.83 (m, IH), 3.48 - 3.38 (m, 2H), 3.31 (br d, *J*=13.1 Hz, 2H), 2.91 (s, 3H), 2.89 - 2.82 (m, 5H), 1.36 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^{+}$ 578.

Example 605: 4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridme-3-carboxamide



[00997] The procedure was similar to Example 100 using 3-fluoro-4-(methylcarbamoyl)phenylboronic acid (25.1 mg, 0.128 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (50 mg, 0.085 mmol) to give the title compound (TFA salt) as an off-white fluffy powder (50.7 mg, 0.061 mmol, 87 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.95 (s, 1H), 7.76 - 7.65 (m, 2H), 7.37 (d, *J*=8.1 Hz, 1H), 7.33 - 7.08 (m, 2H), 7.05 (d, *J*=12.0 Hz, 1H), 6.69 (s, 1H), 3.42 - 3.34 (m, 2H), 3.31 (br d, *J*=13.3 Hz, 2H), 2.87 (s, 3H), 2.85 - 2.79 (m, 5H), 1.33 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^{+}$ 560.

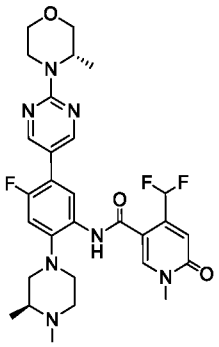
Example 606: 4-(difluoromethyl)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridme-3-carboxamide



[00998] The procedure was similar to Example 100 using N-(5-bromo-4-fiuoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (50 mg, 0.085 mmol) and N-methyl-5-borono-2-fiuorobenzamide (25.1 mg, 0.128 mmol) to give the title compound (TFA salt) as a white powder (42.1 mg, 87 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.96 (s, 1H), 7.81 (dd, *J*=1.2, 6.7 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.32 - 7.09 (m,

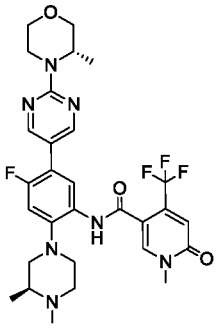
2H), 7.05 (d, *J*=11.7 Hz, IH), 6.72 - 6.67 (m, IH), 3.43 - 3.34 (m, 2H), 3.31 (br d, *J*=13.2 Hz, 2H), 2.88 (s, 3H), 2.86 - 2.78 (m, 5H), 1.33 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^+$ 560.

Example 607: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-ylJ-5-[2-[(3R)-3-methylmorpholin-4-ylJpyrimidin-5-ylJphenylJ-l-methyl-6-oxopyridme-3-carboxamide



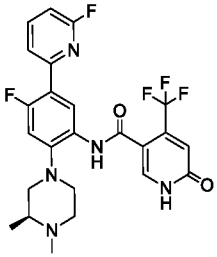
[00999] A procedure similar to that of Example 31 using (S)-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2-dimethylpiperazine and 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid gave the title compound. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.48 (s, IH), 8.53 (d, *J*=0.9 Hz, 2H), 8.36 (s, IH), 7.69 (d, *J*=8.6 Hz, IH), 7.49 - 7.17 (m, IH), 7.09 (d, *J*=12.3 Hz, IH), 6.65 (s, IH), 4.65 (br dd, *J*=2.8, 6.8 Hz, IH), 4.29 (dd, *J*=2.4, 13.5 Hz, IH), 3.93 (dd, *J*=3.5, 11.3 Hz, IH), 3.73 (d, *J*=11.4 Hz, IH), 3.60 (dd, *J*=3.1, 11.4 Hz, IH), 3.52 (s, 3H), 3.44 (dt, *J*=3.0, 11.8 Hz, IH), 3.19 (dt, *J*=3.8, 13.0 Hz, IH), 3.09 - 2.98 (m, 2H), 2.87 - 2.74 (m, 2H), 2.43 (br t, *J*=10.5 Hz, IH), 2.36 (br t, *J*=9.9 Hz, IH), 2.21 (s, 3H), 1.21 (d, *J*=6.7 Hz, 3H), 0.98 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 586.2.

Example 608: N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-meth^ l-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



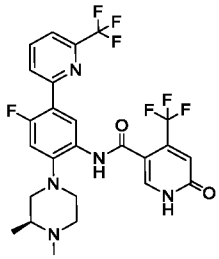
[001000] The procedure used was similar to Example 31 using l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid and (S)-4-(5-fluoro-2-nitro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,2-dimethylpiperazine. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 (s, IH), 8.52 (d, *J*=0.7 Hz, 2H), 8.30 (s, IH), 7.76 (d, *J*=8.4 Hz, IH), 7.10 (d, *J*=12.2 Hz, IH), 6.87 (s, IH), 4.65 (br dd, *J*=2.8, 6.7 Hz, IH), 4.29 (dd, *J*=2.3, 13.6 Hz, IH), 3.93 (dd, *J*=3.5, 11.3 Hz, IH), 3.73 (d, *J*=11.2 Hz, IH), 3.60 (dd, *J*=3.1, 11.4 Hz, IH), 3.44 (dt, *J*=3.1, 11.9 Hz, IH), 3.19 (dt, *J*=3.9, 13.0 Hz, IH), 3.02 (br t, *J*=13.3 Hz, 2H), 2.90 - 2.74 (m, 2H), 2.46 - 2.34 (m, 2H), 2.25 - 2.19 (m, 3H), 1.21 (d, *J*=6.7 Hz, 3H), 0.98 (br d, *J*=6.0 Hz, 3H); LCMS [M+H]+: 604.3.

Example 609: N-[4-fluoro-5-(6-fluoropyridin-2-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



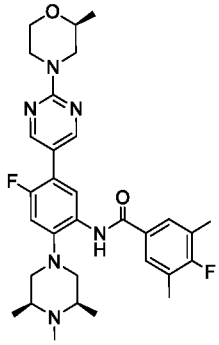
[001001] A procedure similar to Example 384 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (107 mg, 0.133 mmol) and 2-bromo-6-trifluoromethylpyridine (33.2 mg, 0.147 mmol), gave the title compound (15.3 mg, 21% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.38 (d, *J* = 8.1 Hz, IH), 8.09 - 8.04 (m, 2H), 7.99 (s, IH), 7.73 (d, *J* = 7.0 Hz, IH), 7.09 (d, *J* = 12.8 Hz, IH), 6.91 (s, IH), 3.23 - 3.15 (m, 2H), 3.00 (t, *J* = 10.6 Hz, 2H), 2.64 (s, 2H), 2.54 (s, IH), 2.44 (s, 3H), 1.16 (d, *J* = 4.7 Hz, 3H); LCMS [M+l] $^{+}$ = 558.07.

Example 610: N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-(Mfluoromethyl)pyridin-2-yl]phmyl]-6^xo-4-(Mflwrom ethyl)-1H-pyridine-3-carboxamide



[001002] A procedure similar to that of Example 384 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (109 mg, 0.136 mmol) and 2-bromo-6-fluoropyridine (26.3 mg, 0.150 mmol) gave the title compound (9 mg, 13% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.02 - 7.95 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 12.9 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.91 (s, 1H), 3.15 (dd, *J* = 26.8, 11.1 Hz, 2H), 2.95 (t, *J* = 10.9 Hz, 2H), 2.62 - 2.51 (m, 2H), 2.43 (s, 1H), 2.38 (s, 3H), 1.13 (d, *J* = 6.1 Hz, 3H); LCMS [M+l] $^{+}$ = 508.26.

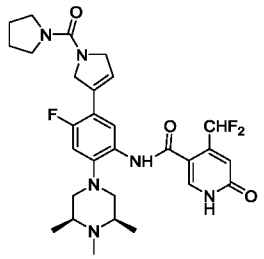
Example 611: 4-fluoro-N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide



[001003] A mixture of 4-fluoro-3,5-dimethylbenzoic acid (757 mg, 4.5 mmol), HATU (1.711 g, 4.5 mmol) and N,N-diisopropylethylamine (0.784 ml, 4.5 mmol) in DMF (6 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (0.949 g, 3 mmol) was added in one portion. The resulting mixture was heated at 60 °C for 4.5 h and 80 °C for 2 h. DMF was removed to give a brown solid which was partitioned between

DCM (50 niL) and sat. $NaHC0_3$ (30 niL) and H_20 (15 niL) then separated. The aq layer was extracted with DCM (30 mL) and the combined extracts were concentrated to give a brown solid. It was purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-5%) to give N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-3,5-dimethylbenzamide as a light pink crystalline solid (608 mg, 37.6% yield based on 86.5% purity). LCMS $[M + H]^+$ 466.1. The title compound (formic acid salt, white solid, 22.0 mg, 36%) was prepared by a procedure similar to Example 29 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.2 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-3,5-dimethylbenzamide (54 mg, 86.5% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.46 (br s, IH), 8.02 (d, *J*=8.3 Hz, IH), 7.70 (d, *J*=6.7 Hz, 2H), 7.13 (d, *J*=12.0 Hz, IH), 4.65 - 4.55 (m, 2H), 3.99 (dd, *J*=2.4, 11.5 Hz, IH), 3.68 - 3.60 (m, 2H), 3.20 (br d, *J*=11.5 Hz, 2H), 3.08 (ddd, *J*=3.5, 12.0, 13.3 Hz, IH), 2.88 - 2.71 (m, 5H), 2.57 (s, 3H), 2.37 (d, *J*=1.8 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 9H); LCMS $[M + H]^+$ 565.4.

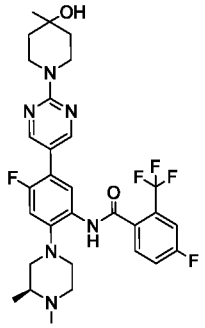
Example 612: 4-(Difluoromethyl)-N-(4-fluoro-5-(l-(pyrrolidine-l-carbonyl)-2, 5-dihydro-lH-pyrrol-3-yl)-2-((3S,5R)-3,4,5-Mmethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide



[001004] The procedure was similar to Example 253 using 1-pyrrolidinecarbonyl chloride (5.81 μï, 0.053 mmol) and 4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, (0.053 mmol) to give the title compound (27.5 mg, 87 % yield). ^{1}H NMR (500MHz, METHANOL-d45 = 8.05 - 8.00 (m, IH), 7.76 - 7.68 (m, IH), 7.44 - 7.19 (m, IH), 7.03 - 6.95 (m, IH), 6.84 - 6.78 (m, IH), 6.38 - 6.31 (m, IH), 4.69 - 4.60 (m, 2H), 4.50 - 4.41 (m, 2H), 3.54 -

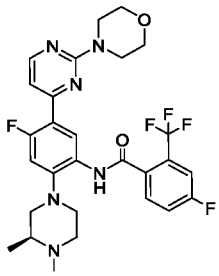
3.44 (m, 4H), 3.12 - 3.02 (m, 2H), 2.63 - 2.55 (m, 2H), 2.54 - 2.46 (m, 2H), 2.39 - 2.33 (m, 3H), 1.99 - 1.88 (m, 4H), 1.20 - 1.10 (m, 6H); LCMS [M+H]+ 573.6.

Example 613: 4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l -yl)pyrimidin-5-ylJ-2-[(3R)-3,4^imethylpiperazin-l-ylJphenylJ-2-(trifluoromethyl)benzamide



[001005] The title compound (formic acid salt, pale beige solid, 26.0 mg, 40%) was prepared by a procedure similar to Example 400 using crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 86% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.53 (s, 2H), 8.39 (br s, IH), 8.04 (d, *J*=8.2 Hz, IH), 7.82 (dd, *J*=5.3, 8.4 Hz, IH), 7.67 (br d, *J*=8.9 Hz, IH), 7.58 (br t, *J*=7.6 Hz, IH), 7.19 (d, *J*=11.7 Hz, IH), 4.31 (br d, *J*=13.2 Hz, 2H), 3.64 - 3.54 (m, 2H), 3.45 - 3.36 (m, IH), 3.25 (br d, *J*=9.7 Hz, 2H), 3.12 (br s, 3H), 2.93 - 2.82 (m, IH), 2.81 - 2.73 (m, 3H), 1.70 - 1.59 (m, 4H), 1.37 - 1.31 (m, 3H), 1.31 - 1.27 (m, 3H); LCMS $[M + H]^+$ 605.3.

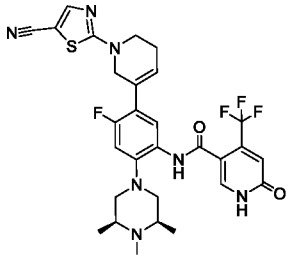
Example 614: 4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3, 4-dimethylpiperazin-1 -yl]phenyl] -2-(trifluoromethyl)benzamide



[001006] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.045 mL, 0.3 mmol) in DCM (3 mL) at rt was added Et_3N (0.084 mL, 0.6 mmol). After

addition, the resulting mixture was stirred at rt for 5 min, before a solution of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-mo rpholinopyrimidin-4-yl)aniline (38.6 mg, 0.1 mmol) in DCM (2 mL) was added. The resulting mixture was stirred overnight at room temperature LC-MS then additional 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.045 mL, 0.3 mmol) in DCM (2 mL) and Et_3N (0.084 mL, 0.6 mmol) was added. After addition, the resulting mixture was stirred at rt for 1.5 h and the reaction was judged complete by LCMS. Standard workup and purification by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-10%, later 1% NH_3 in MeOH/DCM 20%) and prep-HPLC gave the title compound (formic acid salt, light brown solid, 7.5 mg, 12%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.73 (d, *J*=8.2 Hz, 1H), 8.44 (br s, 1H), 8.41 (d, *J*=5.3 Hz, 1H), 7.77 (dd, *J=5A*, 8.3 Hz, 1H), 7.68 (dd, *J*=2.3, 9.0 Hz, 1H), 7.58 (dt, *J*=2.0, 8.2 Hz, 1H), 7.17 (dd, *J*=1.7, 5.1 Hz, 1H), 7.08 (d, *J*=13.1 Hz, 1H), 3.90 - 3.86 (m, 4H), 3.81 - 3.77 (m, 4H), 3.30 - 3.23 (m, 2H), 3.20 - 3.13 (m, 1H), 3.05 (br t, *J*=11.0 Hz, 1H), 2.82 - 2.69 (m, 3H), 2.55 (s, 3H), 1.24 (br d, *J*=5.5 Hz, 3H); LCMS $[M + H]^+$ 577.3.

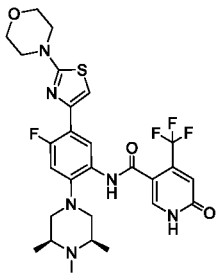
Example 615: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3A,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluorom ethyl)-1H-pyridine-3-carboxamide



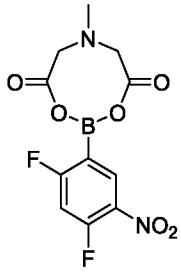
[001007] The procedure followed was similar to that of Example 270 using N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 2-bromo-5-cyanothiazole (9.31 mg, 0.049 mmol) to afford the title compound (24 mg, 75 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.80 (m, 1H), 7.73 - 7.70 (m, 1H), 7.70 - 7.66 (m, 1H), 6.93 - 6.85 (m, 1H), 6.82 - 6.77 (m, 1H), 6.12 - 6.05 (m, 1H), 4.30 - 4.23 (m, 2H), 3.74 - 3.66 (m, 2H), 2.97 -

2.89 (m, 2H), 2.52 - 2.46 (m, 2H), 2.45 - 2.38 (m, 4H), 2.29 - 2.25 (m, 3H), 1.08 - 1.03 (m, 6H); LCMS [M+H]+ 616.6

Example 616: N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-4-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridim -3-carboxamide

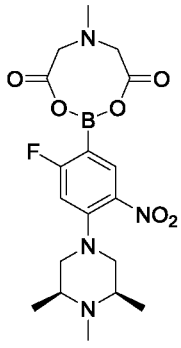


Step 1: 2-(2,4-dif uoro-5-nitrophenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



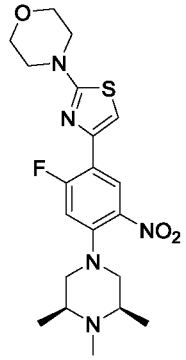
[001008] A mixture of 2,4-difluoro-5-nitrophenylboronic acid (4.5 g, 22 mmol) and methyliminodiacetic acid (3.6 g, 24 mmol) in DMF (36 mL) was heated to 85 °C for 18 h under nitrogen. The DMF was removed in vacuo and the waxy yellow solid was dried under reduced pressure overnight to afford 2-(2,4-difluoro-5-nitrophenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (7 g, quantitative yield) that did not require purification. LCMS [M-H]-: 313.2.

Step 2: 2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l, 3,6,2-dioxazaborocane-4,8-dione



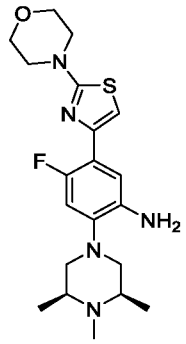
[001009] A solution of cis-l,2,6-trimethylpiperazine (0.42 g, 3.4 mmol) in anhydrous toluene (4 mL) was added to a mixture of 2-(2,4-difluoro-5-nitrophenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (1.0 g, 3.2 mmol) and potassium carbonate (0.22 g, 1.6 mmol) in anhydrous toluene (3 mL) and anhydrous DMSO (1.0 mL). The reaction mixture was heated to 50 °C for 1.5 h. After cooling to room temperature the organic liquid phase was decanted from the inorganics and filtered through a short pad of celite qualitatively rinsing the reaction vial and celite with a solution of DCM and MeOH. Concentration of the filtrate to dryness and drying under reduced pressure overnight afforded the desired product 2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (1.5 g, quantitative yield) as a viscous amber oil that was used without further purification. LCMS [M+H]+: 423.3.

Step 3: 4-(4-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-2-yl)morpholine



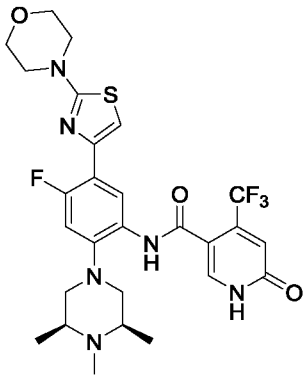
[001010] A reaction vial was charged with a mixture of 2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (0.060 g, 0.14 mmol), 4-(4-bromothiazol-2-yl)mo rpholine (0.042 g, 0.17 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.016 g, 0.014 mmol). The vial was sealed with a septum and evacuated and backfilled with nitrogen. 1,4-Dioxane (4 mL) and 2 M aqueous sodium carbonate (0.9 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 90 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford 4-(4-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-2-yl)mo rpholine (0.051 g, 82 %). LCMS [M+H]+: 436.3.

Step 4: 4-fluoro-5-(2-morpholinothiazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-1-yl)aniline



[001011] A mixture of 4-(4-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-2-yl)mo rpholine (0.051 g, 0.12 mmol) and tin(II) chloride (0.070 g, 0.35 mmol) in MeOH (1.5 mL) and EtOH (1.5 mL) was heated to 50 °C for 1 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH] to afford 4-fluoro-5-(2-morpholinothiazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.080 g, quantitative yield). LCMS [M+H]+: 406.3.

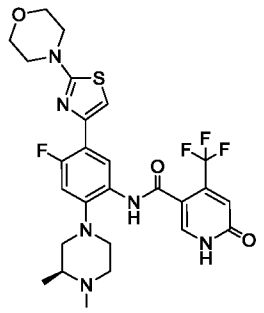
Step 5: N-(4-fluoro-5-(2-morpholinothiazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide



[001012] 4-(Trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.031 g, 0.10 mmol) was activated with HATU (0.040 g, 0.10 mmol) and N,N-diisopropylethylamine (0.017 mL, 0.10 mmol) in DMF (1 mL) at room temperature. The solution of activated acid was added to a solution of 4-fluoro-5-(2-morpholinothiazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.024 g, 0.060 mmol) in DMF (1 mL) and the reaction was heated to 50 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0.5-9.5% MeOH/DCM + 0.5% NH_4OH]. The silyl protected amide was dissolved in DCM (1 mL) and treated with TFA (0.5 mL) at room

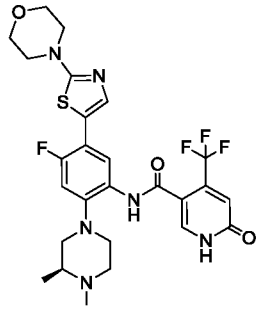
temperature. After stirring for 4 h the volatiles were removed under a stream of air and the title compound was isolated with a catch and release protocol using a SCX2 silica cartridge to afford the title compound N-(4-fluoro-5-(2-mo rpholinothiazol-4-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (0.016 g, 46 %). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.71 - 12.39 (m, 1H), 9.49 (s, 1H), 8.18 (br d, *J*=6.0 Hz, 1H), 7.94 (br s, 1H), 7.12 (d, *J*=2.0 Hz, 1H), 7.03 - 6.93 (m, 1H), 6.81 (s, 1H), 6.84 - 6.78 (m, 1H), 3.75 - 3.71 (m, 4H), 3.64 - 3.54 (m, 1H), 3.43 - 3.40 (m, 4H), 3.15 - 3.02 (m, 3H), 2.33 - 2.18 (m, 3H), 1.04 (br s, 6H); LCMS [M+H]+: 595.2.

Example 617: N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide



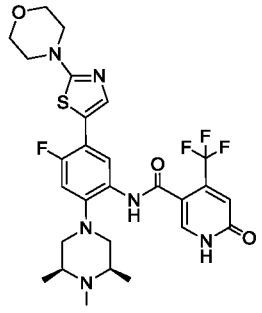
[001013] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using (S)-l,2-dimethylpiperazine dihydrochloride in place of cis-l,2,6-trimethylpiperazine in Step 2. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.47 (s, 1H), 8.17 (br d, *J*=8.2 Hz, 1H), 7.95 (s, 1H), 7.13 (d, *J*=2.1 Hz, 1H), 7.00 (d, *J*=13.2 Hz, 1H), 6.81 (s, 1H), 3.77 - 3.71 (m, 4H), 3.44 - 3.41 (m, 4H), 3.02 (br dd, *J*=11.2, 19.3 Hz, 2H), 2.84 - 2.73 (m, 3H), 2.41 (br t, *J*=10.5 Hz, 1H), 2.35 - 2.29 (m, 1H), 2.21 (s, 3H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 581.2.

Example 618: N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6 -oxo-4-(Mfluorom ethyl)-1H-pyridine-3-carboxamide



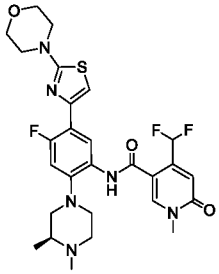
[001014] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using (S)-l,2-dimethylpiperazine dihydrochloride in place of cis-l,2,6-trimethylpiperazine in Step 2 and using 4-(5-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.48 (s, IH), 7.95 (s, IH), 7.81 (d, *J*=8.3 Hz, IH), 7.51 (s, IH), 7.05 (d, *J*=13.0 Hz, IH), 6.82 (s, IH), 3.75 - 3.70 (m, 4H), 3.46 - 3.42 (m, 4H), 3.03 - 2.95 (m, 2H), 2.82 - 2.72 (m, 3H), 2.43 - 2.29 (m, 3H), 2.21 (s, 3H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 581.3.

Example 619: N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



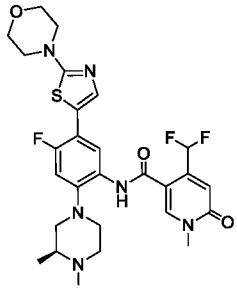
[001015] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 4-(5-bromothiazol-2-yl)morpholine in place of 4-(4-bromothiazol-2-yl)mo rpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.50 (s, IH), 7.94 (s, IH), 7.81 (d, *J*=8.3 Hz, IH), 7.50 (s, IH), 7.03 (d, *J*=12.8 Hz, IH), 6.82 (s, IH), 3.74 - 3.71 (m, 4H), 3.46 - 3.40 (m, 4H), 3.00 (br d, *J*=11.2 Hz, 2H), 2.44 (br t, *J*=ll.l Hz, 2H), 2.39 - 2.30 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 595.3.

Example 620: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridme-3-carboxamide



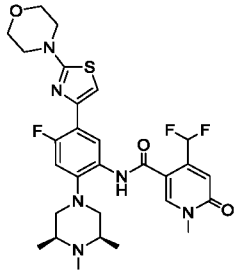
[001016] The title compound was prepared similar to the procedure described above for the preparation of Example 617 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.44 (s, 1H), 8.43 (s, 1H), 8.09 (d, *J*=8.4 Hz, 1H), 7.46 - 7.21 (m, 1H), 7.13 (d, *J*=2.0 Hz, 1H), 6.99 (d, *J*=13.3 Hz, 1H), 6.63 (s, 1H), 3.75 - 3.71 (m, 4H), 3.52 (s, 3H), 3.44 - 3.39 (m, 4H), 3.07 - 2.98 (m, 2H), 2.84 - 2.71 (m, 3H), 2.43 - 2.35 (m, 2H), 2.34 - 2.27 (m, 1H), 2.18 (s, 3H), 0.95 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 577.3.

Example 621: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-l,3-thiazol-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridm^ -3-carboxamide



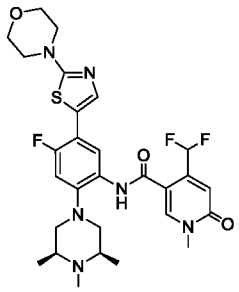
[001017] The title compound was prepared similar to the procedure described above for the preparation of Example 618 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.44 (s, 1H), 8.38 (s, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.51 (s, 1H), 7.46 - 7.21 (m, 1H), 7.06 (d, *J*=12.8 Hz, 1H), 6.64 (s, 1H), 3.74 - 3.70 (m, 4H), 3.52 (s, 3H), 3.45 - 3.41 (m, 4H), 3.06 - 2.93 (m, 3H), 2.85 - 2.71 (m, 3H), 2.42 - 2.28 (m, 3H), 2.19 (s, 3H), 0.96 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 577.1.

Example 622: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001018] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 (s, 1H), 8.43 (s, 1H), 8.08 (d, *J*=8.4 Hz, 1H), 7.48 - 7.21 (m, 1H), 7.12 (d, *J*=2.3 Hz, 1H), 6.97 (d, *J*=13.3 Hz, 1H), 6.63 (s, 1H), 3.76 - 3.70 (m, 4H), 3.51 (s, 3H), 3.45 - 3.38 (m, 4H), 3.04 (br d, *J*=ll.l Hz, 2H), 2.44 (br t, *J*=11.0 Hz, 2H), 2.30 (dt, *J*=3.1, 6.6 Hz, 2H), 2.16 (s, 3H), 0.98 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 591.4.

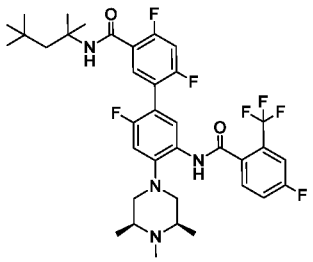
Example 623: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-l, 3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001019] The title compound was prepared similar to the procedure described above for the preparation of Example 619 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.46 (s, 1H), 8.36 (s, 1H), 7.71 (d, *J*=8.3 Hz, 1H), 7.50 (s, 1H), 7.46 - 7.20 (m, 1H), 7.02 (d, *J*=12.8 Hz, 1H), 6.64 (s, 1H), 3.73 - 3.70 (m, 4H), 3.51 (s, 3H), 3.45 - 3.41

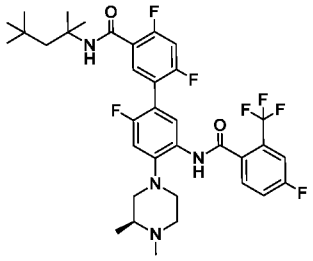
(m, 4H), 3.00 (br d, *J*=10.9 Hz, 2H), 2.47 - 2.41 (m, 2H), 2.34 - 2.29 (m, 2H), 2.17 (s, 3H), 0.98 (d, *J=6.1* Hz, 6H); LCMS [M+H]+: 591.3.

Example 624: 2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-(2,4,4-Mmethylpentan-2-yl)bem amide



[001020] A procedure similar to that of Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (50.0 mg, 0.126 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (40 mg, 0.079 mmol) afforded the title compound as an off-white fluffy powder (39 mg, 0.053 mmol, 67.5 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.84 (d, *J*=7.7 Hz, 1H), 7.75 - 7.51 (m, 4H), 7.45 (dt, *J*=2.3, 8.3 Hz, 1H), 7.07 (t, *J*=10.0 Hz, 1H), 6.99 (d, *J*=11.2 Hz, 1H), 3.00 (br d, *J*=11.4 Hz, 2H), 2.54 (br t, *J*=ll.l Hz, 2H), 2.42 (br s, 2H), 2.26 (br s, 3H), 1.82 (s, 2H), 1.38 (s, 6H), 1.07 (d, *J*=6.1 Hz, 6H), 0.94 (s, 9H); LCMS $[M+H]^+$ 695.

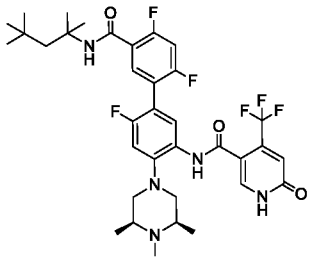
Example 625: 2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-N-(2, 4,4-trimethylpentan-2-yl)benzamide



[001021] A procedure similar to Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (51.4 mg, 0.130 mmol), potassium phosphate tribasic reagent grade, >=98% (51.7 mg, 0.244 mmol) and(S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (40 mg, 0.081 mmol) afforded the title

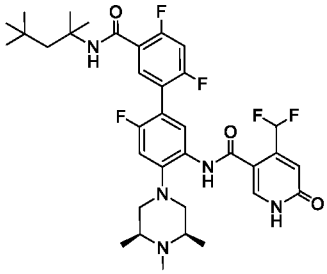
compound as an off-white fluffy powder (33 mg, 0.046 mmol, 56.7 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.84 (d, *J*=7.8 Hz, IH), 7.76 - 7.58 (m, 2H), 7.57 - 7.51 (m, 2H), 7.45 (dt, *J*=2.4, 8.3 Hz, IH), 7.07 (t, *J*=10.0 Hz, IH), 7.03 - 6.99 (m, IH), 3.09 - 3.04 (m, IH), 3.01 (br d, *J*=11.7 Hz, IH), 2.90 - 2.83 (m, 2H), 2.51 (br t, *J*=10.9 Hz, IH), 2.45 (br s, IH), 2.37 - 2.31 (m, IH), 2.29 (br s, 3H), 1.83 (s, 2H), 1.39 (s, 6H), 1.04 (d, *J*=6.2 Hz, 3H), 0.95 (s, 9H); LCMS $[M+H]^+$ 681.

Example 626: N-[5-[2, 4-difluoro-5-(2, 4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



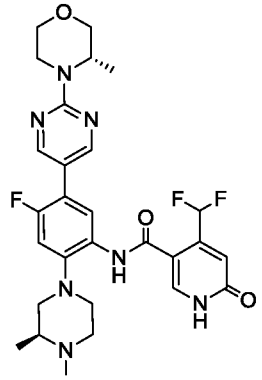
[001022] A sequence similar to Example 100 using 2,4-difluoro-5-(4 ,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (41.8 mg, 0.106 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(mfluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (40 mg, 0.066 mmol) afforded the title compound (TFA salt) as a white fluffy powder (12.7 mg, 0.013 mmol, 94 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.92 (s, IH), 7.79 (d, *J*=7.6 Hz, IH), 7.73 (br s, IH), 7.58 (t, *J*=8.0 Hz, IH), 7.14 - 7.05 (m, 2H), 6.87 - 6.82 (m, IH), 3.47 - 3.38 (m, 2H), 3.33 (br d, *J*=13.1 Hz, 2H), 2.91 (s, 3H), 2.89 - 2.80 (m, 2H), 1.85 (s, 2H), 1.40 (s, 6H), 1.37 (d, *J*=6.5 Hz, 6H), 0.96 (s, 9H); LCMS $[M+H]^+$ 694.

Example 627: 4-(difluoromethyl)-N-[5-[2, 4-difluoro-5-(2, 4,4-trimethylpentan-2-ylcarbamoyl)phenylJ-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridine-3-carboxamide



[001023] A procedure similar to Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (43. 1 mg, 0.109 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg, 0.068 mmol). The title compound (TFA salt) was collected as a white fluffy powder (13 mg, 0.015 mmol, 100 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.95 (s, 1H), 7.69 (br d, *J*=2.2 Hz, 1H), 7.61 (d, *J*=7.6 Hz, 1H), 7.56 (t, *J*=7.9 Hz, 1H), 7.32 - 7.10 (m, 1H), 7.09 - 7.04 (m, 2H), 6.72 - 6.66 (m, 1H), 3.42 - 3.36 (m, 2H), 3.35 - 3.31 (m, 2H), 2.89 (s, 3H), 2.85 - 2.79 (m, 2H), 1.83 (s, 2H), 1.38 (s, 6H), 1.34 (d, *J*=6.4 Hz, 6H), 0.94 (s, 9H); LCMS $[M+H]^+$ 676.

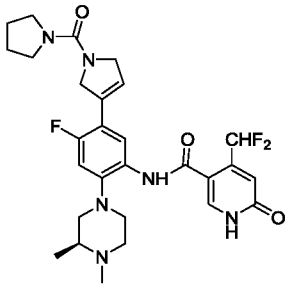
Example 628: 4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6<>x o-1H-pyridine-3-carboxamide



[001024] The title compound was prepared according to a procedure similar to that of Example 39 using (S)-3-methyl-4-(5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimicUn-2-yl)morpholine and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.54 (d, J=1.0 Hz, 2H), 8.03 (s, 1H), 7.82 (d, J=8.3 Hz, 1H), 7.46 - 7.18 (m, 1H), 7.08 (d, J=12.1 Hz, 1H), 6.81 (s, 1H), 4.74 (br dd,

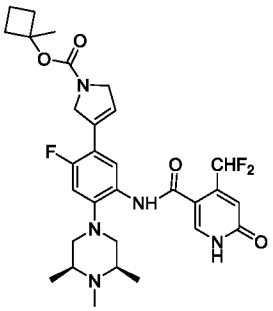
J=2.8, 6.7 Hz, IH), 4.37 (dd, J=2.6, 13.8 Hz, IH), 3.98 (dd, J=3.6, 11.3 Hz, IH), 3.84 - 3.76 (m, IH), 3.75 - 3.68 (m, IH), 3.56 (dt, J=3.1, 11.9 Hz, IH), 3.15 - 3.03 (m, 2H), 2.98 - 2.87 (m, 2H), 2.61 - 2.49 (m, 2H), 2.44 - 2.38 (m, IH), 2.37 (s, 3H), 1.30 (d, J=6.8 Hz, 3H), 1.12 (d, J=6.2 Hz, 3H); LCMS [M+H]+: 572.4.

Example 629: (S)-4-(Sifluoromethyl)-N-(2-(3, 4-dimethylpiperazin-l-yl)-4-fluoro-5-(1-(pyrrolidine-l-carbonyl)-2,5^ihydro-lH-pyrrol-3-yl)pheny l)-6-oxo-1,6-dihydropyridine-3-carboxamide



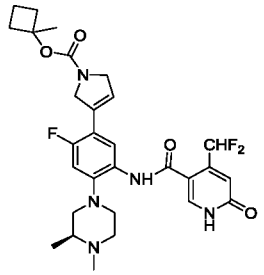
[001025] The procedure followed was similar to Example 253 using (S)-4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.054 mmol) and 1-pyrrolidinecarbonyl chloride (5.99 µï, 0.054 mmol) to give the title compound (25 mg, 78 % yield). ^{1}H NMR (500MHz, METHANOL-d4 δ = 8.07 - 8.01 (m, IH), 7.78 - 7.70 (m, IH), 7.44 - 7.19 (m, IH), 7.05 - 6.97 (m, IH), 6.84 - 6.78 (m, IH), 6.38 - 6.31 (m, IH), 4.70 - 4.58 (m, 2H), 4.51 - 4.39 (m, 2H), 3.55 - 3.43 (m, 4H), 3.15 - 3.02 (m, 2H), 2.97 - 2.87 (m, 2H), 2.58 - 2.48 (m, 2H), 2.42 - 2.34 (m, 4H), 1.97 - 1.87 (m, 4H), 1.11 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+ 559.5.

Example 630: 1-Methylcyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S, 5R)-3, 4,5-trimethylpiperazin-l-yl)phenyl)-2, 5-dihydro-lH-pyrrole-l-carboxylate



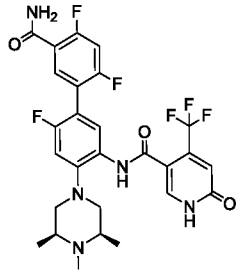
[001026] The procedure used was similar to Example 253 using 4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol), and 1-methylcyclobutyl (4-nitrophenyl) carbonate (18.16 mg, 0.058 mmol) to give the title compound (22 mg, 68 % yield). ^{1}H NMR (500MHz, METHANOL-d4 δ = 8.06 - 7.99 (m, 1H), 7.75 - 7.66 (m, 1H), 7.45 - 7.19 (m, 1H), 7.03 - 6.94 (m, 1H), 6.84 - 6.77 (m, 1H), 6.39 - 6.30 (m, 1H), 4.57 - 4.46 (m, 2H), 4.38 - 4.26 (m, 2H), 3.12 - 3.03 (m, 2H), 2.63 - 2.56 (m, 2H), 2.55 - 2.47 (m, 2H), 2.45 - 2.35 (m, 5H), 2.21 - 2.12 (m, 2H), 1.91 - 1.81 (m, 1H), 1.78 - 1.67 (m, 1H), 1.61 (d, *J*=3.4 Hz, 3H), 1.18 - 1.13 (m, 6H); LCMS [M+H]+ 588.6.

Example 631: 1-Methylcyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-l -yl)-2-fluorophenyl)-2, 5-dihydro-lH-pyrrole-l -carboxylate



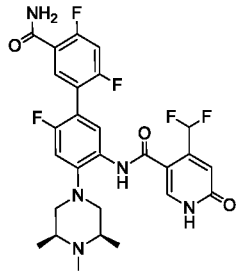
[001027] The procedure followed was similar to Example 253 using (S)-4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.054 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (18.71 mg, 0.060 mmol) to afford the title compound (18 mg, 55 % yield). ^{1}H NMR (500MHz, METHANOL-d4 δ = 8.07 - 8.00 (m, 1H), 7.78 - 7.68 (m, 1H), 7.45 - 7.20 (m, 1H), 7.05 - 6.97 (m, 1H), 6.85 - 6.79 (m, 1H), 6.39 - 6.30 (m, 1H), 4.59 - 4.47 (m, 2H), 4.38 - 4.27 (m, 2H), 3.16 - 3.03 (m, 2H), 2.97 - 2.87 (m, 2H), 2.59 - 2.49 (m, 2H), 2.45 - 2.35 (m, 6H), 2.23 - 2.12 (m, 2H), 1.91 - 1.81 (m, 1H), 1.78 - 1.68 (m, 1H), 1.65 - 1.58 (m, 3H), 1.15 - 1.09 (m, 3H); LCMS [M+H]+ 574.5.

Example 632: N-[5-(5-carbamoyl-2, 4-difluorophenyl)-4-fluoro-2-[(3R, 5S)-3, 4, 5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-c^ rboxamide



[001028] A procedure similar to that of Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (41.8 mg, 0.106 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg, 0.066 mmol) gave the title compound (TFA salt) as an off-white fluffy powder (32 mg, 96 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.90 (s, 1H), 7.82 (t, *J*=8.2 Hz, 1H), 7.78 (d, *J*=7.6 Hz, 1H), 7.14 (t, *J*=10.2 Hz, 1H), 7.09 (d, *J*=10.9 Hz, 1H), 6.84 - 6.79 (m, 1H), 3.41 (ddd, *J*=2.9, 6.8, 10.2 Hz, 2H), 3.31 (br d, *J*=13.2 Hz, 2H), 2.89 (s, 3H), 2.88 - 2.81 (m, 2H), 1.35 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^+$ 582.

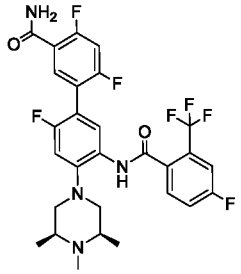
Example 633: N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6<>xo-lH^yridine -3-carboxamide



[001029] A procedure similar to Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (43. 1 mg, 0.109 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (40 mg, 0.068 mmol) afforded the title compound (TFA salt) as an off-white fluffy powder (35 mg, 0.042 mmol, 93 % yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 7.03 (s, 1H), 6.89 (t, *J*=8.2 Hz, 1H), 6.70 (d, *J*=7.6 Hz, 1H), 6.39 - 6.16 (m, 2H), 6.14 (d, *J*=11.0 Hz, 1H),

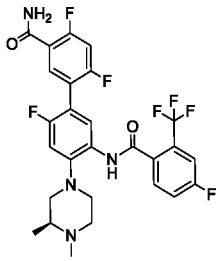
5.79 - 5.76 (m, 1H), 2.50 - 2.43 (m, 2H), 2.41 (br d, *J*=14.1 Hz, 2H), 1.96 (s, 3H), 1.91 (br t, *J*=12.0 Hz, 2H), 0.41 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^+$ 564.

Example 634: 2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[001030] A procedure similar to Example 100 was followed using 2,4-difluoro-5-(4,4,5,54etramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,44rimethylpentan-2-yl)benzamide (50.0 mg, 0.126 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzarnide (40 mg, 0.079 mmol). The title compound (TFA salt) was collected as an off-white fluffy powder (40 mg, 0.047 mmol, 93 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.90 (d, *J*=7.7 Hz, 1H), 7.83 (t, *J*=8.1 Hz, 1H), 7.69 (dd, *J*=5.3, 8.4 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.46 (dt, *J*=2.1, 8.3 Hz, 1H), 7.15 (t, *J*=10.2 Hz, 1H), 7.11 (d, *J*=11.0 Hz, 1H), 3.44 - 3.35 (m, 2H), 3.33 (br d, *J*=13.4 Hz, 2H), 2.90 - 2.81 (m, 5H), 1.35 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^+$ 583.

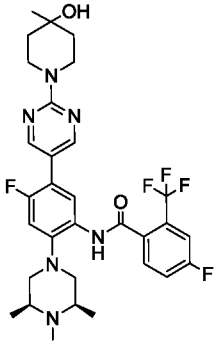
Example 635: 2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[001031] A coupling procedure similar to that of Example 100 using 2,4-difluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (51.4 mg, 0.130 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (40 mg, 0.081 mmol) afforded the title compound (TFA salt) as an off-white fluffy powder (28 mg, 87 %

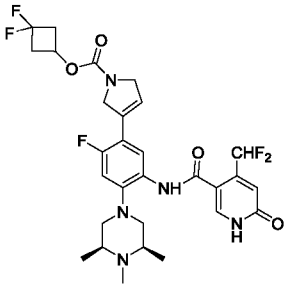
yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 (d, *J*=7.6 Hz, IH), 7.83 (t, *J*=8.1 Hz, IH), 7.70 (br dd, *J*=5.3, 8.3 Hz, IH), 7.58 - 7.53 (m, IH), 7.46 (dt, *J*=2.0, 8.2 Hz, IH), 7.15 (t, *J*=10.3 Hz, IH), 7.11 (d, *J*=11.0 Hz, IH), 3.55 (br d, *J*=12.2 Hz, IH), 3.36 - 3.28 (m, 3H), 3.09 - 2.99 (m, IH), 2.87 (s, 3H), 2.86 - 2.79 (m, 2H), 1.33 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 569.

Example 636: 4-Fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l -yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



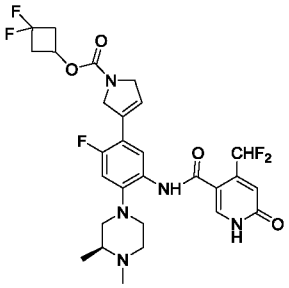
[001032] The title compound (formic acid salt, pale beige solid, 24.5 mg, 37%) was prepared by a procedure similar to that of Example 39 using crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (57 mg, 89% purity, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.53 (s, 2H), 8.40 (br s, IH), 8.05 (d, *J*=8.2 Hz, IH), 7.81 (dd, *J*=5.3, 8.4 Hz, IH), 7.67 (dd, *J*=1.9, 9.1 Hz, IH), 7.59 (t, *J*=8.2 Hz, IH), 7.18 (d, *J*=11.7 Hz, IH), 4.31 (td, *J*=4.0, 13.3 Hz, 2H), 3.63 - 3.55 (m, 2H), 3.25 (br d, *J*=12.5 Hz, 2H), 3.21 - 3.11 (m, 2H), 2.91 - 2.81 (m, 2H), 2.75 (br s, 3H), 1.70 - 1.59 (m, 4H), 1.35 (br d, *J*=6.1 Hz, 6H), 1.29 (s, 3H); LCMS $[M + H]^+$ 619.5.

Example 637: 3,3-Difluorocyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phen^ l)-2,5-dihydro-1H-pyrrole-l-carboxylate



[001033] A procedure similar to Example 253 using 4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol, in turn prepared from the intermediate in Step 1, Example 397 using procedures similar to Example 100) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.80 mg, 0.058 mmol) gave the title compound (25 mg, 74 % yield). ¾ NMR (500MHz, METHANOL-d4 δ = 8.06 - 7.98 (m, 1H), 7.76 - 7.66 (m, 1H), 7.44 - 7.19 (m, 1H), 7.04 - 6.94 (m, 1H), 6.83 - 6.76 (m, 1H), 6.40 - 6.28 (m, 1H), 4.99 - 4.91 (m, 1H), 4.62 - 4.50 (m, 2H), 4.43 - 4.30 (m, 2H), 3.12 - 2.98 (m, 4H), 2.83 - 2.67 (m, 2H), 2.64 - 2.56 (m, 2H), 2.55 - 2.47 (m, 2H), 2.41 - 2.34 (m, 3H), 1.15 (d, *J=6.1* Hz, 6H); LCMS [M+H]+ 610.4.

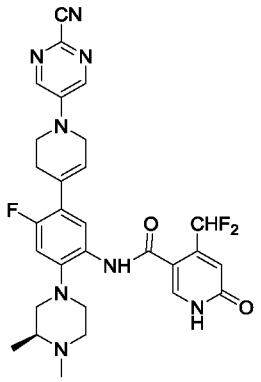
Example 638: 3,3-Difluorocyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-l-yl)-2-fluorophenyl)-2, 5-dihydro-lH-pyrrole-l-carboxylate



[001034] The procedure followed was similar to Example 253 using (S)-4-(difluoromethyl)-N-(5-(2,5-dihydro-lH-pyrrol-3-yl)-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.054 mmol, prepared from the intermediate 1, Example 396 from a couple procedure similar to that described in Example 100) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate

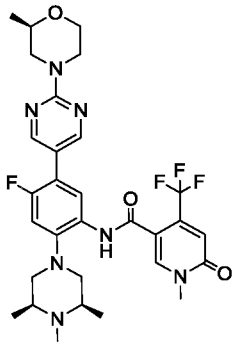
(16.28 mg, 0.060 mmol) to give the title compound (25 mg, 74 % yield). ^{1}H NMR (500MHz, METHANOL-d4 δ = 8.07 - 8.00 (m, 1H), 7.78 - 7.67 (m, 1H), 7.45 - 7.19 (m, 1H), 7.06 - 6.97 (m, 1H), 6.86 - 6.79 (m, 1H), 6.41 - 6.31 (m, 1H), 5.00 - 4.92 (m, 1H), 4.63 - 4.52 (m, 2H), 4.44 - 4.32 (m, 2H), 3.16 - 3.01 (m, 4H), 2.96 - 2.88 (m, 2H), 2.83 - 2.68 (m, 2H), 2.58 - 2.48 (m, 2H), 2.44 - 2.33 (m, 4H), 1.12 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+ 596.4.

Example 639: (S)-N-(5-(l-(2-cyanopyrimidin-5-yl)-l, 2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoro methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



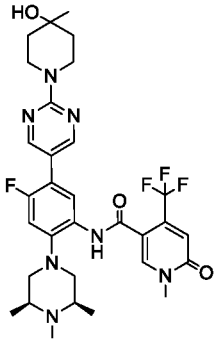
[001035] The procedure was similar to that of Example 270 using 5-bromo-2-cyanopyrimidine (14.51 mg, 0.079 mmol) and (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (30 mg, 0.063 mmol, prepared using similar methods to those described in the Example 638) to afford the title compound as an off white solid (8 mg). ^{1}H NMR (500MHz, METHANOL-d4 δ = 9.61 - 9.41 (m, 1H), 8.71 - 8.46 (m, 2H), 8.38 - 8.13 (m, 1H), 8.09 - 7.91 (m, 1H), 7.65 - 7.52 (m, 1H), 7.50 - 7.16 (m, 1H), 7.06 - 6.86 (m, 1H), 6.67 - 6.51 (m, 1H), 6.13 - 5.98 (m, 1H), 4.16 - 4.07 (m, 2H), 3.74 (t, *J*=5.6 Hz, 2H), 3.04 - 2.93 (m, 2H), 2.84 - 2.71 (m, 2H), 2.62 - 2.55 (m, 2H), 2.42 - 2.36 (m, 1H), 2.36 - 2.28 (m, 1H), 2.24 - 2.17 (m, 4H), 1.00 - 0.93 (m, 3H); LCMS [M+H]+ 579.5

Example 640: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)p^ ridine-3-carboxamide



[001036] The title compound (formic acid salt, light beige solid, 31.4 mg, 47%) was prepared according a procedure similar to Example 31 using crude (R)-(2-(2-methylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (52 mg, 0.1 mmol). ¾NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.53 - 8.33 (m, 1H), 8.30 (s, 1H), 7.93 (d, *J*=8.2 Hz, 1H), 7.17 (d, *J*=11.9 Hz, 1H), 6.96 (s, 1H), 4.65 - 4.55 (m, 2H), 3.99 (dd, *J*=2.6, 11.5 Hz, 1H), 3.71 - 3.58 (m, 5H), 3.26 - 3.05 (m, 5H), 2.90 - 2.80 (m, 2H), 2.77 - 2.70 (m, 4H), 1.34 (br d, *J*=5.3 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^+$ 618.3.

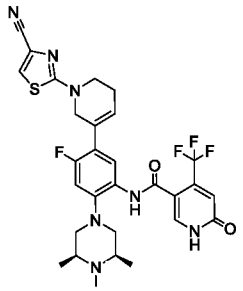
Example 641: N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]pheriyl]-l-methyU6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



[001037] The title compound (formic acid salt, pale beige solid, 27.6 mg, 40%) was prepared according to a procedure similar to Example 31 using crude (2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (52 mg, 0.1 mmol). ^{1}H NMR

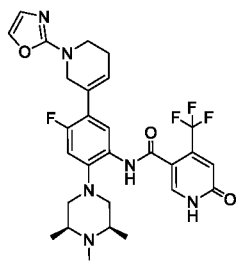
(500MHz, METHANOL-d4) δ = 8.52 (s, 2H), 8.41 (br s, 1H), 8.31 (s, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 7.18 (d, *J*=11.7 Hz, 1H), 6.96 (s, 1H), 4.34 - 4.27 (m, 2H), 3.67 (s, 3H), 3.63 - 3.53 (m, 2H), 3.31 - 3.21 (m, 4H), 2.89 (br d, *J*=11.2 Hz, 2H), 2.80 (br d, *J*=6.1 Hz, 3H), 2.68 (s, 1H), 1.70 - 1.58 (m, 4H), 1.37 (br d, *J*=6.0 Hz, 6H), 1.29 (s, 3H); LCMS $[M + H]^+$ 632.5.

Example 642: N-[5-[l-(4-cyano-l, 3-thiazol-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-l^ -pyridine-3-carboxamide



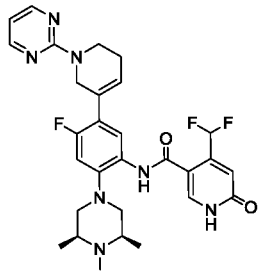
[001038] A procedure similar to Example 270 using N-(4-fluoro-5-(l, 2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) and 2-bromo-4-cyanothiazole (9.31 mg, 0.049 mmol) afforded the title compound (19 mg, 60 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 - 7.81 (m, 1H), 7.74 - 7.64 (m, 1H), 7.55 - 7.47 (m, 1H), 6.91 - 6.85 (m, 1H), 6.83 - 6.77 (m, 1H), 6.12 - 6.04 (m, 1H), 4.22 - 4.16 (m, 2H), 3.68 - 3.61 (m, 2H), 2.97 - 2.89 (m, 2H), 2.53 - 2.47 (m, 2H), 2.47 - 2.42 (m, 2H), 2.41 - 2.36 (m, 2H), 2.29 - 2.24 (m, 3H), 1.08 - 1.02 (m, 6H); LCMS [M+H]+ 616.5.

Example 643: N-[4-fluoro-5-[l-(l,3-oxazol-2-yl)-3,6-dihydro-2H-pyridin-5-ylJ-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH^yridine-3-carboxamide



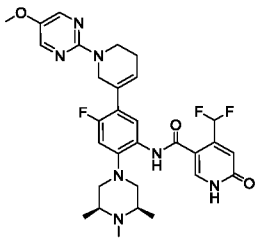
[001039] A procedure similar to Example 270 using N-(4-fluoro-5-(l, 2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol), 2-iodooxazole (9.60 mg, 0.049 mmol) afforded the title compound (6 mg, 20 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.82 (m, 1H), 7.71 - 7.64 (m, 1H), 7.35 - 7.28 (m, 1H), 6.89 - 6.83 (m, 1H), 6.80 - 6.77 (m, 1H), 6.77 - 6.70 (m, 1H), 6.07 - 6.01 (m, 1H), 4.23 - 4.15 (m, 2H), 3.62 - 3.55 (m, 2H), 2.96 - 2.88 (m, 2H), 2.52 - 2.46 (m, 2H), 2.45 - 2.39 (m, 2H), 2.37 - 2.30 (m, 2H), 2.28 - 2.25 (m, 3H), 1.06 - 1.03 (m, 6H); LCMS [M+H]+ 575.5

Example 644: 4-(difluoromethyl)-N-[4-fluoro-5-(l-pyrimidin-2-yl-3, 6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridim -3-carboxamide



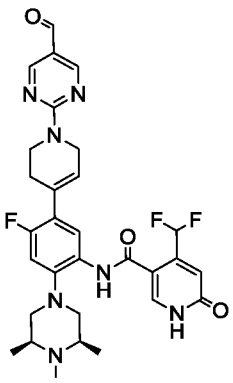
[001040] A procedure similar to Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and 2-bromopyrimidine 95% (12.18 mg, 0.077 mmol) afforded the title compound (29 mg, 79 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.28 - 8.18 (m, 2H), 7.94 - 7.86 (m, 1H), 7.63 - 7.55 (m, 1H), 7.35 - 7.08 (m, 1H), 6.89 - 6.81 (m, 1H), 6.74 - 6.68 (m, 1H), 6.52 - 6.46 (m, 1H), 6.09 - 6.00 (m, 1H), 4.45 - 4.39 (m, 2H), 3.91 - 3.85 (m, 2H), 2.97 - 2.91 (m, 2H), 2.52 - 2.44 (m, 2H), 2.43 - 2.37 (m, 2H), 2.33 - 2.28 (m, 2H), 2.26 - 2.23 (m, 3H), 1.06 - 1.02 (m, 6H); LCMS [M+H]+ 568.6.

Example 645: 4-(difluoromethyl)-N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide



[001041] A procedure similar to that of Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and 2-bromo-5-methoxypyrimidine (16.22 mg, 0.086 mmol) afforded the title compound (24 mg, 62 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.11 - 7.99 (m, 2H), 7.94 . 7.84 (m, 1H), 7.62 - 7.53 (m, 1H), 7.34 - 7.07 (m, 1H), 6.88 - 6.80 (m, 1H), 6.72 - 6.66 (m, 1H), 6.06 - 5.96 (m, 1H), 4.39 - 4.29 (m, 2H), 3.83 - 3.79 (m, 2H), 3.77 - 3.67 (m, 3H), 2.97 - 2.91 (m, 2H), 2.51 - 2.44 (m, 2H), 2.43 - 2.36 (m, 2H), 2.31 - 2.26 (m, 2H), 2.26 - 2.23 (m, 3H), 1.06 - 1.03 (m, 6H); LCMS [M+H]+ 598.5.

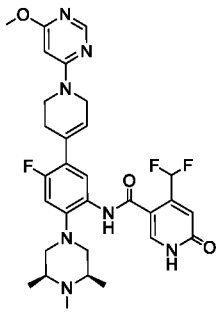
Example 646: 4-(difluoromethyl)-N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6 -oxo-1H-pyridine-3-carboxamide



[001042] The procedure followed was similar to that of Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (40 mg, 0.082 mmol) and 2-bromo-pyrimidine-5-carbaldehyde (19.86 mg, 0.106 mmol) to afford the title compound (32.5 mg, 63 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.70 - 9.54 (m, 1H), 8.75 - 8.61 (m, 2H), 7.93 - 7.82 (m, 1H), 7.63 - 7.55 (m, 1H), 7.33 - 7.06 (m, 1H), 6.88 - 6.77 (m, 1H), 6.73 - 6.64 (m, 1H), 6.04 - 5.92 (m,

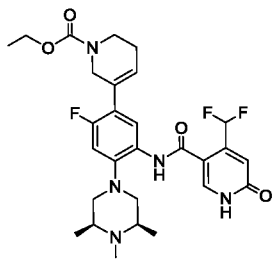
1H), 4.49 - 4.37 (m, 2H), 4.14 - 4.03 (m, 2H), 2.96 - 2.88 (m, 2H), 2.54 - 2.49 (m, 2H), 2.49 - 2.43 (m, 2H), 2.43 - 2.36 (m, 2H), 2.27 - 2.22 (m, 3H), 1.03 (d, *J=6.1* Hz, 6H); LCMS [M+H]+ 596.5.

Example 647: 4-(difluoromethyl)-N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-^ -oxo-1H-pyridine-3-carboxamide



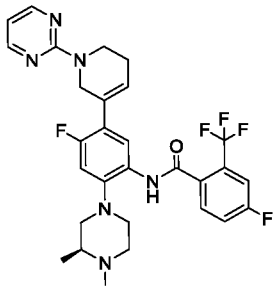
[001043] A procedure similar to Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and 4-iodo-6-methoxypyrimidine (18.80 mg, 0.080 mmol) gave the title compound (28 mg, 73 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.15 - 8.06 (m, 1H), 7.92 - 7.85 (m, 1H), 7.64 - 7.55 (m, 1H), 7.32 - 7.07 (m, 1H), 6.82 (d, *J*=12.5 Hz, 1H), 6.72 - 6.66 (m, 1H), 6.04 - 5.96 (m, 1H), 5.94 - 5.87 (m, 1H), 4.11 - 4.00 (m, 2H), 3.84 - 3.74 (m, 5H), 2.95 - 2.89 (m, 2H), 2.53 - 2.43 (m, 4H), 2.43 - 2.36 (m, 2H), 2.25 (s, 3H), 1.04 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+ 598.5.

Example 648: Ethyl 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonylJammoJ-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-3,6^ihydro-2H^yridme-l-carboxylate



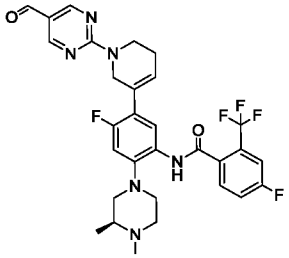
[001044] The procedure followed was similar to Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.061 mmol) and ethyl chloroformate (5.83 µï, 0.061 mmol) to give the title compound (29 mg, 80 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.93 - 7.83 (m, 1H), 7.60 - 7.50 (m, 1H), 7.34 - 7.06 (m, 1H), 6.88 - 6.78 (m, 1H), 6.73 - 6.63 (m, 1H), 6.03 - 5.92 (m, 1H), 4.21 - 4.10 (m, 2H), 4.09 - 4.01 (m, 2H), 3.57 - 3.45 (m, 2H), 2.96 - 2.88 (m, 2H), 2.50 - 2.43 (m, 2H), 2.43 - 2.36 (m, 2H), 2.27 - 2.20 (m, 5H), 1.21 - 1.16 (m, 3H), 1.07 - 1.01 (m, 6H); LCMS [M+H]+ 562.5.

Example 649: 4-fluoro-N-[4-fluoro-5-(l-pyrimidin-2-yl-3, 6-dihydro-2H-pyridin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide



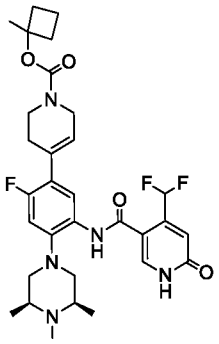
[001045] The procedure followed was similar to that of Example 270 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (30 mg, 0.061 mmol) and 2-bromopyrimidine 95% (12.06 mg, 0.076 mmol) to afford the title compound (26 mg, 71 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.41 - 8.30 (m, 2H), 7.97 - 7.89 (m, 1H), 7.82 - 7.74 (m, 1H), 7.69 - 7.62 (m, 1H), 7.60 - 7.51 (m, 1H), 7.07 - 6.96 (m, 1H), 6.61 (t, *J*=4.8 Hz, 1H), 6.21 - 6.10 (m, 1H), 4.63 - 4.49 (m, 2H), 4.07 - 3.96 (m, 2H), 3.13 - 3.01 (m, 2H), 2.97 - 2.86 (m, 2H), 2.60 - 2.51 (m, 1H), 2.50 - 2.44 (m, 1H), 2.44 - 2.40 (m, 2H), 2.37 - 2.29 (m, 4H), 1.12 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+ 573.5.

Example 650: 4-fluoro-N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3, 6-dihydro-2H-pyridin-5-ylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-2-(trifluoromethyl)benzamide



[001046] The procedure followed was similar to Example 270 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (35mg, 0.071 mmol) and 2-bromo-pyrirnidine-5-carbaldehyde (17.21 mg, 0.092 mmol) to give the title compound (33 mg, 74 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.80 - 9.73 (m, 1H), 8.87 - 8.76 (m, 2H), 7.98 - 7.89 (m, 1H), 7.81 - 7.74 (m, 1H), 7.69 - 7.62 (m, 1H), 7.60 - 7.53 (m, 1H), 7.08 - 6.98 (m, 1H), 6.23 - 6.16 (m, 1H), 4.78 - 4.72 (m, 2H), 4.23 - 4.15 (m, 2H), 3.13 - 3.00 (m, 2H), 2.98 - 2.88 (m, 2H), 2.60 - 2.51 (m, 1H), 2.50 - 2.42 (m, 3H), 2.37 - 2.31 (m, 4H), 1.14 - 1.10 (m, 3H); LCMS [M+H]+ 601.5.

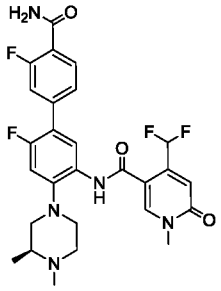
Example 651: (1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-3,6^ hydro-2H-pyridine-l-carboxylate



[001047] The procedure followed was similar to Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3 -carboxamide (25 mg, 0.051 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (22 mg, 0.070 mmol) to give the title compound (16.5 mg, 37 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.92 - 7.85 (m, 1H), 7.59 - 7.52 (m, 1H), 7.32 - 7.06 (m, 1H), 6.87 - 6.77 (m, 1H), 6.72 - 6.67 (m, 1H), 5.93 - 5.80 (m, 1H), 4.06 - 3.89 (m, 2H), 3.61 - 3.46 (m, 2H),

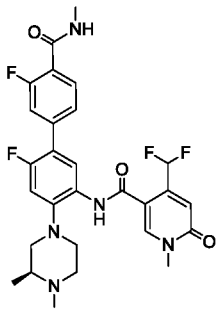
3.21 (td, *J*=1.6, 3.2 Hz, 8H), 2.96 - 2.87 (m, 2H), 2.50 - 2.43 (m, 2H), 2.42 - 2.36 (m, 4H), 2.30 - 2.22 (m, 5H), 2.08 - 1.99 (m, 2H), 1.79 - 1.68 (m, 1H), 1.65 - 1.55 (m, 1H), 1.51 - 1.41 (m, 3H), 1.06 - 1.02 (m, 6H); LCMS [M+H]+ 602.6.

Example 652: N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



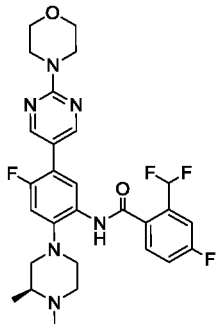
[001048] The procedure followed was similar to Example 100 using 4-carbamoyl-3-fluorophenylboronic acid, 96% (22.52 mg, 0.123 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l -methyl-6-oxo- l,6-dihydropyridine-3-carboxamide (40 mg, 0.082 mmol, from Example 461 Step 1) to afford the title compound as a white fluffy powder (8.4 mg, 17.8% yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.23 (s, 1H), 7.81 (t, *J*=8.0 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.39 (d, *J*=8.1 Hz, 1H), 7.34 (d, *J*=12.3 Hz, 1H), 7.30 - 7.07 (m, 1H), 7.03 (d, *J*=12.2 Hz, 1H), 6.74 - 6.67 (m, 1H), 3.55 (s, 3H), 3.17 - 3.09 (m, 3H), 2.98 - 2.90 (m, 1H), 2.83 - 2.74 (m, 2H), 2.68 - 2.60 (m, 1H), 2.53 (s, 3H), 1.15 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 546.

Example 653: 4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridme-3-carboxamide



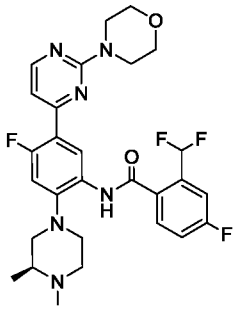
[001049] The procedure followed was similar to that of Example 100 using 3-fluoro-4-(methylcarbamoyl)phenylboronic acid (24.25 mg, 0.123 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (40 mg, 0.082 mmol). The title compound was isolated as a beige fluffy powder (34.8 mg, 72.0 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.19 (s, 1H), 7.75 (d, *J*=8.3 Hz, 1H), 7.72 (t, *J*=7.9 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 1H), 7.32 (d, *J*=12.2 Hz, 1H), 7.30 - 7.06 (m, 1H), 6.98 (d, *J*=12.3 Hz, 1H), 6.73 - 6.69 (m, 1H), 3.55 (s, 3H), 3.05 (br dd, *J*=2.0, 11.5 Hz, 1H), 3.00 (dd, *J*=2.3, 11.7 Hz, 1H), 2.88 - 2.79 (m, 5H), 2.56 (s, 1H), 2.49 - 2.38 (m, 2H), 2.33 - 2.27 (m, 1H), 2.26 (s, 3H), 1.02 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 560.

Example 654: 2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



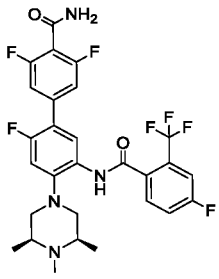
[001050] The title compound (formic acid salt, light brown solid, 48.2 mg, 39%) was prepared in a manner similar to the sequence described above for the preparation of Example 331 using (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-5-yl)aniline (77 mg, 0.2 mmol) and 2-(difluoromethyl)-4-fluorobenzoic acid (prepared as described in *Angew. Chem. Int. Ed.* **2014,** 53, 5955 - 5958). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.55 (s, 2H), 8.36 (s, 1H), 7.95 (br d, *J*=8.1 Hz, 1H), 7.88 (br dd, *J*=5.4, 8.0 Hz, 1H), 7.54 (dd, *J*=2.4, 9.2 Hz, 1H), 7.48 - 7.23 (m, 2H), 7.17 (d, *J*=12.0 Hz, 1H), 3.87 - 3.81 (m, 4H), 3.79 - 3.72 (m, 4H), 3.39 (br d, *J*=10.8 Hz, 1H), 3.30 - 3.23 (m, 2H), 3.17 - 3.03 (m, 3H), 2.86 (br dd, *J*=10.1, 12.6 Hz, 1H), 2.76 (s, 3H), 1.31 (d, *J*=6.5 Hz, 3H); LCMS $[M + H]^+$ 559.4.

Example 655: 2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[001051] The title compound (formic acid salt, light brown solid, 34.3 mg, 28%) was prepared in a manner similar to the procedure described for the preparation of Example 331 using (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-4-yl)aniline (84 mg, 91.6% purity, 0.2 mmol) and 2-(difluoromethyl)-4-fluorobenzoic acid. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (br d, *J*=7.9 Hz, 1H), 8.38 (d, *J*=5.3 Hz, 1H), 8.33 (br s, 1H), 7.92 - 7.81 (m, 1H), 7.54 (dd, *J*=2.3, 9.3 Hz, 1H), 7.48 - 7.22 (m, 2H), 7.16 - 7.07 (m, 2H), 3.89 - 3.80 (m, 4H), 3.80 - 3.71 (m, 4H), 3.40 - 3.32 (m, 3H), 3.18 - 3.01 (m, 3H), 2.86 (br dd, *J*=10.2, 12.5 Hz, 1H), 2.75 (s, 3H), 1.30 (d, *J*=6.4 Hz, 3H); LCMS $[M + H]^+$ 559.3.

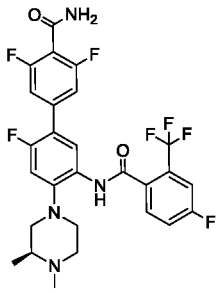
Example 656: 2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[001052] A coupling procedure similar to that in Example 100 using 4-(aminocarbonyl)-3,5-difluorophenylboronic acid (23.81 mg, 0.119 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (40 mg, 0.079 mmol) afforded the title compound as a beige fluffy powder (25 mg, 0.041 mmol, 51.6 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 (d, *J*=8.2 Hz, 1H), 7.66 (dd, *J*=5.3, 8.4 Hz, 1H), 7.55 (dd, *J*=2.3, 9.0 Hz, 1H), 7.46 (dt, *J*=2.3, 8.3 Hz, 1H), 7.18 (d, *J*=8.6 Hz, 2H), 7.03 - 6.96

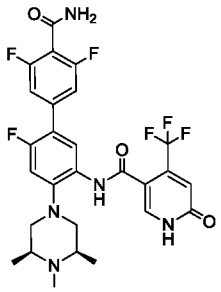
(m, IH), 2.99 (br d, *J*=11.4 Hz, 2H), 2.52 (t, *J*=11.2 Hz, 2H), 2.40 - 2.30 (m, 2H), 2.22 (s, 3H), 1.05 (d, *J*=6.2 Hz, 6H); LCMS $[M+H]^+$ 583.

Example 657: 2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[001053] A procedure followed similar to that of Example 100 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (40 mg, 0.081 mmol) and 4-(aminocarbonyl)-3,5-difluorophenylboronic acid (24.49 mg, 0.122 mmol) gave the title compound as a light yellow fluffy powder (31 mg, 0.052 mmol, 63.8 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 (d, *J*=8.2 Hz, IH), 7.68 (dd, *J*=5.3, 8.4 Hz, IH), 7.55 (dd, *J*=2.4, 9.0 Hz, IH), 7.46 (dt, *J*=2.4, 8.3 Hz, IH), 7.18 (d, *J*=8.6 Hz, 2H), 7.02 (d, *J*=12.3 Hz, IH), 3.05 (br dd, *J*=2.2, 11.5 Hz, IH), 3.01 - 2.96 (m, IH), 2.87 - 2.83 (m, IH), 2.83 - 2.77 (m, IH), 2.47 (t, *J*=10.9 Hz, IH), 2.37 (dt, *J*=2.8, 11.2 Hz, IH), 2.23 (s, 3H), 1.01 (d, *J*=6.4 Hz, 3H); LCMS $[M+H]^+$ 569.

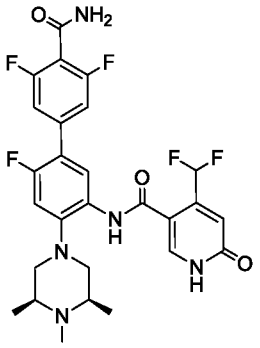
Example 658: N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[001054] A procedure similar to that of Example 100 using 4-(aminocarbonyl)-3,5-difiuorophenylboronic acid (19.91 mg, 0.099 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-4-(trifluoromethyl)-6-(2-

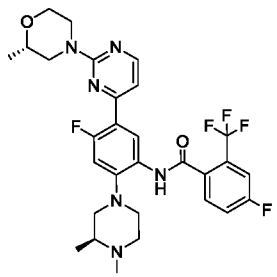
(trimethylsilyl)ethoxy)nicotinamide (40 mg, 0.066 mmol) afforded the title compound (TFA salt) as an off-white fluffy powder (34 mg, 0.040 mmol, 85 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.92 (s, 1H), 7.86 (d, J =8.2 Hz, 1H), 7.17 (d, J =8.6 Hz, 2H), 7.08 (d, J =12.0 Hz, 1H), 6.85 - 6.81 (m, 1H), 3.46 - 3.36 (m, 2H), 3.30 (br d, J =13.2 Hz, 2H), 2.89 (s, 3H), 2.88 - 2.81 (m, 2H), 1.34 (d, J =6.4 Hz, 6H); LCMS $[M+H]^+$ 582.

Example 659: N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6 -9xo-1H-pyridine-3-carboxamide



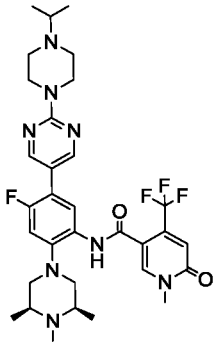
[001055] A procedure similar to that of Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (40 mg, 0.068 mmol) and 4-(aminocarbonyl)-3,5-difluorophenylboronic acid (20.52 mg, 0.102 mmol) afforded the title compound (TFA salt) as an off-white fluffy powder (40 mg, 0.048 mmol, 91 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.97 (s, 1H), 7.71 (d, J =8.2 Hz, 1H), 7.34 - 7.09 (m, 3H), 7.06 (d, J =12.1 Hz, 1H), 6.72 - 6.67 (m, 1H), 3.43 - 3.35 (m, 2H), 3.32 (br d, J =13.4 Hz, 2H), 2.88 (s, 3H), 2.86 - 2.79 (m, 2H), 1.33 (d, J =6.5 Hz, 6H); LCMS $[M+H]^+$ 564.

Example 660: 4-fluoro-N-[4-fluoro-2-[(3R)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-4-ylJphenylJ-2-(trifluoromethyl)benzamide



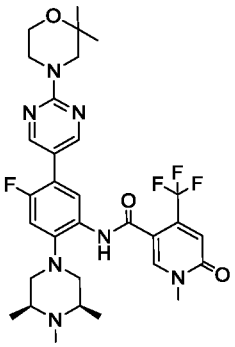
[001056] To a 20 mL microwave vial charged with (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (572 mg, 86% purity, 1 mmol), bis(pinacolato)diboron (508 mg, 2 mmol), $Pd(dppf)Cl_2$ (37 mg, 0.05 mmol) and KOAc (294 mg, 3 mmol) was added dioxane (10 mL) and the resulting mixture was heated at 110 °C in microwave for 6 h. The crude (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide was diluted with dioxane to a total volume of 20 mL and it was divided equally into 5 portions (each 4 mL, 0.2 mmol) for reactions with various substrates. To a mixture of the above crude ((S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,54etramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-4-fluoro-2-(tafluoromethyl)benzamide in dioxane (0.2 mmol assuming full conversion) and (S)-4-(4-bromopyrimidin-2-yl)-2-methylmo ϕ holine (62 mg, 0.24 mmol) was added bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (14 mg, 0.02 mmol) and 1 M K_3PO4 (0.6 mL, 0.6 mmol). The resulting mixture was heated in microwave at 110 °C for 2 h. After diluting with brine (5 mL), it was extracted with EtOAc (15 mL x 2). The combined extracts were concentrated and purified by flash chromatography (gradient: EtOAc/hex 0-100% then MeOH/DCM 0-10%), prep-HPLC and Biotage SCX-2 column to give a white solid. It was redissolved in MeOH (10 mL), treated with 2 drops of HCO_2H, evaporated and dried to give the title compound as a pale beige solid (formic acid salt, 71.6 mg, 56% over two steps). ¾H NMR (500MHz, METHANOL-d4) δ = 8.74 (d, *J*=8.3 Hz, 1H), 8.47 - 8.41 (m, 1H), 8.40 (d, *J*=5.3 Hz, 1H), 7.77 (dd, *J*=5.3, 8.4 Hz, 1H), 7.68 (dd, *J*=2.2, 9.0 Hz, 1H), 7.58 (dt, *J*=2.3, 8.3 Hz, 1H), 7.16 (dd, *J*=1.7, 5.1 Hz, 1H), 7.09 (d, *J*=13.1 Hz, 1H), 4.68 (br d, *J*=13.1 Hz, 1H), 4.61 (br d, *J*=13.4 Hz, 1H), 3.98 (dd, *J*=2.4, 11.5 Hz, 1H), 3.69 - 3.60 (m, 2H), 3.39 - 3.26 (m, 3H), 3.14 - 3.03 (m, 2H), 2.99 - 2.89 (m, 2H), 2.87 - 2.77 (m, 1H), 2.73 (dd, *J*=10.5, 13.1 Hz, 1H), 2.69 - 2.65 (m, 3H), 1.30 (d, *J*=6.4 Hz, 3H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS $[M+H]^+$ 591.3.

Example 661: N-[4-fluoro-5-[2-(4^ropan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluorom ethyl)pyridine-3-carboxamide



[001057] The title compound (di-formic acid salt, light beige solid, 42.4 mg, 57%) was prepared according to a procedure similar to Example 31 using crude (2-(4-isopropylpiperazin-l-yl)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (52 mg, 0.1 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.61 (s, 2H), 8.50 (br s, IH), 8.46 (br s, IH), 8.28 (br s, IH), 7.94 (d, *J*=8.2 Hz, IH), 7.16 (br d, *J*=11.9 Hz, IH), 6.96 (s, IH), 4.12 (br s, 4H), 3.67 (s, 3H), 3.17 (br s, 6H), 3.06 - 2.89 (m, 2H), 2.79 (br d, *J*=11.5 Hz, 2H), 2.65 - 2.57 (m, 3H), 1.34 (d, *J*=6.6 Hz, 6H), 1.31 - 1.26 (m, 6H); LCMS $[M + H]^{+}$ 645.4.

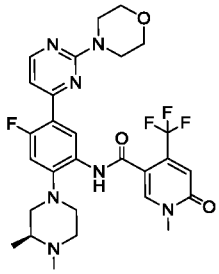
Example 662: N-[5-[2-(2, 2-dimethylmorpholin-4-yl)pyrimidin-5-ylJ-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluorom ethyl)pyridine-3-carboxamide



[001058] The title compound (formic acid salt, light beige solid, 32.9 mg, 48%) was prepared according to a procedure similar to Example 31 using crude (2-(2,2-dimethylmorpholino)pyrimidin-5-yl)boronic acid (0.3 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (52 mg, 0.1 mmol). ^{1}H NMR

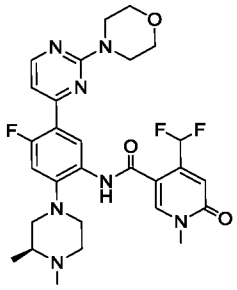
(500MHz, METHANOL-d4) δ = 8.58 - 8.53 (m, 2H), 8.45 (br s, IH), 8.29 (s, IH), 7.92 (d, *J*=8.3 Hz, IH), 7.16 (d, *J*=11.9 Hz, IH), 6.96 (s, IH), 3.89 - 3.80 (m, 4H), 3.74 (s, 2H), 3.67 (s, 3H), 3.20 (br d, *J*=12.0 Hz, 2H), 3.00 (br s, 2H), 2.85 - 2.74 (m, 2H), 2.65 (s, 3H), 1.30 (d, *J*=6.4 Hz, 6H), 1.27 (s, 6H); LCMS [M+ H]$^+$ 632.4.

Example 663: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-ylj 'phenyl]'-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide



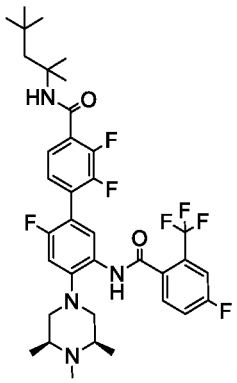
[001059] A mixture of l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (44 mg, 0.2 mmol), HATU (76 g, 0.2 mmol) and N,N-diisopropylethylamine (0.052 ml, 0.3 mmol) in DMF (2 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-mo rpholinopyrimidin-4-yl)aniline (39 mg, 0.1 mmol) was added in one portion. The resulting mixture was heated at 60 °C overnight. Solvents were removed and the residue was purified by prep-HPLC and Biotage SCX-2 column to give the title compound as a light brown solid (34.8 mg, 58%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.60 (d, *J*=8.2 Hz, IH), 8.39 (d, *J*=5.3 Hz, IH), 8.25 (s, IH), 7.15 (dd, *J*=1.8, 5.1 Hz, IH), 7.05 (d, *J*=13.2 Hz, IH), 6.96 (s, IH), 3.89 - 3.84 (m, 4H), 3.80 - 3.76 (m, 4H), 3.66 (s, 3H), 3.24 - 3.13 (m, 2H), 3.01 - 2.91 (m, 2H), 2.64 - 2.51 (m, 2H), 2.43 (br s, IH), 2.38 (s, 3H), 1.14 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 590.4.

Example 664: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001060] A mixture of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (41 mg, 0.2 mmol), HATU (76 g, 0.2 mmol) and N,N-diisopropylethylamine (0.052 ml, 0.3 mmol) in DMF (2 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-mo rpholinopyrimidin-4-yl)aniline (39 mg, 0.1 mmol) was added in one portion. The resulting mixture was heated at 60 °C ovemight. Solvents were removed and the residue was purified by prep-HPLC and Biotage SCX-2 column to give the title compound as a brown solid (25.2 mg, 43%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.43 (d, *J*=8.2 Hz, 1H), 8.40 - 8.37 (m, 1H), 8.31 (s, 1H), 7.28 (t, *J*=55.0 Hz, 1H), 7.13 (dd, *J*=1.7, 5.0 Hz, 1H), 7.03 (d, *J*=13.2 Hz, 1H), 6. 82 (s, 1H), 3.88 - 3.83 (m, 4H), 3.79 - 3.73 (m, 4H), 3.64 (s, 3H), 3.26 - 3.13 (m, 2H), 3.01 - 2.90 (m, 2H), 2.62 - 2.50 (m, 2H), 2.46 - 2.35 (m, 4H), 1.13 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^{+}$ 572.4.

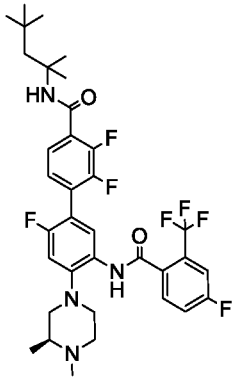
Example 665: 2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-N-(2,4,4-trimethylpentan-2-yl)benza mide



[001061] A coupling procedure similar to Example 100 using 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (68.4 mg, 0.173 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51.5 mg,

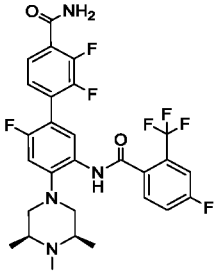
0.102 mmol) afforded the title compound as an off-white fluffy powder (59 mg, 79 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 (d, *J*=7.7 Hz, 1H), 7.65 (dd, *J*=5.3, 8.4 Hz, 1H), 7.54 (dd, *J*=2.3, 9.0 Hz, 1H), 7.45 (dt, *J*=2.3, 8.3 Hz, 1H), 7.31 (br t, *J*=7.0 Hz, 1H), 7.22 - 7.17 (m, 1H), 7.02 (d, *J*=11.2 Hz, 1H), 3.05 (br d, *J*=9.7 Hz, 2H), 2.59 (br s, 4H), 2.34 (br s, 3H), 1.84 (s, 2H), 1.39 (s, 6H), 1.11 (br s, 6H), 0.96 (s, 9H); LCMS $[M+H]^+$ 695.

Example 666: 2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-f(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-N-(2, 4,4-trimethylpentan-2-yl)benzamide



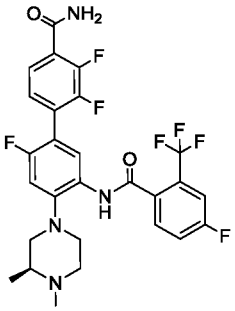
[001062] A coupling procedure similar to Example 100 using 2,3-difluoro-4-(4,4,5,54etramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,44rimethylpentan-2-yl)benzamide (70.3 mg, 0.178 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51.5 mg, 0.105 mmol) afforded the title compound as a beige fluffy powder (52 mg, 69.4 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.86 (d, *J*=7.6 Hz, 1H), 7.66 (dd, *J*=5.3, 8.5 Hz, 1H), 7.54 (dd, *J*=2.4, 9.0 Hz, 1H), 7.45 (dt, *J*=2.3, 8.3 Hz, 1H), 7.31 (br t, *J*=7.0 Hz, 1H), 7.23 - 7.18 (m, 1H), 7.04 (d, *J*=11.2 Hz, 1H), 3.09 (br d, *J*=12.1 Hz, 1H), 3.04 (br d, *J*=11.6 Hz, 1H), 2.94 - 2.84 (m, 2H), 2.57 - 2.47 (m, 2H), 2.46 - 2.37 (m, 1H), 2.32 (br s, 3H), 1.85 (s, 2H), 1.40 (s, 6H), 1.06 (br d, *J*=6. 1 Hz, 3H), 0.97 (s, 9H); LCMS $[M+H]^+$ 681.

Example 667: 2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



[001063] A coupling procedure similar to Example 100 using 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (68.4 mg, 0.173 mmol) and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51.5 mg, 0.102 mmol) followed by deprotection afforded the title compound (TFA salt) which was isolated as a beige fluffy powder (60 mg, 0.068 mmol, 91 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.05 (d, *J*=7.6 Hz, 1H), 7.81 (dd, *J*=5.3, 8.4 Hz, 1H), 7.70 - 7.65 (m, 2H), 7.58 (dt, *J*=2.3, 8.3 Hz, 1H), 7.36 (br t, *J*=7.0 Hz, 1H), 7.25 (d, *J*=10.9 Hz, 1H), 3.56 - 3.49 (m, 2H), 3.46 (br d, *J*=13.0 Hz, 2H), 3.03 - 2.96 (m, 5H), 1.48 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^{+}$ 583.

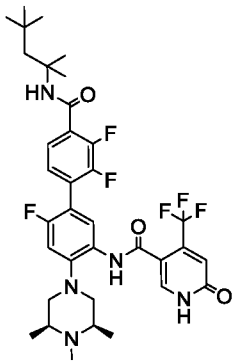
Example 668: 2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide



[001064] A coupling procedure similar to Example 100 using 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (70.3 mg, 0.178 mmol) and (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluoro-2-(trifluoromethyl)benzamide (51.5 mg, 0.105 mmol) followed by acidic deprotection afforded the title compound (TFA salt) as a beige fluffy powder (55 mg, 93 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.04 (d, *J*=7.6 Hz, 1H), 7.82 (br dd, *J*=5.4, 8.2 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.58 (dt,

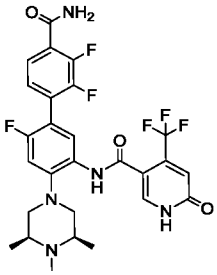
J=2.1, 8.3 Hz, IH), 7.37 (br t, *J*=6.9 Hz, IH), 7.25 (d, *J*=10.9 Hz, IH), 3.67 (br d, *J*=12.3 Hz, IH), 3.44 (br s, 3H), 3.21 - 3.12 (m, IH), 3.00 (s, 3H), 2.99 - 2.92 (m, 2H), 1.45 (br d, *J*=6.2 Hz, 3H); LCMS $[M+H]^+$ 569.

Example 669: N-[5-[2,3-difluoro-4-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



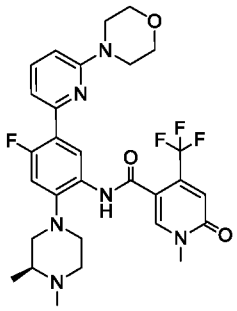
[001065] A coupling procedure similar to that in Example 100 using 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (69.7 mg, 0.176 mmol) and 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (69.7 mg, 0.176 mmol) afforded the title compound (TFA salt) as a white fluffy powder (17 mg, 0.020 mmol, 93 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.92 (s, IH), 7.86 (s, IH), 7.81 (d, *J*=7.5 Hz, IH), 7.34 (t, *J*=6.7 Hz, IH), 7.23 - 7.18 (m, IH), 7.12 (d, *J*=11.0 Hz, IH), 6.87 - 6.83 (m, IH), 3.48 - 3.39 (m, 2H), 3.34 (br d, *J*=13.2 Hz, 2H), 2.92 (s, 3H), 2.90 - 2.84 (m, 2H), 1.87 (s, 2H), 1.42 (s, 6H), 1.37 (d, *J*=6.5 Hz, 6H), 0.98 (s, 9H); LCMS $[M+H]^+$ 694.

Example 670: N-[5-(4-carbamoyl-2,3-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[001066] A coupling procedure similar to that in Example 100 using 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (69.7 mg, 0.176 mmol) and 2,3-difluoro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (69.7 mg, 0.176 mmol) afforded the title compound (TFA salt) which was isolated as a beige fluffy powder (50 mg, 0.059 mmol, 90 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 (s, 1H), 7.80 (d, *J*=7.5 Hz, 1H), 7.55 - 7.50 (m, 1H), 7.22 (t, *J*=6.8 Hz, 1H), 7.10 (d, *J*=11.0 Hz, 1H), 6.85 - 6.80 (m, 1H), 3.46 - 3.36 (m, 2H), 3.31 (br d, *J*=13.2 Hz, 2H), 2.89 (s, 3H), 2.88 - 2.82 (m, 2H), 1.34 (d, *J*=6.5 Hz, 6H); LCMS $[M+H]^+$ 582.

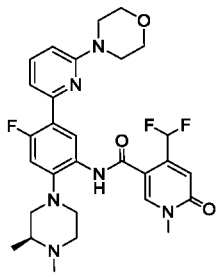
Example 671: N-[4-fluoro-5-(5-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenylJ-l-methyl-6<>xo-4-(trifluoromethyl)pyridme-3-carboxamide



[001067] To a 20 mL microwave vial charged with (S)-5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluoroaniline (907 mg, 3 mmol), bis(pinacolato)diboron (1.524 g, 6 mmol), Pd(dppf)Cl_2 (110 mg, 0.15 mmol) and KOAc (883 mg, 9 mmol) was added dioxane (12 mL) and the resulting mixture was heated at 110 °C in microwave for 7 h. The crude product (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)aniline in dioxane was split into 2 equal volumes and used directly for subsequent Suzuki couplings. To a mixture of crude (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)aniline in dioxane (1.5 mmol assuming full conversion) and 4-(6-bromopyridin-2-yl)morpholine (438 mg, 1.8 mmol) was added bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (53 mg, 0.075 mmol) and 1 M K_3PO4 (3 mL, 3 mmol). The resulting mixture was heated in microwave at 110 °C for 2 h. After diluting with brine (5 mL), it was extracted with EtOAc (15 mL x 2). The combined extracts were concentrated and purified by flash chromatography (gradient:

EtOAc/hex 0-100% then MeOH/DCM 0-10%) to give (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-mo rpholinopyridin-2-yl)aniline as a brown foam (403 mg, 61% yield over two steps based on 87.44% purity). LCMS $[M + H]^+$ 386.4. A mixture of 1-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxylic acid (44 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol) and N,N-diisopropylethylamine (0.052 ml, 0.3 mmol) in DMF (1 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before a solution of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-mo rpholinopyridin-2-yl)aniline (44 mg, 87.44% purity, 0.1 mmol) in DMF (1 mL) was added in one portion. The resulting mixture was heated at 60 °C overnight. Solvent were removed and the residue was purified by prep-HPLC and Biotage SCX-2 column to give the title compound as a beige solid (27.1 mg, 45%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.53 (d, *J*=8.3 Hz, 1H), 8.23 (s, 1H), 7.63 (t, *J*=7.9 Hz, 1H), 7.23 (dd, *J*=1.7, 7.5 Hz, 1H), 7.03 (d, *J*=13.0 Hz, 1H), 6.95 (s, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 3.86 - 3.80 (m, 4H), 3.66 (s, 3H), 3.62 - 3.55 (m, 4H), 3.18 - 3.06 (m, 2H), 2.99 - 2.90 (m, 2H), 2.61 - 2.50 (m, 2H), 2.44 - 2.34 (m, 4H), 1.14 (d, *J*=6.4 Hz, 3H); LCMS $[M + H]^+$ 589.4.

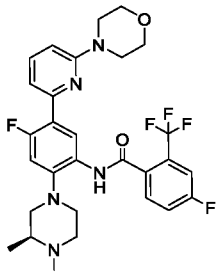
Example 672: 4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridm-2-yl)-2-[(3R)-3,4-dimethylpiperazm-l-ylJphenylJ-l-methyl-6<>xopyridine-3-carboxamide



[001068] A mixture of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (41 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol) and N,N-diisopropylethylamine (0.052 ml, 0.3 mmol) in DMF (1 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before a solution of (S)-2-(3,4-dimethylpiperazin- 1-yl)-4-fiuoro-5 -(6-morpholinopyridin-2-yl)aniline (44 mg, 87.44% purity, 0.1 mmol) in DMF (1 mL) was added in one portion. The resulting mixture was heated at 60 °C overnight. Solvent were removed and the residue was purified by prep-HPLC and Biotage SCX-2 column to give the title compound as a brown solid (20.5 mg, 35%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.38 - 8.33

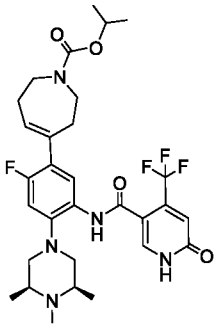
(m, *J*=8.3 Hz, 1H), 8.31 (s, 1H), 7.63 (t, *J*=8.0 Hz, 1H), 7.41 - 7.17 (m, 2H), 7.01 (d, *J*=12.8 Hz, 1H), 6.82 (s, 1H), 6.79 - 6.75 (m, *J*=8.4 Hz, 1H), 3.83 - 3.78 (m, 4H), 3.64 (s, 3H), 3.60 - 3.54 (m, 4H), 3.20 - 3.08 (m, 2H), 2.99 - 2.87 (m, 2H), 2.60 - 2.48 (m, 2H), 2.45 - 2.34 (m, 4H), 1.13 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 571.3.

Example 673: 4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1 -yl]phenyl] -2-(trifluoromethyl)benzamide



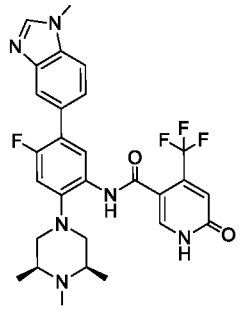
[001069] To a solution of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.045 mL, 0.3 mmol) in DCM (3 mL) at rt was added Et_3N (0.084 mL, 0.6 mmol). After addition, the resulting mixture was stirred at rt for 5 min, before a solution of (S)-2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(6-mo rpholinopyridin-2-yl)aniline (44 mg, 87.44% purity, 0.1 mmol) in DCM (2 mL) was added. The resulting mixture was stirred for 18 h at rt. Solvent were removed and the residue was purified by prep-HPLC to give the title compound as a brown solid (formic acid salt, 19.8 mg, 31%). ^1H NMR (500MHz, METHANOL-d4) δ = 8.70 - 8.65 (m, *J*=8.3 Hz, 1H), 8.34 (br s, 1H), 7.79 (dd, *J*=5.3, 8.3 Hz, 1H), 7.71 - 7.55 (m, 3H), 7.26 (br d, *J*=6.4 Hz, 1H), 7.10 (d, *J*=12.6 Hz, 1H), 6.82 - 6.77 (m, *J*=8.4 Hz, 1H), 3.89 - 3.80 (m, 4H), 3.64 - 3.57 (m, 4H), 3.42 (br d, *J*=10.9 Hz, 1H), 3.37 - 3.34 (m, 1H), 3.31 - 3.29 (m, 1H), 3.17 - 3.04 (m, 3H), 2.91 - 2.83 (m, 1H), 2.79 (s, 3H), 1.35 (d, *J*=6.4 Hz, 3H); LCMS $[M+ H]^+$ 576.2.

Example 674: Propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate



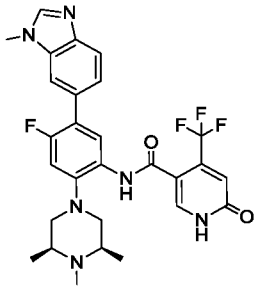
[001070] To a solution of *N*-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (32 mg, 0.061 mmol, prepared in a similar manner to Example 372 using tert-Butyl 4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-2,3,6,7-tetrahydro-lH-azepine-1 -carboxylate and N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide) and *N N*-diisopropylethylamine (0.021 ml, 0.123 mmol) in DCM (3 ml) was added isopropyl chloroformate (0.031 ml, 0.031 mmol in 0.5 ml of DCM. After 5 min, LCMS showed reaction completion. The reaction mixture was diluted with water and DCM. The organic layer was separated. The aqueous layer was extracted several times with DCM .The combined organic layers were dried over Na_2S0_4, concentrated down, loaded onto celite and dried. It was then purified by reverse phase Isco (C18 13.3 g cartridge, eluent: 10%, 10-100%, then 100% AcCN/water). The title compound was lyophilized from water/acetonitrile and collected as a white fluffy powder (25 mg, 0.039 mmol, 63.7 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.92 (br d, *J*=7.1 Hz, 1H), 7.71 - 7.63 (m, 1H), 6.96 - 6.91 (m, 2H), 6.02 - 5.94 (m, 1H), 4.09 (br dd, *J*=4.8, 14.4 Hz, 2H), 3.70 (t, *J*=5.9 Hz, 2H), 3.68 - 3.58 (m, 1H), 3.03 (br d, *J*=7.9 Hz, 2H), 2.65 - 2.55 (m, 6H), 2.41 (s, 3H), 1.97 - 1.86 (m, 2H), 1.32 - 1.25 (m, 7H), 1.18 (br d, *J*=5.3 Hz, 6H); LCMS $[M+H]^+$ 608.

Example 675: N-[4-fluoro-5-(l-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



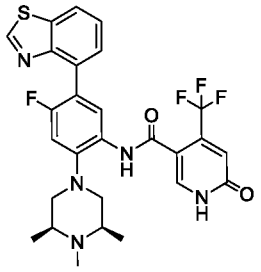
[001071] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 5-bromo-l-methyl-lH-benzo[d] imidazole in place of 4-(4-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.52 (br s, IH), 9.51 (s, IH), 8.24 (s, IH), 7.94 (s, IH), 7.84 (br d, *J*=8.6 Hz, IH), 7.75 (s, IH), 7.67 (d, *J*=8.4 Hz, IH), 7.41 (br d, *J*=8.4 Hz, IH), 7.04 (d, *J*=12.5 Hz, IH), 6.81 (s, IH), 3.88 (s, 3H), 3.05 (br d, *J*=10.9 Hz, 2H), 2.40 - 2.34 (m, 2H), 2.21 (s, 3H), 1.03 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 557.2.

Example 676: N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-ca^ boxamide



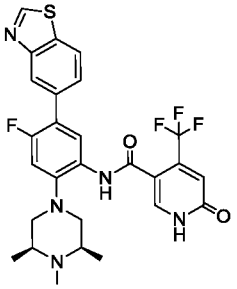
[001072] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 6-bromo-l-methyl-lH-benzo[d] imidazole in place of 4-(4-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.55 (br s, IH), 9.51 (s, IH), 8.23 (s, IH), 7.95 (br s, IH), 7.83 (br d, *J*=8.3 Hz, IH), 7.73 (br d, *J*=8.3 Hz, IH), 7.66 (s, IH), 7.34 (br d, *J*=8.4 Hz, IH), 7.06 (br d, *J*=12.2 Hz, IH), 6.79 (s, IH), 3.88 (s, 3H), 3.05 (br d, *J*=10.6 Hz, 3H), 2.37 (br d, *J*=7.5 Hz, 3H), 2.21 (s, 3H), 1.03 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 557.1.

Example 677: N-[5-(1,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



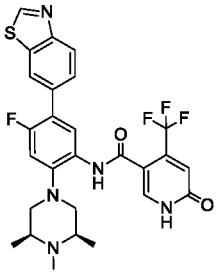
[001073] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 4-bromo-l,3-benzothiazole in place of 4-(4-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.52 (br s, IH), 9.53 (br d, ***J***=3.2 Hz, IH), 9.39 - 9.34 (m, IH), 8.23 (dd, ***J=3.2,*** 7.5 Hz, IH), 7.91 (br s, IH), 7.87 - 7.79 (m, IH), 7.62 - 7.56 (m, IH), 7.54 - 7.48 (m, IH), 7.06 (br dd, ***J***=3.8, 11.4 Hz, IH), 6.80 (br d, ***J***=3.2 Hz, IH), 3.08 (br d, ***J***=9.5 Hz, 3H), 2.39 (br s, 3H), 2.23 (br s, 3H), 1.04 (br d, ***J***=5.9 Hz, 6H); LCMS [M+H]+: 560.2.

Example 678: N-[5-(1,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



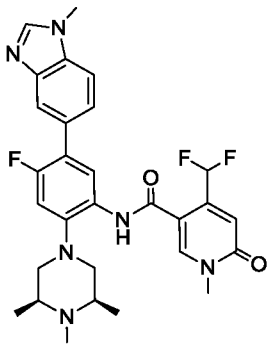
[001074] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 5-bromobenzothiazole in place of 4-(4-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.45 (br s, IH), 9.56 (s, IH), 9.47 (s, IH), 8.28 (d, ***J***=8.4 Hz, IH), 8.19 (s, IH), 7.95 (s, IH), 7.89 (br d, ***J***=8.6 Hz, IH), 7.63 (br d, ***J***=8.2 Hz, IH), 7.08 (d, ***J***=12.6 Hz, IH), 6.81 (s, IH), 3.08 (br d, ***J***=11.0 Hz, 3H), 2.38 (br d, ***J***=7.0 Hz, 3H), 2.21 (s, 3H), 1.03 (**d, *J***=6.1 Hz, 6H); LCMS [M+H]+: 560.2.

Example 679: N-[5-(1,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide



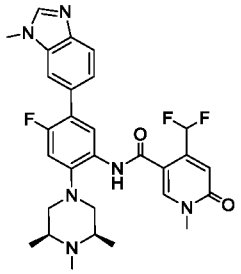
[001075] The title compound was prepared similar to the procedure described above for the preparation of Example 616 using 5-bromobenzothiazole in place of 4-(4-bromothiazol-2-yl)morpholine in Step 3. ^{1}H NMR (500MHz, DMSO-d6) δ = 12.43 (br s, IH), 9.55 (s, IH), 9.44 (s, IH), 8.32 (s, IH), 8.18 (d, *J*=8.6 Hz, IH), 7.94 (s, IH), 7.87 (br d, *J*=8.4 Hz, IH), 7.67 (br d, *J*=8.6 Hz, IH), 7.08 (d, *J*=12.5 Hz, IH), 6.81 (s, IH), 3.07 (br d, *J*=11.2 Hz, 3H), 2.42 - 2.32 (m, 3H), 2.21 (s, 3H), 1.03 (br d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 560.3.

Example 680: 4-(difluoromethyl)-N-[4-fluoro-5-(l-methylbenzimidazol-5-yl)-2-[(3R, 5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridme-3-carboxamide



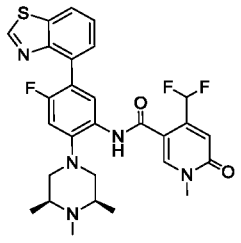
[001076] The title compound was prepared from 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (0.017 g, 0.054 mmol) and 4-fluoro-5-(l-methyl-lH-benzo[d]imidazol-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (0.010 g, 0.027 mmol) the latter reagent which was prepared by a route similar to Example 616 using 2-(2-fluoro-5-nitro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione and 5-bromo-l-methyl-lH-benzo[d]imidazole. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.49 (s, IH), 8.37 (s, IH), 8.24 (s, IH), 7.79 - 7.73 (m, 2H), 7.67 (d, *J*=8.4 Hz, IH), 7.48 - 7.23 (m, 2H), 7.05 (d, *J*=12.5 Hz, IH), 6.65 (s, IH), 3.88 (s, 3H), 3.53 (s, 3H), 3.06 (br d, *J*=11.0 Hz, 3H), 2.42 - 2.32 (m, 3H), 2.20 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 553.3.

Example 681: 4-(difluoromethyl)-N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001077] The title compound (13 mg, 79% yield) was prepared according to a procedure similar to that described above for the preparation of Example 616 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (0.012 g, 0.060 mmol) and 4-fluoro-5-(l-methyl-lH-benzo[d]imidazol-6-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (0.011 g, 0.030 mmol) in the final step. The latter reagent was prepared according to a route similar to Example 616 starting from 2-(2-fluoro-5-nitro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (0.075 g, 0.178 mmol), 6-bromo-l-methyl-lH-benzo[d] imidazole (0.056 g, 0.266 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.021 g, 0.018 mmol). ^{1}H NMR (**500MHZ,** DMSO-d6) δ = 9.50 (s, 1H), 8.38 (s, 1H), 8.23 (s, 1H), 7.74 (t, *J*=8.7 Hz, 2H), 7.66 (s, 1H), 7.47 - 7.23 (m, 2H), 7.06 (d, *J*=12.5 Hz, 1H), 6.65 (s, 1H), 3.88 (s, 3H), 3.53 (s, 3H), 3.06 (br d, *J*=10.9 Hz, 2H), 2.36 (td, *J*=3.4, 6.7 Hz, 3H), 2.20 (s, 3H), 1.02 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 553.1.

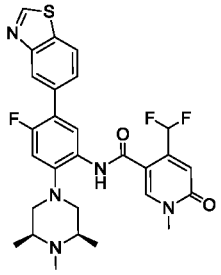
Example 682: N-[5-(1,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



[001078] The title compound was prepared similar to the procedure described above for the preparation of Example 677 using 4-(difluoromethyl)-l-methyl-6-oxo-

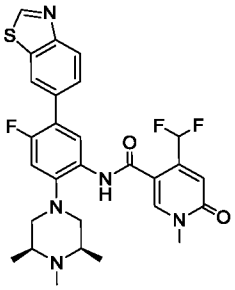
l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.49 (s, IH), 9.37 (s, IH), 8.36 (s, IH), 8.22 (d, *J*=8.1 Hz, IH), 7.76 (d, *J*=7.9 Hz, IH), 7.57 (d, *J*=7.9 Hz, IH), 7.51 (br d, *J*=7.3 Hz, IH), 7.43 - 7.18 (m, IH), 7.07 (d, *J*=11.6 Hz, IH), 6.63 (s, IH), 3.51 (s, 3H), 3.08 (br d, *J*=ll.l Hz, 2H), 2.38 (br d, *J*=6.4 Hz, 3H), 2.20 (s, 3H), 1.02 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 556.3.

Example 683: N-[5-(1,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5SJ-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



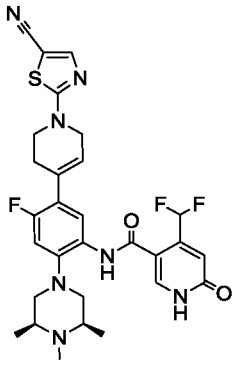
[001079] The title compound was prepared similar to the procedure described above for the preparation of Example 678 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.45 (s, IH), 9.39 (s, IH), 8.30 (s, IH), 8.20 (d, *J*=8.3 Hz, IH), 8.11 (s, IH), 7.75 (d, *J*=8.4 Hz, IH), 7.56 (br d, *J*=8.7 Hz, IH), 7.40 - 7.15 (m, IH), 7.02 (d, *J*=12.6 Hz, IH), 6.58 (s, IH), 3.45 (s, 3H), 3.02 (br d, *J*=11.4 Hz, 2H), 2.30 (br d, *J*=6.5 Hz, 3H), 2.13 (s, 3H), 0.95 (d, *J=6.1* Hz, 6H); LCMS [M+H]+: 556.3.

Example 684: N-[5-(1,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide



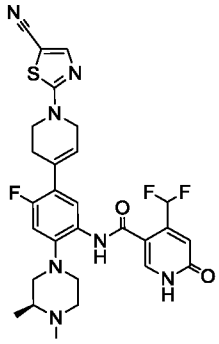
[001080] The title compound was prepared similar to the procedure described above for the preparation of Example 679 using 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in place of 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in Step 5. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.48 (s, IH), 9.42 (s, IH), 8.36 (s, IH), 8.31 (s, IH), 8.17 (d, *J*=8.6 Hz, IH), 7.80 (br d, *J*=8.4 Hz, IH), 7.66 (br d, *J*=8.3 Hz, IH), 7.46 - 7.21 (m, IH), 7.09 (br d, *J*=12.5 Hz, IH), 6.65 (s, IH), 3.52 (s, 3H), 3.08 (br d, *J*=10.8 Hz, 2H), 2.37 (br d, *J=6.1* Hz, 2H), 2.20 (s, 3H), 1.02 (br d, *J=6.1* Hz, 6H); LCMS [M+H]+: 556.1.

Example 685: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6<>xo-1H-pyridine-3-carboxamide



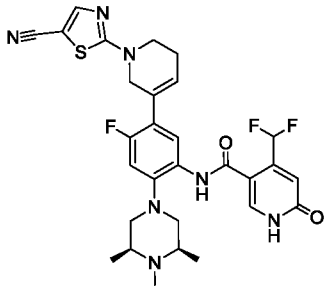
[001081] The procedure used was similar to Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and 2-bromo-5-cyanothiazole (9.65 mg, 0.051 mmol) to afford the title compound (22 mg, 69 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.89 (s, IH), 7.71-7.76 (m, IH), 7.57-7.63 (m, IH), 7.08-7.33 (m, IH), 6.84 (d, *J*=12.47 Hz, IH), 6.70 (s, IH), 5.98 (br. s., IH), 4.10 (d, *J*=2.69 Hz, 2H), 3.76 (t, *J*=5.75 Hz, 2H), 2.90-2.95 (m, 2H), 2.93 (d, *J*=11.25 Hz, 2H), 2.58 (br. s., 2H), 2.44-2.50 (m, 2H), 2.35-2.42 (m, 2H), 2.25 (s, 3H), 1.04 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 598.5.

Example 686: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide



[001082] The procedure followed was similar to Example 270 using (S)-4-(difluoromethyl)-N-(2-(3 ,4-dimethylpiperazin- 1-yl)-4-fluoro-5 -(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol) and 2-bromo-5-cyanothiazole (9.94 mg, 0.053 mmol) to afford the title compound (23.5 mg, 73 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.92 - 7.88 (m, 1H), 7.77 - 7.71 (m, 1H), 7.65 - 7.59 (m, 1H), 7.32 - 7.07 (m, 1H), 6.90 - 6.84 (m, 1H),6.73 - 6.69 (m, 1H), 6.02 - 5.95 (m, 1H), 4.13 - 4.07 (m, 2H), 3.80 - 3.74 (m, 2H), 3.02 - 2.89 (m, 2H), 2.83 - 2.76 (m, 2H), 2.62 - 2.56 (m, 2H), 2.46 - 2.37 (m, 2H), 2.31 - 2.24 (m, 4H), 1.03 - 0.98 (m, 3H); LCMS [M+H]+ 584.5.

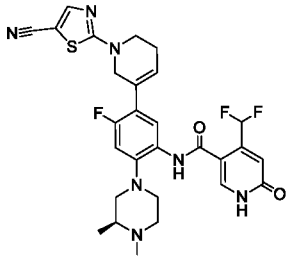
Example 687: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6<>^o-1H-pyridine-3-carboxamide



[001083] The procedure followed was similar to Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and 2-bromo-5-cyanothiazole (9.65 mg, 0.051 mmol) to give the title compound (22 mg, 69 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.89 (s, 1H), 7.69-7.73 (m, 1H), 7.69-7.73 (m, 1H), 7.60 (d, *J*=8.07 Hz, 1H), 7.08-7.33 (m, 1H),

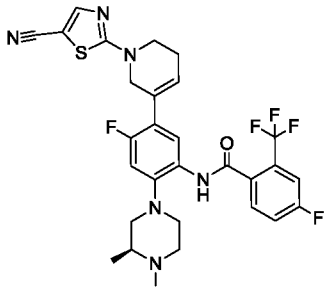
6.84-6.88 (m, 1H), 6.70 (s, 1H), 6.06-6.11 (m, 1H), 6.06-6.11 (m, 1H), 4.25 (d, *J*=1.59 Hz, 2H), 3.67-3.72 (m, 2H), 3.67-3.72 (m, 2H), 2.94 (d, *J*=11.25 Hz, 2H), 2.45-2.51 (m, 2H), 2.37-2.42 (m, 4H), 2.25 (s, 3H), 1.02-1.05 (m, 6H), 1.04 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 598.6.

Example 688: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide



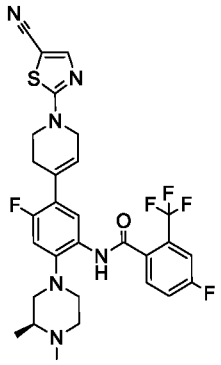
[001084] The procedure followed was similar to Example 270 using (S)-4-(difluoromethyl)-N-(2-(3 ,4-dimethylpiperazin- 1-yl)-4-fluoro-5 -(1,2,5,6-tetrahydropyridin-3-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol), 2-bromo-5-cyanothiazole (9.94 mg, 0.053 mmol)to afford the title compound (15 mg, 46 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.94 - 7.87 (m, 1H), 7.75 - 7.68 (m, 1H), 7.65 - 7.57 (m, 1H), 7.32 - 7.07 (m, 1H), 6.92 - 6.86 (m, 1H), 6.73 - 6.67 (m, 1H), 6.14 - 6.06 (m, 1H), 4.30 - 4.24 (m, 2H), 3.73 - 3.68 (m, 2H), 3.02 - 2.96 (m, 1H), 2.95 - 2.90 (m, 1H), 2.85 - 2.78 (m, 2H), 2.45- 2.38 (m, 4H), 2.31 - 2.24 (m, 4H), 1.03 - 0.99 (m, 3H); LCMS [M+H]+ 584.4.

Example 689: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-fluoro-2-(Mfluoromethyl)benzamide



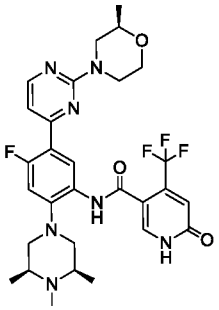
[001085] The procedure followed was similar to Example 270 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol) and 2-bromo-5-cyanothiazole (9.56 mg, 0.051 mmol) to afford the title compound (26.5 mg, 83 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.84 - 7.78 (m, 1H), 7.74 - 7.69 (m, 1H), 7.68 - 7.62 (m, 1H), 7.56 - 7.51 (m, 1H), 7.48 - 7.42 (m, 1H), 6.95 - 6.88 (m, 1H), 6.13 - 6.07 (m, 1H), 4.27 (br s, 2H), 3.78 - 3.68 (m, 2H), 3.02 - 2.94 (m, 1H), 2.94 - 2.89 (m, 1H), 2.85 - 2.75 (m, 2H), 2.47 - 2.39 (m, 3H), 2.39 - 2.32 (m, 1H), 2.25 - 2.19 (m, 4H), 1.03 - 0.98 (m, 3H); LCMS [M+H]+ 603.5.

Example 690: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-fluoro-2-(Mfluoromethyl)benzamide



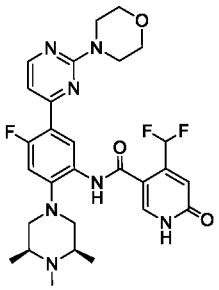
[001086] The procedure used was similar to Example 270 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol, prepared using procedures similar to those described hereinabove) and 2-bromo-5 -cyanothiazole (9.56 mg, 0.051 mmol) to give the title compound (22 mg, 69 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.84 - 7.79 (m, 1H), 7.77 - 7.71 (m, 1H), 7.68 - 7.62 (m, 1H), 7.56 - 7.52 (m, 1H), 7.48 - 7.41 (m, 1H), 6.93 - 6.85 (m, 1H), 6.03 - 5.97 (m, 1H), 4.16 - 4.07 (m, 2H), 3.84 - 3.74 (m, 2H), 2.99 - 2.94 (m, 1H), 2.94 - 2.88 (m, 1H), 2.84 - 2.77 (m, 2H), 2.64 - 2.56 (m, 2H), 2.47 - 2.39 (m, 1H), 2.38 - 2.30 (m, 1H), 2.26 - 2.19 (m, 4H), 1.03 - 0.98 (m, 3H); LCMS [M+H]+ 603.5

Example 691: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH^yridine-3-carboxamide

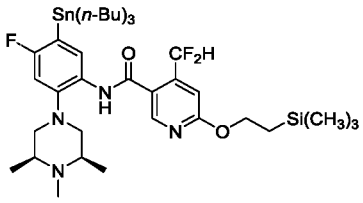


[001087] The title compound (21.7 mg, 26% yield) was prepared using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (102 mg, 0.125 mmol) and (R)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine (35.5 mg, 0.138 mmol) by a procedure similar to that described in Example 384. ^{1}H NMR (500 MHz, MeOD) δ 8.60 (d, *J* = 8.1 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 7.90 (s, 1H), 7.12 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.00 (d, *J* = 13.2 Hz, 1H), 6.92 (s, 1H), 4.65 (d, *J* = 13.1 Hz, 1H), 4.59 (d, *J* = 13.2 Hz, 1H), 3.97 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.66 - 3.60 (m, 2H), 3.16 (d, *J* = 11.2 Hz, 2H), 3.08 - 3.02 (m, 1H), 2.70 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.66 - 2.61 (m, *J* = 11.2 Hz, 2H), 2.59 - 2.53 (m, 2H), 2.38 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 6H); LCMS HSS $[M+l]^{+}$ = 604.34.

Example 692: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-6<>xo-lH^yridme-3-carboxamide

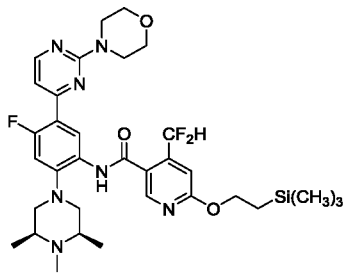


Step 1: 4-(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy)m cotinamide



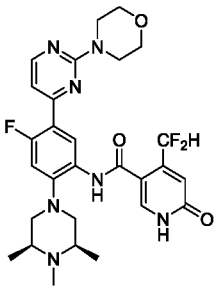
[001088] The title compound was prepared similar to the sequence described above for the preparation of Example 384, Step 1 using a stirred solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(difluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (10 g, 17.1 mmol, leq) in toluene (60 mL) degassed with argon for 15min, then adding hexabutylditin (17.3 mL, 34.12 mmol, 2eq), followed by $Pd_2(dppf)_2Cl_2$.DCM (1.39 g, 1.71 mmol, O.leq) after that heating to reflux under argon atmosphere for 24h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; and the filtrate was evaporated under reduced pressure. The crude compound was purified by column chromatography (neutral alumina) using 0-5% EtOAc in pet ether as an eluent to afford 4-(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (5.2 g, 36.6% yield) as a pale yellow Solid. TLC: 50% EtoAC in petether; R_f: 0.5.

Step 2: 4-(difluoromethyl)-N-(4-fluoro-5-(2-morpholinopyrimidin-4-yl)-2-(('3S,5R)-3,4,5-Mmethylpiperazin-l-yl)phenyl)-6-(2-(Mmethylsilyl)etho xy)nicotinamide



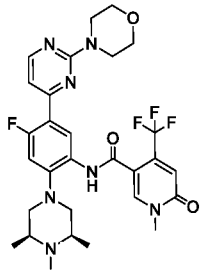
[001089] In N,N-dimethylformamide (DMF) (537 µï) was dissolved 4-(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (107 mg, 0.134 mmol). To the solution was added 4-(4-bromopyrimidin-2-yl)morpholine (36.0 mg, 0.148 mmol), lithium chloride (17.06 mg, 0.402 mmol) and bis(triphenylphosphine)palladium(II) dichloride (5.18 mg, 7.38 µmoï) at room temperature and then it was microwaved at the temperature of 120 °C for 3 hours. To the reaction mixture was added water and then extracted with dichloromethane. The organic layer was separated, concentrated and purified by column chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford the title compound. LCMS $[M+l]^+$ = 672.43.

Step 3: 4-(difluoromethyl)-N-(4-fluoro-5-(2-morpholinopyrimidin-4-yl)-2-(〔3S,5RJ-3,4,5-trimethylpiperazin-l-yl)phenyl)-6<>xo-l,6-dihydropyridme-3-carbommide

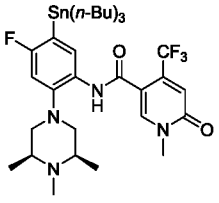


[001090] The product was dissolved in 2 mL of DCM and TFA (1027 μï, 13.41 mmol) was added. The purple solution was stirred for 1 h and the solvent was evaporated. The residue was purified by a cation exchange column eluting with MeOH:NH_4OH and freeze dried for 2 days to afford the product as a white powder. ^1H NMR (500 MHz, MeOD) δ 8.43 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.01 (s, 1H), 7.31 (t, *J* = 55.1 Hz, 1H), 7.12 (dd, *J* = 5.2, 1.9 Hz, 1H), 6.99 (d, *J* = 13.2 Hz, 1H), 6.81 (s, 1H), 3.85 - 3.82 (m, 4H), 3.77 - 3.74 (m, 4H), 3.16 (d, *J* = 11.5 Hz, 2H), 2.62 (t, *J* = 11.2 Hz, 2H), 2.52 (s, 2H), 2.36 (s, 3H), 1.15 (d, *J* = 6.2 Hz, 6H); ^{19}F NMR (471 MHz, MeOD) δ -115.98 (s), -121.71 (s); LCMS $[M+l]^+$ = 572.44.

Example 693: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylj phenyl] '-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide

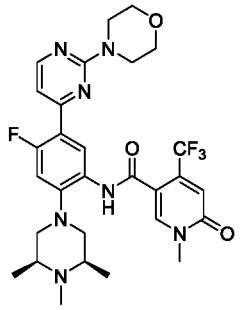


Step 1: 4-(difluoromethyl)-N-(4-fluoro-5-(Mbutylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[001091] To a stirred solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)- 1-methyl-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (2g, 3.86mmol, leq, procedure described in Example 226) in toluene(70mL) degassed with argon for 15min, then hexabutylditin (4.47g, 7.72mmol, 2eq) was added, followed by $Pd_2(dppf)_2Cl_2$ (315mg, 0.386mmol, O.leq) and after that heated to reflux under argon atmosphere for 24h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; and the filtrate was evaporated under reduced pressure. The crude compound was purified by column chromatography (Basic alumina) using 0-5% MeOH in DCM as an eluent to afford 4-(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (1.4 g, 50%) as a pale yellow solid. LCMS $[M+l]^+$ = 731.4.

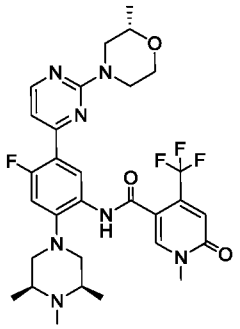
Step 2: N-(4-fluoro-5-(2-morpholinopyrimidin-4-yl)-2-((3S, 5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6<>xo-4-(Mfluoromethyl)-l,6-dihydropyridine-^ -carboxamide



[001092] In N,N-dimethylformamide (DMF) (592 μï) was dissolved N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-a^hydropyridine-3-carboxarnide (108 mg, 0.148 mmol). To the solution was added 4-(4-bromopyrimidin-2-yl)moipholine (39.8 mg, 0.163 mmol), lithium chloride (18.83 mg, 0.444 mmol) and bis(triphenylphosphine)palladium(II) dichloride (5.72 mg, 8.14 μmoï) at room temperature and then it was microwaved at the temperature of 120 °C for 3 hours. To the reaction mixture was added water and then extracted with dichloromethane. The organic layer was separated, concentrated and purified by column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4AC/CH_2CI_2) the fractions were concentrated and freeze dried for 2 days to afford the product as a white powder. ¾Ⅰ NMR (500 MHz, MeOD) δ 8.58 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.13 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.01 (d, *J* = 13.2 Hz,

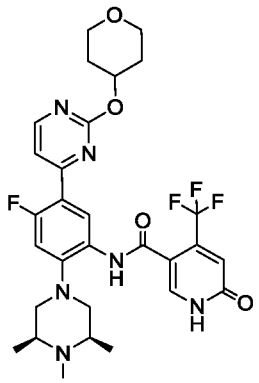
1H), 6.94 (s, 1H), 3.86 - 3.83 (m, 4H), 3.77 - 3.75 (m, 4H), 3.64 (s, 3H), 3.13 (d, *J* = 11.6 Hz, 2H), 2.62 (t, *J* = 11.3 Hz, 2H), 2.53 - 2.48 (m, 2H), 2.34 (s, 3H), 1.15 (d, *J* = 6.3 Hz, 6H); LCMS HSS $[M+l]^+$ = 604.34.

Example 694: N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3S, 5R)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxo-4-(trifluoromethyl)pyridme -3-carboxamide

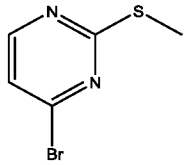


[001093] The title compound was prepared similar to the sequence described above for the preparation of Example 693 using (S)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine in place of 4-(4-bromopyrimidin-2-yl)morpholine. ^{1}H NMR (500 MHz, MeOD) δ 8.61 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 1H), 7.12 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.01 (d, *J* = 13.2 Hz, 1H), 6.94 (s, 1H), 4.65 (d, *J* = 13.2 Hz, 1H), 4.59 (d, *J* = 13.4 Hz, 1H), 3.96 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.64 (s, 3H), 3.62 - 3.59 (m, 1H), 3.14 (d, *J* = 11.5 Hz, 2H), 3.07 - 3.01 (m, 1H), 2.70 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.63 (t, *J* = 11.2 Hz, 2H), 2.52 (ddd, *J* = 10.1, 7.6, 4.5 Hz, 2H), 2.35 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 6H); LCMS $[M+l]^+$ = 618.34.

Example 695: N-[4-fluoro-5-[2-(oxan-4-yloxy)pyrimidin-4-yl]-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyr idine-3-carboxamide

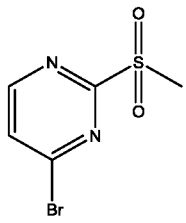


Step 1: 4-bromo-2-(methylthio)pyrimidine



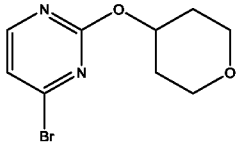
[001094] To a stirred solution of 2-(methylthio)pyrimidin-4(3H)-one (5 g, 35.21 mmol, leq) in ACN (lOOmL) was added $POBr_3$ (12.1 g, 42.3 mmol, 1.2 eq) at RT, then the reaction mixture was heated to 80°C for 5h. Monitored by TLC, the reaction mixture was cooled to RT and quenched in ice cold water then extracted with EtOAc (2X100mL). The combined organic layer was dried over Na_2SO_4 and concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-10% EtOAc in pet ether as eluent to afford 4-bromo-2-(methylthio)pyrimidine (6g, 83%) as off-white solid. LCMS: [M+H]+ 204.9.

Step 2: 4-bromo-2-(methylsulfonyl)pyrimidine



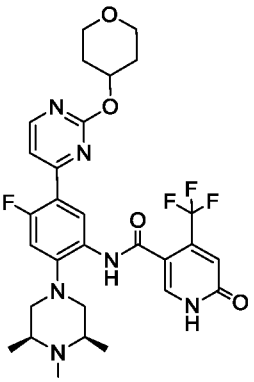
[001095] To stirred 30% H_2O_2 (6g, 29.4 mmol, 1 eq) was added ammonium molybdate tetrahydrate (1.09g, 0.88mmol, 0.03eq) at 0°C portion wise then stirred for 20min., and then a solution of 4-bromo-2-(methylthio)pyrimidine (6g, 29.41mmol, leq) slowly added at 0°C then allowed to RT for 3h. Monitored by TLC, the reaction mixture was concentrated to crude residue, which was diluted with cold water then extracted with DCM (3X100mL). The combined organic layer was washed with 5% H_2SO_4 solution and water then dried over Na_2SO_4 and concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-40% EtOAc in pet ether as eluent to afford 4-bromo-2-(methylsulfonyl)pyrimidine (6g, 86%) as off-white solid. LCMS: [M+H]+ 238.84.

Step 3: 4-bromo-2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidine



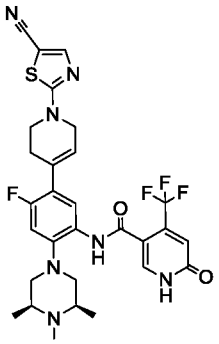
[001096] To a stirred solution of tetrahydro-2H-pyran-4-ol (1.66 mL, 16.31 mmol, l.leq) in THF was added K-fOBu (17.79 mL, 17.79 mmol, 1.2eq, 1M in THF) at 0°C and continued for 20min., then the reaction mixture was cooled to -78°C and to it was added slowly a solution of 4-bromo-2-(methylsulfonyl)pyrimidine (3.5g, 14.83 mmol, leq, in 50 mL of THF) and continued at -78°C for 3h. After monitoring by TLC, the reaction mixture was diluted with diethyl ether (200mL) and washed with water. The organic layer was dried over Na_2S0_4 and concentrated to crude compound. The crude compound was purified by column chromatography (silica gel, 100-200 mesh) using 0-20% EtOAc in pet ether as eluent to afford 4-bromo-2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidine (3.2g, 83%) as white solid. LC-MS: [M+H]+ 259.09.

Step 4: N-[4-fluoro-5-[2-(oxan-4-yloxy)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



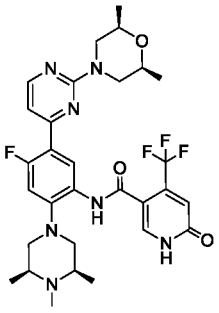
[001097] The title compound (10.2 mg, 12.3% yield) was prepared similar to the coupling procedure described above for the preparation of Example 384 using N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (108 mg, 0.132 mmol) and 4-bromo-2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidine (37.7 mg, 0.146 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.72 (d, *J* = 8.3 Hz, 1H), 8.57 (d, *J* = 5.4 Hz, 1H), 7.92 (s, *J* = 4.6 Hz, 1H), 7.56 (dd, *J* = 4.1 Hz, 1H), 7.06 (d, *J* = 13.3 Hz, 1H), 6.93 (s, 1H), 5.35 (ddd, *J* = 13.0, 8.7, 4.2 Hz, 1H), 4.00 (dt, *J* = 12.0, 4.4 Hz, 2H), 3.67 (ddd, *J* = 12.0, 9.3, 2.9 Hz, 2H), 3.17 (dt, *J* = 3.4, 1.6 Hz, 2H), 2.65 (t, *J* = 11.4 Hz, 2H), 2.58 - 2.54 (m, 2H), 2.37 (s, 3H), 2.21 - 2.16 (m, 2H), 1.88 - 1.81 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 6H); LCMS [M+l] $^+$ = 605.39.

Example 696: N-[5-[l-(5-cyano-l, 3-thiazol-2-yl)-3, 6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)- 1H-pyridine-3-carboxamide

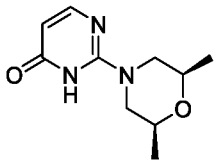


[001098] A procedure similar to Example 270 using N-(4-fluoro-5-(l, 2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(ljifluorome1iiyl)-l,6-a^hydropyridine-3-carboxarnide (25 mg, 0.049 mmol) and 2-bromo-5-cyanothiazole (9.31 mg, 0.049 mmol) afforded the title compound (10.5 mg, 33 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.82 (m, 1H), 7.77 - 7.72 (m, 1H), 7.72 - 7.64 (m, 1H), 6.89 - 6.83 (m, 1H), 6.82 - 6.78 (m, 1H), 6.03 - 5.96 (m, 1H), 4.13 - 4.08 (m, 2H), 3.82 - 3.71 (m, 2H), 2.97 - 2.87 (m, 2H), 2.64 - 2.54 (m, 2H), 2.52 - 2.39 (m, 4H), 2.30 - 2.24 (m, 3H), 1.08 - 1.03 (m, 6H); LCMS [M+H]+ 616.4.

Example 697: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)- 1H-pyridine-3-carboxamide

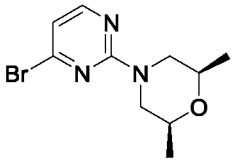


Step 1: 2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin- -4(3H)-one



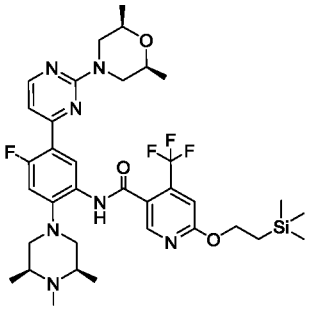
[001099] To 2-methylthio-4-pyrimidone (0.6 g, 4.22 mmol) was added cis-2,6-dimethylmorpholine (0.650 niL, 5.28 mmol). The mixture was heated to 145 °C for 2 hours in the microwave, then cooled to room temperature. The solid was crystallized from ethanol. The white needles were washed with EtOH and collected by centrifugation at 4000 RPM. The product was freeze dried for 2 days to afford 2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-4(3H)-one (308 mg, 35% yield) as a white powder. ^{1}H NMR (500 MHz, MeOD) δ 7.63 (d, *J* = 3.5 Hz, 1H), 5.77 (d, *J* = 6.7 Hz, 1H), 4.18 (d, *J* = 13.0 Hz, 2H), 3.64 (dqd, *J* = 12.5, 6.2, 2.4 Hz, 2H), 2.62 (dd, *J* = 13.2, 10.7 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 6H); LCMS C18 [M+l] $^+$ = 210.0.

Step 2: (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine



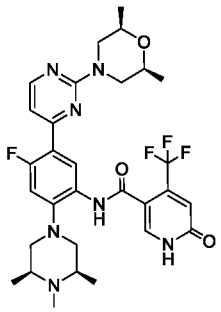
[001100] A mixture of 2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-4(3H)-one (108 mg, 0.516 mmol) and phosphorus(V) oxybromide (192 mg, 0.671 mmol) in acetonitrile (5161 μĭ) was heated at 82 °C for 1 hour. The reaction was cooled to room temperature, concentrated, and poured over ice. The resulting mixture was neutralized with a saturated solution of NaHCCb, and then extracted with methylene chloride. The organic phase was concentrated and purified by flash column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2C1_2) to afford (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmo rpholine (106 mg, 74% yield). ^{1}H NMR (500 MHz, MeOD) δ 8.07 (d, *J* = 5.1 Hz, 1H), 6.75 (d, *J* = 5.1 Hz, 1H), 4.52 (dd, *J* = 13.2, 1.2 Hz, 2H), 3.60 (dqd, *J* = 12.5, 6.2, 2.4 Hz, 2H), 2.56 (dd, *J* = 13.3, 10.7 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 6H); LCMS HSS [M+l] $^+$ = 271.77.

Step 3: N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-4-yl)-4-fluoro-2-^^3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide



[001101] In N,N-dimethylformamide (DMF) (539 μΐ) was dissolved N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (110 mg, 0.135 mmol). To the solution was added (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmo rpholine (40.4 mg, 0.148 mmol), lithium chloride (17.15 mg, 0.405 mmol) and bis(triphenylphosphine)palladium(II) dichloride (5.21 mg, 7.42 μηιοΐ) at room temperature and then it was microwaved at the temperature of 120 °C for 3 hours. To the reaction mixture was added water and then it was extracted with dichloromethane. The organic layer was separated, concentrated and purified by column chromatography on silica gel (0-100%, 89% CH_2C1_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) to afford N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide. LCMS $[M+l]^+$ = 718.26.

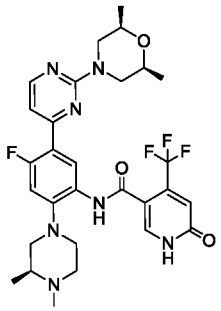
Step 4: N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3S, 5R)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH^yridim -3-carboxamide



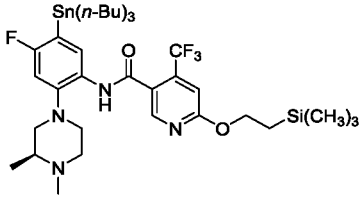
[001102] The product was dissolved in 2 mL of DCM and TFA (1033 μΐ, 13.49 mmol) was added. The purple solution was stirred for 1 h and the solvent was evaporated. The residue was purified using a preparative HPLC followed by a cation

exchange column eluting with MeOH:NH_4OH and freeze dried for 2 days to afford N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (19 mg, 23% yield) as a white powder. ^{1}H NMR (500 MHz, MeOD) δ 8.53 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 5.2 Hz, 1H), 7.78 (s, 1H), 7.01 (dd, *J* = 5.2, 1.7 Hz, 1H), 6.90 (d, *J* = 13.2 Hz, 1H), 6.82 (s, 1H), 4.57 (d, *J* = 12.8 Hz, 2H), 3.56 (ddd, *J* = 10.4, 6.3, 2.4 Hz, 2H), 3.06 (d, *J* = 11.2 Hz, 2H), 2.56 - 2.45 (m, 6H), 2.28 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 6H), 1.08 (d, *J* = 6.1 Hz, 6H); 19F NMR (471 MHz, MeOD) δ -63.66 (s), -115.74 (s); LCMS [M+l] $^+$ = 618.34.

Example 698: N-[4-fluoro-5-[2-[(2R, 6SJ-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethy l)-1H-pyridine-3-carboxamide



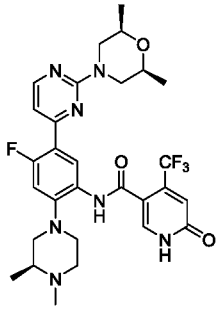
Step 1: (S)-N-(2-(3,4-dimethylpiperazin-l -yl)-4-fluoro-5-(ributylstannyl)phenyl)-4-(Mfluoromethyl)-6-(2-(Mmethylsilyl)ethoxy)nicotinamide



[001103] A stirred solution of (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (4 g, 6.77mmol, leq) in toluene (40mL) was degassed with argon for 15mins, then hexabutylditin (6.89mL, 13.5mmol, 2eq) was added, followed by Pd2(dppf)2Cl2 (0.55g, 0.67mmol, O.leq) and after that heated to reflux under argon atmosphere for 16h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; the filtrate was evaporated under reduced pressure. The

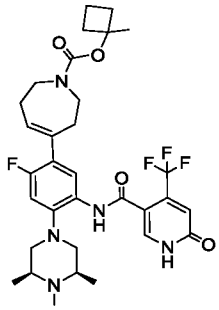
crude compound was purified by column chromatography (neutral alumina) using 0-30% EtOAc in pet ether as an eluent to afford (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(mbutylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (2.8 g, 51%) as a pale yellow liquid. LCMS: [M+H]+ 803.16.

Step 2: N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-4-yl)-2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-6<>xo-4-(Mfluoromethyl)-l,6-dih^ dropyridine-3-carboxamide



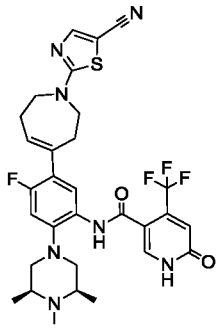
[001104] The title compound (10.1 mg, 12% yield) was prepared similar to the sequence described above for the preparation of Example 697 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (115 mg, 0.143 mmol) and (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine (42.9 mg, 0.158 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.63 (d, *J* = 8.2 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 7.90 (s, 1H), 7.11 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.02 (d, *J* = 13.2 Hz, 1H), 6.92 (s, 1H), 4.67 (d, *J* = 13.0 Hz, 2H), 3.66 (ddd, *J* = 10.3, 6.2, 2.3 Hz, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 3.15 (d, *J* = 12.4 Hz, 1H), 2.96 (t, *J* = 10.2 Hz, 2H), 2.63 - 2.57 (m, 4H), 2.45 (s, 1H), 2.39 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.15 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (471 MHz, MeOD) δ -63.74 (s), -115.95 (s); LCMS HSS $[M+l]^{+}$ = 604.27.

Example 699: (1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3^arbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate



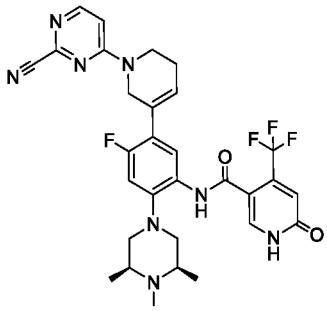
[001105] To a solution of *N*-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (30.6 mg, 0.059 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (15.48 mg, 0.062 mmol) in DCM (3 ml) was added pyridine (0.019 ml, 0.235 mmol). The reaction mixture was heated at 90°C for lh. It was cooled down and concentrated onto celite. The crude was purified on Isco (4 g silica column, eluting with DCM containing 0-5 % MeOH and 0-0.5 % NH_4OH). The desired product was lyophilized from water/acetonitrile to afford the title compound as a white fluffy powder (18 mg, 0.027 mmol, 46.0 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.91 (br d, *J*=3.9 Hz, 1H), 7.70 - 7.59 (m, 1H), 6.95 - 6.87 (m, 2H), 6.00 - 5.88 (m, 1H), 4.04 (br s, 2H),3.69 - 3.61 (m, 2H), 3.61 - 3.52 (m, 1H), 3.00 (br d, *J*=10.9 Hz, 2H), 2.61 (br d, *J*=5.7 Hz, 2H), 2.56 (br d, *J*=11.2 Hz, 2H), 2.52 - 2.41 (m, 2H), 2.36 (s, 3H), 2.34 - 2.25 (m, 2H), 2.17 - 2.04 (m, 2H), 1.92 (br d, *J*=5.7 Hz, 1H), 1.81 (br dd, *J*=2.2, 5.1 Hz, 1H), 1.75 - 1.62 (m, 1H), 1.59 - 1.53 (m, 3H), 1.15 (d, *J*=5.9 Hz, 6H); LCMS 634.

Example 700: N-[5-[l-(5-cyano-l,3-thiazol-2-yl)-2,3,6, 7-tetrahydroazepin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluorometty l)-1H-pyridine-3-carboxamide



[001106] A procedure similar to Example 270 using *N*-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxarnide (30 mg, 0.058 mmol) and 2-bromo-5-cyanothiazole (10.87 mg, 0.058 mmol) afforded the title compound as a white fluffy powder (23 mg, 0.035 mmol, 60.3 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.81 (s, 1H), 7.68 (s, 1H), 7.55 (br d, *J*=8.1 Hz, 1H), 6.85 - 6.79 (m, 2H), 6.02 - 5.95 (m, 1H), 4.24 (br d, *J*=5.1 Hz, 2H), 3.81 (br t, *J*=5.4 Hz, 3H), 2.89 (br d, *J*=11.0 Hz, 3H), 2.59 - 2.53 (m, 3H), 2.45 (br d, *J*=11.4 Hz, 3H), 2.41 (br d, *J*=4.5 Hz, 2H), 2.25 (s, 4H), 2.02 - 1.95 (m, 2H), 1.04 (d, *J*=6.0 Hz, 6H); LCMS $[M+H]^+$ 630.

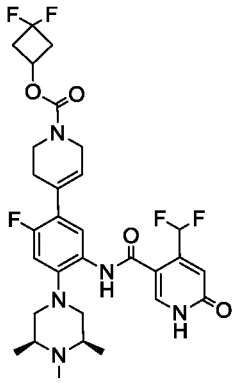
Example 701: N-[5-[l-(2-cyanopyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3A,5-trimethylpiperazin-l-yl]phenyl]-6 -oxo-4-(Mfluorom ethyl)-1H-pyridine-3-carboxamide



[001107] A mixture of cesium carbonate (32.1 mg, 0.099 mmol),4-bromopyrimidine-2-carbonitrile (9.97 mg, 0.054 mmol), and N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) in NMP was heated in an oil bath at 85°C for 0.5 - 5 h. The reaction mixture was concentrated to dryness, partitioned between DCM and water, the org phase was separated, aq phase was extracted with DCM (2x), the combined org phase was washed with brine, dried over Na_2SO_4 and concentrated to afford a brown residue which was concentrated onto celite and purified on Isco (4 g) column, eluting with DCM containing 0-5 % MeOH and 0-0.5 % NH40H. The desired product was isolated as an off white solid (10 mg, 32 %) ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.12 - 8.07 (m, 1H), 7.87 - 7.82 (m, 1H), 7.71 - 7.64 (m, 1H), 6.93 - 6.85 (m, 2H), 6.82 - 6.78 (m, 1H), 6.14 - 6.04 (m, 1H), 4.50 - 4.18 (m, 2H), 3.97 - 3.69 (m, 2H), 3.00 -

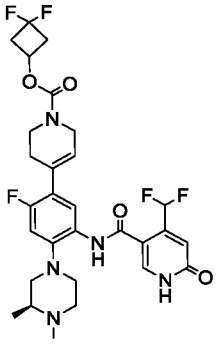
2.91 (m, 2H), 2.52 - 2.46 (m, 2H), 2.46 - 2.40 (m, 2H), 2.38 - 2.33 (m, 2H), 2.28 - 2.25 (m, 3H), 1.07 - 1.04 (m, 6H), 0.04 - 0.02 (m, 1H); LCMS [M+H]+ 611.5.

Example 702 (3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino] -2-fluoro-4-[(3R, 5S)-3, 4, 5-trimethylpiperazin-l-yl]phenyl]-3, 6-dihydro-2H-pyridine-l-carboxylate



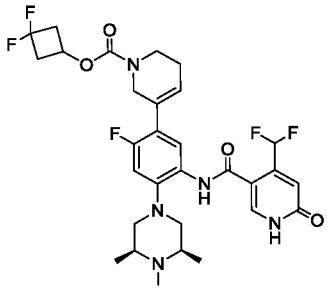
[001108] The procedure followed was similar to Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and 3,3-difluorocyclobutyl-(4-nitrophenyl) carbonate (15.35 mg, 0.056 mmol) to give the title compound (21 mg, 63 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.85-7.91 (m, 1H), 7.56 (d, *J*=8.19 Hz, 1H), 7.07-7.32 (m, 1H), 6.81 (d, *J*=12.47 Hz, 1H), 6.69 (s, 1H), 5.88 (br. s., 1H), 4.78-4.84 (m, 1H), 3.95-4.08 (m, 2H), 3.51-3.62 (m, 2H), 2.88-2.97 (m, 4H), 2.55-2.67 (m, 2H), 2.55-2.67 (m, 2H), 2.36-2.48 (m, 6H), 2.24 (s, 3H), 1.03 (d, *J*=5.99 Hz, 6H); LCMS [M+H]+ 624.5.

Example 703: (3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino] -2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l -yljphenyl] -3,6-dihydro-2H-pyridine-l-carboxylate



[001109] The procedure was similar to that of Example 253 using (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxarnide (25 mg, 0.053 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.80 mg, 0.058 mmol) to give the title compound (26 mg, 77 % yield). ¾ NMR (500MHz, METHANOL-d4) δ 7.86-7.92 (m, 1H), 7.57 (d, *J*=8.19 Hz, 1H), 7.07-7.31 (m, 1H), 6.84 (d, *J*=12.47 Hz, 1H), 6.70 (s, 1H), 5.88 (br. s., 1H), 4.79-4.86 (m, 1H), 3.95-4.10 (m, 2H), 3.51-3.63 (m, 2H), 2.88-2.99 (m, 4H), 2.75-2.83 (m, 2H), 2.54-2.68 (m, 2H), 2.37-2.45 (m, 4H), 2.22-2.29 (m, 4H), 1.00 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 610.5.

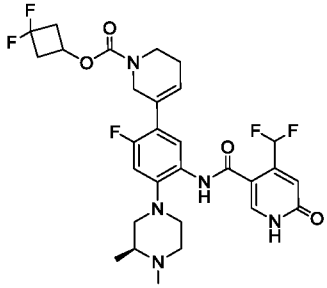
Example 704: (3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



[001110] The procedure followed was similar to Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.35 mg, 0.056 mmol) to give the title compound (26 mg, 77 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.88 (s, 1H), 7.55 (d, *J*=8.07 Hz, 1H), 7.07-7.32 (m, 1H), 6.84 (d,

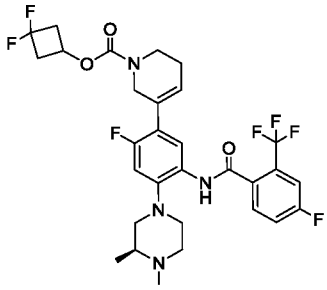
J=12.35 Hz, 1H), 6.70 (s, 1H), 5.99 (br. s., 1H), 4.78-4.84 (m, 1H), 4.15 (d, *J*=17.12 Hz, 2H), 3.52 (d, *J*=19.81 Hz, 2H), 2.93 (d, *J*=11.13 Hz, 4H), 2.60 (d, *J*=6.36 Hz, 2H), 2.43-2.50 (m, 2H), 2.35-2.43 (m, 2H), 2.25 (s, 5H), 1.04 (d, *J*=5.99 Hz, 6H); LCMS [M+H]+ 624.

Example 705: (3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino] -2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l -yljphenyl] -3, 6-dihydro-2H-pyridine-l-carboxylate



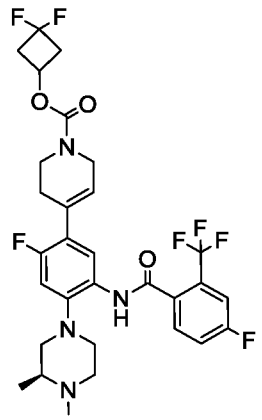
[001111] The procedure followed was similar to that of Example 253 using (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxarnide (25 mg, 0.053 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.80 mg, 0.058 mmol) to give the title compound (23 mg, 68 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 11.86-11.88 (m, 1H), 7.86-7.92 (m, 1H), 7.57 (d, *J*=8.07 Hz, 1H), 7.07-7.32 (m, 1H), 7.07-7.32 (m, 1H), 7.07-7.32 (m, 1H), 6.86 (d, *J*=12.23 Hz, 1H), 6.70 (s, 1H), 5.99 (br. s., 1H), 4.78-4.85 (m, 1H), 4.15 (d, *J*=17.36 Hz, 2H), 3.53 (d, *J*=19.68 Hz, 2H), 2.88-3.00 (m, 4H), 2.76-2.83 (m, 2H), 2.60 (d, *J*=5.50 Hz, 2H), 2.37-2.44 (m, 2H), 2.23-2.31 (m, 6H), 1.00 (d, *J*=6.24 Hz, 3H); LCMS [M+H]+ 610.5.

Example 706: (3,3-difluorocyclobutyl) 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyljbenzoyl] amino]-4-[(3R)-3, 4-dimethylpiperazin-l -yljphenyl]-3, 6-dihydro-2H-pyridine-l-carboxylate



[001112] The procedure was similar to Example 253 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.19 mg, 0.056 mmol) to give the title compound (22.5 mg, 67 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.79 - 7.73 (m, 1H), 7.67 - 7.62 (m, 1H), 7.56 - 7.52 (m, 1H), 7.47 - 7.42 (m, 1H), 6.93 - 6.86 (m, 1H), 6.05 - 5.99 (m, 1H), 4.85 - 4.78 (m, 1H), 4.23 - 4.13 (m, 2H), 3.58 - 3.48 (m, 2H), 2.99 - 2.88 (m, 4H), 2.84 - 2.77 (m, 2H), 2.66 - 2.54 (m, 2H), 2.47 - 2.39 (m, 1H), 2.38 - 2.32 (m, 1H), 2.29 - 2.20 (m, 6H), 1.02 - 0.99 (m, 3H); LCMS [M+H]+ 629.4.

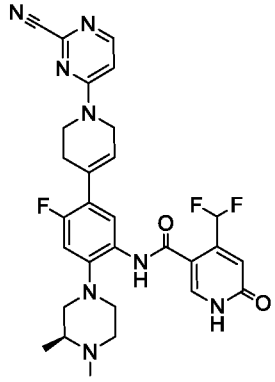
Example 707: (3,3-difluorocyclobutyl) 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyljbenzoylj amino]-4-[(3R)-3,4-dimethylpiperazin-l -yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate



[001113] The procedure followed was similar to that of Example 253 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (15.19 mg, 0.056 mmol) to afford the title compound (17 mg, 51 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.77 (d,

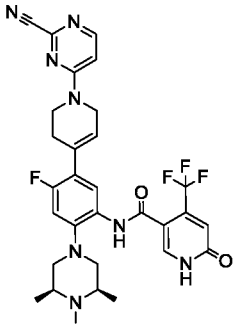
J=8.07 Hz, IH), 7.64 (dd, *J*=5.32, 8.50 Hz, IH), 7.54 (dd, *J*=2.38, 9.11 Hz, IH), 7.45 (dt, *J*=2.38, 8.28 Hz, IH), 6.87 (d, *J*=12.35 Hz, IH), 5.90 (br. s., IH), 4.79-4.85 (m, IH), 3.98-4.09 (m, 2H), 3.54-3.63 (m, 2H), 2.88-2.98 (m, 4H), 2.76-2.82 (m, 2H), 2.56-2.67 (m, 2H), 2.39-2.47 (m, 3H), 2.31-2.37 (m, IH), 2.19-2.25 (m, 4H), 0.99 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 629.5.

Example 708: N-[5-[l-(2-cyanopyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide



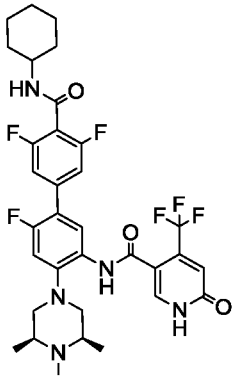
[001114] The procedure followed was similar to that of Example 270 using cesium carbonate (34.3 mg, 0.105 mmol),4-bromopyrimidine-2-carbonitrile (10.64 mg, 0.058 mmol) and (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol) in NMP to give the title compound (5.5 mg, 17 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.35 - 8.19 (m, IH), 8.15 - 8.08 (m, IH), 7.98 - 7.90 (m, IH), 7.62 - 7.53 (m, IH), 7.31 - 7.06 (m, IH), 6.95 - 6.81 (m, 2H), 6.72 - 6.68 (m, IH), 6.06 - 5.99 (m, IH), 4.31 - 4.03 (m, 2H), 4.01 - 3.72 (m, 2H), 3.28 - 3.23 (m, IH), 3.15 - 3.07 (m, 2H), 3.01 - 2.89 (m, 3H), 2.72 - 2.61 (m, 4H), 2.54 (br s, 2H), 1.21 - 1.19 (m, 3H); LCMS [M+H]+ 579.5.

Example 709: N-[5-[l-(2-cyanopyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

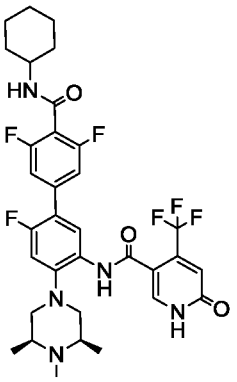


[001115] The procedure followed was similar to Example 270 using cesium carbonate (32.1 mg, 0.099 mmol), 4-bromopyrimidine-2-carbonitrile (9.97 mg, 0.054 mmol) and N-(4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.049 mmol) in NMP to give the title compound (6 mg, 19 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.14 - 8.09 (m, 1H), 7.89 - 7.83 (m, 1H), 7.75 - 7.69 (m, 1H), 6.95 - 6.90 (m, 1H), 6.89 - 6.79 (m, 2H),6.08 - 5.99 (m, 1H), 4.31 - 4.05 (m, 2H), 4.00 - 3.73 (m, 2H), 3.08 - 3.03 (m, 2H), 3.01 - 2.88 (m, 2H), 2.70 - 2.63 (m, 2H), 2.58 - 2.53 (m, 5H), 1.20- 1.18 (m, 6H); LCMS [M+H]+ 611.4.

Example 710: N-[5-[4-(cyclohexylcarbamoyl)-3, 5-difluorophenyl] '-4-fluoro-2-f(3R, 5S)-3, 4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide

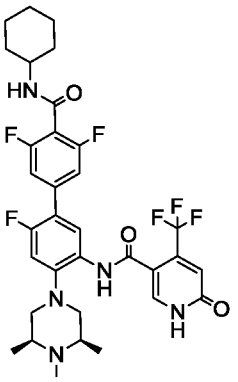


Step 1: 2',3,5-trifluoro-5'-(5-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamido)-4'-((3S, 5R)-3, 4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenylJ-4-carboxylic acid



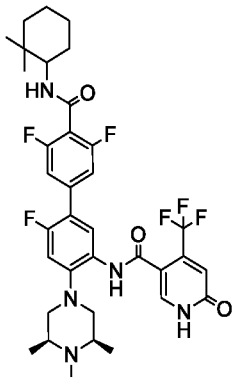
[001116] N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (300 mg, 0.495 mmol), 3,5-difluoro-4-carboxyphenylboronic acid (200 mg, 0.991 mmol) and potassium phosphate tribasic reagent grade, >=98% (158 mg, 0.743 mmol) were mixed in 1,4-dioxane (10 ml). Water was added and the vial was flushed with nitrogen. The reaction mixture was heated in a microwave reactor to lh at 100 °C. The reaction mixture was cooled to RT, partitioned between DCM and water, and neutralized with citric acid (IN, 0.8 ml, PH 5-6). The aq phase was extracted several times with DCM/i-PrOH/$CHCl_3$. The compound formed a suspension. Some brine and some water were added to break up the suspension. The milky organic layer was evaporated as is without drying. The crude product was suspended in DCM (5 ml), and TFA (2 ml) was added. The suspension was stirred at rt for 30 min upon which LCMS showed completion. The solvents were evaporated off and the residue was taken up in MeOH and passed through a cation exchange resin cartridge (2 g porapak, 20 cc capacity) prewashed with MeOH, it was eluted with MeOH then 3% NH_4OH in MeOH. The fractions containing all the product were concentrated down. The residue was taken in some acetonitrile, some water was added. It was then lyophilized to afford the product as a light yellow fluffy powder. LCMS [M+H]+ 583.2.

Step 2: N-[5-[4-(cyclohexylcarbamoyl)-3, 5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3, 4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



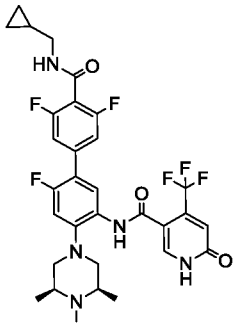
[001117] HATU (29.4 mg, 0.077 mmol), cyclohexylamine (7.66 mg, 0.077 mmol) and 2',3,5-trifluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,1'-biphenyl]-4-carboxylic acid (30 mg, 0.052 mmol) were charged into a 30 ml vial. *N N*-dimethylformamide (1.5 ml) was added then the mixture was stirred at rt for 5 min upon which *NN*-diisopropylethylamine (0.036 ml, 0.206 mmol) was added. The mixture was stirred at ambient temperature for 30 min and the reaction was stopped. It was purified by reverse phase Isco (CI 8 13.3 g column; eluent:10%, 10-70%, then 70% AcCN/water) to give the title compound after lyophilization as a white fluffy powder (6.7 mg, 9.59 μηιοΐ, 18.6 % yield) . ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 (s, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.16 (d, *J*=8.4 Hz, 2H), 6.97 (d, *J*=12.3 Hz, 1H), 6.82 - 6.77 (m, 1H), 3.82 - 3.72 (m, 1H), 2.99 (br d, *J*=11.2 Hz, 2H), 2.89 (s, 1H), 2.54 - 2.49 (m, 2H), 2.47 - 2.39 (m, 2H), 2.26 (s, 3H), 1.92 - 1.84 (m, 2H), 1.75 -1.66 (m, 2H), 1.62 - 1.54 (m, 1H), 1.38 - 1.28 (m, 2H), 1.27 - 1.10 (m, 4H), 1.06 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ 664.

Example 711: N-[5-[4-[(2, 2-dimethylcyclohexyl)carbamoyl]-3, 5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluorometty l)-1H-pyridine-3-carboxamide



[001118] Example 711 was prepared by a similar procedure to that of Example 710 using 2,2-dimethylcyclohexanamine (10.16 mg, 0.080 mmol) and 2',3,5-trifluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,l'-biphenyl]-4-carboxylic acid (31 mg, 0.053 mmol) to give the title compound as a white fluffy powder (3 mg, 4.08 μηιοΐ, 7.7 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.98 (s, 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.17 (br d, *J*=8.3 Hz, 2H), 6.97 (d, *J*=12.3 Hz, 1H), 6.71 - 6.66 (m, 1H), 3.79 (dd, *J*=4.1, 11.4 Hz, 1H), 2.99 (br d, *J*=11.5 Hz, 3H), 2.87 (br d, *J*=11.4 Hz, 1H), 2.54 - 2.48 (m, 2H), 2.45 - 2.37 (m, 2H), 2.25 (s, 3H), 1.73 - 1.66 (m, 1H), 1.61 - 1.55 (m, 1H), 1.51 - 1.40 (m, 4H), 1.39 - 1.23 (m, 4H), 1.05 (d, *J*=6.2 Hz, 6H), 0.93 (s, 3H), 0.84 (s, 3H); LCMS $[M+H]^{+}$ 692.

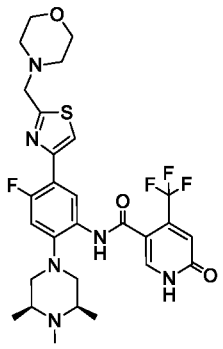
Example 712: N-[5-[4-(cyclopropylmethylcarbamoyl)-3, 5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3A,5-trimethylpiperazin -ι -yl]phenyl]-6 -oxo-4-(Mfluorom ethyl)-1H-pyridine-3-carboxamide



[001119] Example 712 was prepared by a similar procedure to that of Example 710 using aminomethylcyclopropane (5.49 mg, 0.077 mmol) and 2',3,5-trifluoro-5'-(6-oxo-4-(mfluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,l'-biphenyl]-4-carboxylic acid (30 mg, 0.052 mmol) to give the

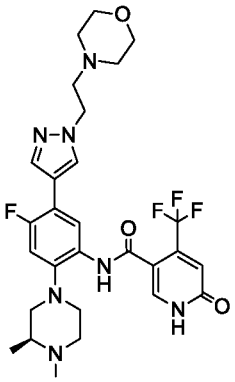
title compound as a white fluffy powder (5.7 mg, 8.52 μηιοϊ, 16.54 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.91 (s, 1H), 7.84 (br d, *J*=8.2 Hz, 1H), 7.18 (br d, *J*=8.6 Hz, 2H), 6.98 (d, *J*=12.3 Hz, 1H), 6.79 - 6.72 (m, 1H), 2.99 (br d, *J*=11.2 Hz, 2H), 2.55 - 2.48 (m, 2H), 2.47 - 2.37 (m, 2H), 2.26 (s, 3H), 1.06 (d, *J*=6.2 Hz, 6H), 0.99 (ddd, *J*=5.1, 7.2, 12.0 Hz, 1H), 0.47 - 0.43 (m, 2H), 0.20 (q, *J*=4.9 Hz, 2H); LCMS [M+H]$^{+}$ 636.

Example 713: N-[4-fluoro-5-[2-(morpholin-4-ylmethyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine- 3-carboxamide



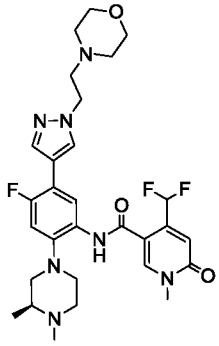
[001120] The title compound was prepared using a sequence similar to that used for the preparation of Example 482 from 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid (16.48 mg, 0.054 mmol), HATU (20.39 mg, 0.054 mmol) and 4-fluoro-5-(2-(morpholinomethyl)thiazol-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (15 mg, 0.036 mmol) to afford the title compound (6.2 mg, 29 % yield). ^{1}H NMR (500MHz, DMSO-d6) δ = 12.81 - 12.20 (m, 1H), 9.49 (s, 1H), 8.30 (d, *J*=8.3 Hz, 1H), 7.95 (s, 1H), 7.82 (d, *J*=2.3 Hz, 1H), 7.02 (d, *J*=13.1 Hz, 1H), 6.79 (s, 1H), 3.88 (s, 2H), 3.65 - 3.58 (m, 4H), 3.03 (br d, *J*=11.0 Hz, 2H), 2.54 (br s, 4H), 2.48 - 2.43 (m, 2H), 2.37 - 2.31 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 609.2.

Example 714: N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyrid^ ne-3-carboxamide



[001121] The title compound (13 mg, 26% yield) was prepared in a manner similar to that described in Example 39 from (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (0.050 g, 0.085 mmol) and 1-(2^ orpηo1iηo6^1)-1 H-pyrazoϊe-4-bθΓοηic acid, pinacol ester (0.031 g, 0.101 mmol). ¾NMR (500MHz, DMSO-d6) δ = 12.53 (br s, IH), 9.44 (s, IH), 8.11 (s, IH), 7.95 (s, IH), 7.87 (d, *J*=8.3 Hz, IH), 7.76 (s, IH), 7.02 (d, *J*=12.7 Hz, IH), 6.81 (s, IH), 4.28 (t, *J*=6.5 Hz, 2H), 3.55 (t, *J*=4.5 Hz, 4H), 3.02 - 2.94 (m, 2H), 2.81 - 2.71 (m, 4H), 2.42 (br s, 4H), 2.40 - 2.29 (m, 3H), 2.21 (s, 3H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 592.4.

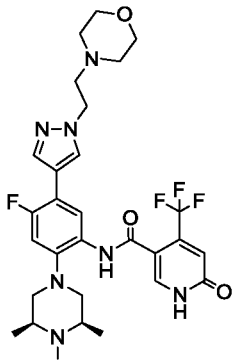
Example 715: 4-(difluoromethyl)-N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-ylJ-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridme-3-carboxamide



[001122] The title compound was prepared according to a procedure similar to that described in the preparation of Example 217 using (S)-N-(5-bromo-2-(3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (0.050 g, 0.103 mmol) and 1-(2-morpholinoethyl)-lH-pyrazole-4-boronic acid, pinacol ester (0.038 g, 0.123 mmol). ^{1}H NMR (500MHz,

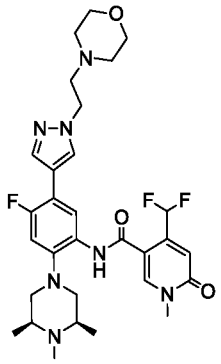
DMSO-d6) δ = 9.42 (s, IH), 8.40 (s, IH), 8.12 (d, *J=1.2* Hz, IH), 7.87 (s, IH), 7.80 (d, *J*=8.3 Hz, IH), 7.76 (s, IH), 7.48 - 7.23 (m, IH), 7.03 (d, *J*=12.6 Hz, IH), 6.66 (s, IH), 4.28 (t, *J*=6.5 Hz, 2H), 4.20 (t, *J*=6.6 Hz, IH), 3.56 - 3.53 (m, 8H), 3.03 - 2.94 (m, 2H), 2.83 - 2.69 (m, 5H), 2.44 - 2.39 (m, 7H), 2.32 (dt, *J*=2.7, 10.9 Hz, IH), 2.20 (s, 4H), 0.97 (d, *J*=6.2 Hz, 3H); LCMS [M+H]+: 588.2.

Example 716: N-[4-fluoro-5-[l -(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R,5SJ-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



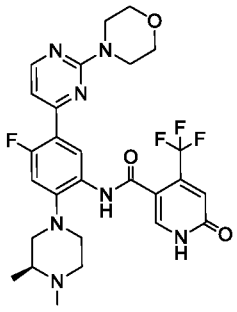
[001123] The title compound (19 mg, 38% yield) was prepared in a manner similar to that described in Example 39 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (0.050 g, 0.083 mmol) and l-(2-morpholinoethyl)-lH-pyrazole-4-boronic acid, pinacol ester (0.030 g, 0.099 mmol). IH NMR (500MHz, DMSO-d6) δ = 12.55 (br s, IH), 9.46 (s, IH), 8.11 (d, *J*=1.0 Hz, IH), 7.94 (s, IH), 7.86 (d, *J*=8.2 Hz, IH), 7.75 (s, IH), 6.99 (d, *J*=12.6 Hz, IH), 6.81 (s, IH), 4.28 (t, *J*=6.5 Hz, 2H), 3.55 (t, *J*=4.5 Hz, 4H), 2.98 (br d, *J*=10.9 Hz, 2H), 2.73 (t, *J*=6.5 Hz, 2H), 2.44 - 2.39 (m, 5H), 2.35 - 2.29 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 606.4.

Example 717: 4-(difluoromethyl)-N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001124] The title compound (33 mg, 55% yield) was prepared by a procedure similar to that of Example 461 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(difluoromethyl)- 1-methyl-6-oxo- 1,6-dihydropyridine-3-carboxamide (0.050 g, 0.100 mmol) and 1-(2^ orpηo1iηo6^1)-1 H-pyrazoϊe-4^ θrοηic acid, pinacol ester (0.037 g, 0.120 mmol). ¾ NMR (500MHz, DMSO-d6) δ = 9.44 (s, IH), 8.39 (s, IH), 8.12 (d, *J*=l.l Hz, IH), 7.87 (s, 2H), 7.79 (d, *J*=8.4 Hz, IH), 7.76 (s, IH), 7.49 - 7.24 (m, IH), 7.00 (d, *J*=12.7 Hz, IH), 6.66 (s, IH), 4.28 (t, *J*=6.6 Hz, 2H), 3.57 - 3.52 (m, 8H), 3.00 (br d, *J*=10.9 Hz, 2H), 2.75 - 2.68 (m, 5H), 2.41 (br d, *J*=3.4 Hz, 6H), 2.18 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 602.5.

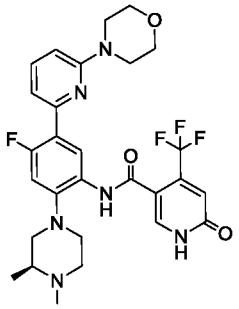
Example 718: N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3, 4-dimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine -3-carboxamide



[001125] To a 5 mL microwave vial charged with (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (120 mg, 0.15 mmol), 4-(4-bromopyrimidin-2-yl)morpholine (44 mg, 0.18 mmol), LiCl (19 mg, 0.45 mmol) and bis(triphenylphosphine)palladium(II) dichloride (10.5 mg, 0.15 mmol, 10 mol%) was added DMF (1.5 mL). The resulting mixture was irradiated in microwave at 120 °C for 3 h. It was diluted with MeOH (20 mL), passed through SCX-2 column (2 g, 15cc)

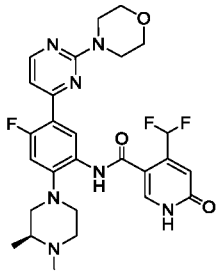
and dried to give crude (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-4-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide as a light brown solid. LCMS $[M + H]^+$ 676.4. The above intermediate was redissolved in 2 mL of DCM and treated with TFA (0.92 mL, 12 mmol). The resulting mixture was stirred at rt for 2 h. The volatiles were removed and the residue purified by prep-HPLC and Biotage SCX-2 column to give the title compound as a light beige solid (12.8 mg, 15%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.60 (br d, *J*=8.1 Hz, 1H), 8.39 (d, *J*=5.1 Hz, 1H), 7.95 (s, 1H), 7.15 (dd, *J*=1.8, 5.1 Hz, 1H), 7.04 (d, *J*=13.2 Hz, 1H), 6.94 (s, 1H), 3.91 - 3.83 (m, 4H), 3.81 - 3.75 (m, 4H), 3.26 - 3.13 (m, 2H), 3.03 - 2.91 (m, 2H), 2.65 - 2.54 (m, 2H), 2.50 - 2.43 (m, 1H), 2.40 (s, 3H), 1.16 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 576.3.

Example 719: N-[4-fluoro-5-(5-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl] -6-oxo-4-(rifluoromethyl)-lH-pyridine-3-carboxamide



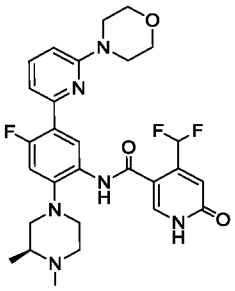
[001126] The title compound (light beige solid, 18.5 mg, 21%) was prepared similar to the 2-step sequence described above for the preparation of Example 718 using 4-(6-bromopyridin-2-yl)morpholine and (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.53 (br d, *J*=8.1 Hz, 1H), 7.94 (s, 1H), 7.63 (t, *J*=7.9 Hz, 1H), 7.23 (dd, *J*=1.5, 7.5 Hz, 1H), 7.02 (d, *J*=13.0 Hz, 1H), 6.94 (s, 1H), 6.77 (d, *J*=8.3 Hz, 1H), 3.87 - 3.80 (m, 4H), 3.64 - 3.54 (m, 4H), 3.20 - 3.10 (m, 2H), 3.00 - 2.93 (m, 2H), 2.62 - 2.53 (m, 2H), 2.48 - 2.43 (m, 1H), 2.40 (s, 3H), 1.16 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^+$ 575.3.

Example 720: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridme-3-carboxamide



[001127] The title compound (light beige solid, 18.2 mg, 16%) was prepared similar to the 2-step sequence described above for the preparation of Example 718 using (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tribu†ylstamyl)phenyl)-6-(2-(†jimethylsilyl)ethoxy)nicotinamide (157 mg, 0.2 mmol) in place of (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.46 (d, *J* =8.3 Hz, IH), 8.39 (d, *J* =5.3 Hz, IH), 8.03 (s, IH), 7.32 (t, *J* =55.0 Hz, IH), 7.13 (dd, *J* =1.8, 5.1 Hz, IH), 7.03 (d, *J* =13.2 Hz, IH), 6.82 (s, IH), 3.89 - 3.83 (m, 4H), 3.80 - 3.75 (m, 4H), 3.24 - 3.14 (m, 2H), 3.02 - 2.89 (m, 2H), 2.63 - 2.50 (m, 2H), 2.46 - 2.35 (m, 4H), 1.13 (d, *J* =6.4 Hz, 3H); LCMS $[M + H]^{+}$ 558.3.

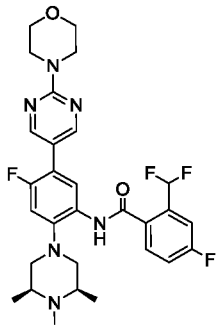
Example 721: 4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-ylJphenylJ-6-oxo-lH-pyridme-3-carboxamide



[001128] The title compound (off white solid, 8.0 mg, 7%) was prepared similar to the 2-step sequence described above for the preparation of Example 718 using (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (157 mg, 0.2 mmol) and 4-(6-bromopyridin-2-yl)morpholine (58 mg, 0.24 mmol) in place of (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(tributylstannyl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide and 4-(4-bromopyrimidin-2-yl)morpholine. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.39 (d, *J* =8.3 Hz, IH), 8.02 (s, IH), 7.63

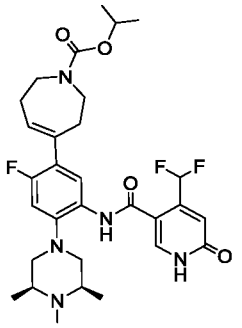
(t, *J*=8.0 Hz, 1H), 7.44 - 7.20 (m, 2H), 7.01 (d, *J*=13.0 Hz, 1H), 6.83 (s, 1H), 6.77 (d, *J*=8.6 Hz, 1H), 3.86 - 3.78 (m, 4H), 3.63 - 3.55 (m, 4H), 3.21 - 3.10 (m, 2H), 3.03 - 2.92 (m, 2H), 2.59 (br t, *J*=10.8 Hz, 2H), 2.47 (br s, 1H), 2.41 (s, 3H), 1.15 (d, *J*=6.2 Hz, 3H); LCMS [M+ H]$^+$ 557.3.

Example 722: 2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide



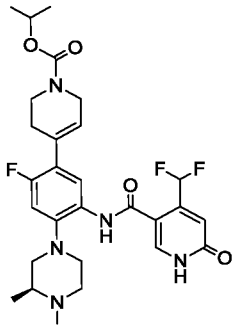
[001129] A mixture of 2-(difluoromethyl)-4-fluorobenzoic acid (76 mg, 0.4 mmol), HATU (152 mg, 0.4 mmol) and N,N-diisopropylethylamine (0.11 ml, 0.6 mmol) in DM F (2 mL) was heated at 60 °C for 5 min to afford a clear colorless solution before 4-fluoro-5-(2-morpholinopyrirnidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (80 mg, 0.2 mmol) was added in one portion. The resulting mixture was heated at 60 °C for 1 h. Solvent were removed and the residue was purified by prep-HPLC and Biotage SCX-2 column to give a light beige solid. It was suspended in MeOH (10 mL), treated with HC0 $_2$H (0.05 mL, filtered and the filtrate was concentrated and dried to give the title compound as a light brown solid (formic acid salt, 35.4 mg, 28%). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.58 (s, 2H), 8.41 (s, 1H), 7.97 (br d, *J*=8.1 Hz, 1H), 7.88 (br dd, *J*=5.6, 7.8 Hz, 1H), 7.56 (dd, *J*=2.3, 9.3 Hz, 1H), 7.51 - 7.25 (m, 2H), 7.17 (d, *J*=11.9 Hz, 1H), 3.90 - 3.82 (m, 4H), 3.82 - 3.75 (m, 4H), 3.25 (br d, *J*=12.2 Hz, 2H), 3.11 - 2.95 (m, 2H), 2.87 - 2.77 (m, 2H), 2.68 (s, 3H), 1.31 (d, *J*=6.4 Hz, 6H); LCMS [M + H]$^+$ 573.3.

*Example 723: propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino]-2-fluoro-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2, 3,6,*7*-tetrahydroazepine-l-carboxylate*



[001130] The procedure followed was similar to that of Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.060 mmol) and isopropyl chloroformate (0.060 ml, 0.060 mmol) to afford the title compound as a white fluffy powder (24 mg, 0.039 mmol, 64.9 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.90 - 7.84 (m, 1H), 7.49 - 7.42 (m, 1H), 7.34 - 7.05 (m, 1H), 6.80 (d, *J*=11.9 Hz, 1H), 6.70 (s, 1H), 5.93 -5.72 (m, 1H), 3.96 (br dd, *J*=5.0, 13.8 Hz, 1H), 3.58 (t, *J*=6.0 Hz, 1H), 3.56 - 3.46 (m, 1H), 2.90 (br d, *J*=ll.l Hz, 2H), 2.58 - 2.49 (m, 2H), 2.48 -2.42 (m, 2H), 2.39 (br d, *J*=6.5 Hz, 3H), 2.24 (s, 3H), 1.84 - 1.76 (m, 1H), 1.16 (br t, *J*=5.2 Hz, 6H), 1.03 (d, *J*=6.0 Hz, 6H); LCMS $[M+H]^{+}$ 590.

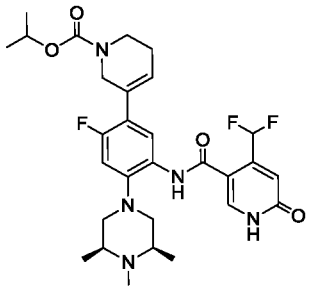
Example 724: propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l-yl]pfa nyl]-3,6-dihydro-2H-pyridine- 1-carboxylate



[001131] The procedure followed was similar to Example 253 using (S)-4-(difluoromethyl)-N-(2-(3 ,4-dimethylpiperazin- 1-yl)-4-fluoro-5 -(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol) and isopropyl chloroformate (0.045 ml, 0.045 mmol) to give the title compound (20.5 mg, 66 % yield). ^{1}H NMR (500MHz, METHANOL-d45 7.86-7.93

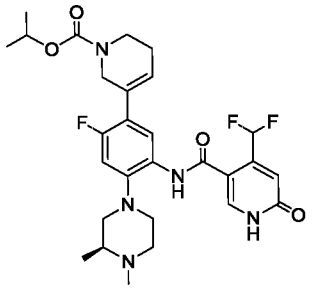
(m, 1H), 7.89 (s, 1H), 7.54-7.60 (m, 1H), 7.07-7.31 (m, 1H), 6.80-6.87 (m, 1H), 6.70 (s, 1H), 5.88 (br. s., 1H), 4.80-4.86 (m, 1H), 4.00 (br. s., 2H), 3.55 (br. s., 2H), 2.93-3.00 (m, 1H), 2.88-2.93 (m, 1H), 2.75-2.83 (m, 2H), 2.36-2.44 (m, 4H), 2.22-2.31 (m, 4H), 1.18 (d, *J*=6.24 Hz, 6H), 1.00 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 562.5.

Example 725: propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonylJaminoJ-2-fluoro-4-[(3R5S)-3,4,5-trimethylpiperazm-l-ylJphenylJ-3,6-dihydro-2H-pyridine-l-carboxylate



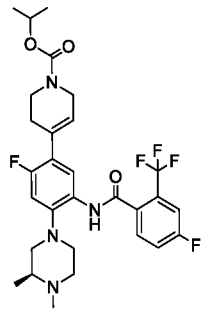
[001132] The procedure was similar to that of Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (25 mg, 0.051 mmol) and isopropyl chloroformate (0.049 ml, 0.049 mmol) to give the title compound (23 mg, 74 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.89 (s, 1H), 7.55 (d, *J*=7.95 Hz, 1H), 7.07-7.32 (m, 1H), 6.83 (d, *J*=12.23 Hz, 1H), 6.69 (s, 1H), 5.98 (br. s., 1H), 4.79-4.85 (m, 1H), 4.13 (br. s., 2H), 3.50 (br. s., 2H), 2.93 (d, *J*=11.25 Hz, 2H), 2.43-2.50 (m, 2H), 2.36-2.42 (m, 2H), 2.24 (s, 3H), 2.19-2.23 (m, 2H), 1.15-1.18 (m, 6H), 1.15-1.18 (m, 6H), 1.17 (d, *J*=6.24 Hz, 6H), 1.03 (d, *J*=6.11 Hz, 6H); LCMS [M+H]+ 576.5.

Example 726: propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonylJaminoJ-2-fluoro-4-[(3R)-3,4-dimethylpiperazm-l-ylJphenylJ-3,6-dihydro-2H-pyridine-l-carboxylate



[001133] The procedure used was similar to Example 253 using (S)-4-(difluoromethyl)-N-(2-(3 ,4-dimethylpiperazin- 1-yl)-4-fluoro-5 -(1,2,5,6-tetrahydropyridin-3-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol) and isopropyl chloroformate (0.050 mL, 0.050 mmol) to give the title compound (25.5 mg, 82 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.90 (s, 1H), 7.57 (d, *J*=7.95 Hz, 1H), 7.07-7.32 (m, 1H), 6.85 (d, *J*=12.35 Hz, 1H), 6.70 (s, 1H), 5.98 (br. s., 1H), 4.78-4.85 (m, 1H), 4.13 (br. s., 2H), 3.50 (br. s., 2H), 2.95-3.01 (m, 1H), 2.92 (d, *J*=11.49 Hz, 1H), 2.75-2.83 (m, 2H), 2.37-2.45 (m, 2H),2.20-2.31 (m, 6H), 1.13-1.19 (m, 6H), 1.00 (d, *J*=6.24 Hz, 3H); LCMS [M+H]+ 562.5.

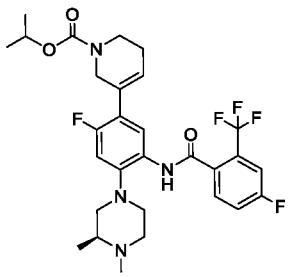
Example 727: propan-2-yl 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazm-l-ylJphenylJ-3,6-dihydro-2H^yridine-l-carbo xylate



[001134] The procedure was similar to Example 253 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol) and isopropyl chloroformate (0.048 ml, 0.048 mmol) to give the title compound (21 mg, 68 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.73-7.80 (m, 1H), 7.64 (dd, *J*=5.32, 8.38 Hz, 1H), 7.53 (dd, *J*=2.32, 9.05 Hz, 1H), 7.44 (dt, *J*=2.32, 8.25 Hz, 1H), 6.80-6.93 (m, 1H), 5.82-5.96 (m, 1H), 4.79-4.87 (m, 1H), 4.01 (br. s., 2H), 3.56 (br. s., 2H), 2.92-2.99 (m, 1H), 2.89 (d, *J*=11.49 Hz, 1H), 2.76-2.83 (m, 2H), 2.38-2.51 (m, 3H), 2.29-2.37

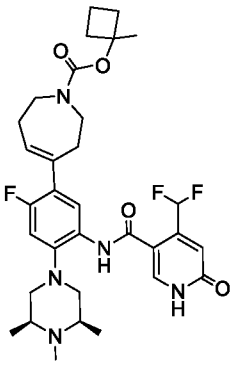
(m, IH), 2.19-2.26 (m, 4H), 1.16-1.20 (m, 6H), 1.18 (d, *J*=6.24 Hz, 6H), 0.99 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 581.6.

Example 728: propan-2-yl 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H^yridm e-1-carboxylate



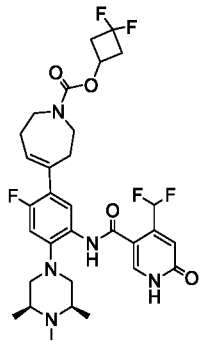
[001135] The procedure was similar to that of Example 253 using (S)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-4-fluoro-2-(trifluoromethyl)benzamide (25 mg, 0.051 mmol) and isopropyl chloroformate (0.048 mL, 0.048 mmol) to give the title compound (22 mg, 71 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ 7.85-7.92 (m, IH), 7.76 (dd, *J*=5.38, 8.44 Hz, IH), 7.65 (dd, *J*=2.32, 9.05 Hz, IH), 7.57 (dt, *J*=2.32, 8.3 IHz, IH), 7.00 (d, *J*=12.23 Hz, IH), 6.12 (br. s., IH), 4.90-4.97 (m, IH), 4.27 (d, *J*=1.59 Hz, 2H), 3.64 (br. s., 2H), 3.06-3.13 (m, IH), 3.03 (d, *J*=11.49 Hz, IH), 2.87-2.96 (m, 2H), 2.55 (t, *J*=10.82 Hz, IH), 2.43-2.51 (m, IH), 2.30-2.40 (m, 6H), 1.28-1.32 (m, 6H), 1.12 (d, *J*=6.36 Hz, 3H); LCMS [M+H]+ 581.5.

*Example 729: (1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino]-2-fluoro-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2, 3,6,***7-***tetrahydroazepine-l-carboxylate*



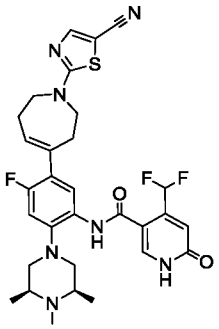
[001136] The procedure used was similar to that of Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.060 mmol) and 1-methylcyclobutyl (4-nitrophenyl) carbonate (15.72 mg, 0.063 mmol) to afford the title compound a white fluffy powder (29 mg, 0.045 mmol, 75 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 (s, 1H), 7.51 - 7.43 (m, 1H), 7.32 - 7.07 (m, 1H), 6.80 (br dd, *J*=3.3, 11.9 Hz, 1H), 6.70 (s, 1H), 5.92- 5.78 (m, 1H), 3.93 (br s, 1H), 3.59 - 3.50 (m, 2H), 3.50 - 3.40 (m, 1H), 2.90 (br d, *J*=ll.l Hz, 2H), 2.58 - 2.49 (m, 2H), 2.48 - 2.43 (m, 2H), 2.42 -2.33 (m, 3H), 2.28 - 2.18 (m, 5H), 2.06 - 1.98 (m, 2H), 1.81 (br d, *J*=5.1 Hz, 1H), 1.76 - 1.66 (m, 1H), 1.63 - 1.52 (m, 1H), 1.49 - 1.43 (m, 3H), 1.03 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ 616.

Example 730: (3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl] amino]-2-fluoro-4-[(3R, 5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2, 3,6,7-tetrahydroazepine-l-carboxylate



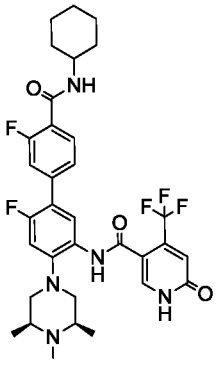
[001137] A procedure similar to that of Example 253 using 4-(difluoromethyl)-N-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.060 mmol) and 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (17.90 mg, 0.066 mmol) afforded the title compound was collected as a white fluffy powder (26 mg, 65.0 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 (br s, 1H), 7.51 - 7.41 (m, 1H), 7.31 - 7.07 (m, 1H), 6.80 (br d, *J*=11.9 Hz, 1H), 6.70 (s, 1H), 5.93 -5.79 (m, 1H), 3.98 (d, *J*=5.3 Hz, 1H), 3.60 (td, *J*=5.9, 15.2 Hz, 2H), 3.56 - 3.46 (m, 1H), 2.97 - 2.83 (m, 4H), 2.62 - 2.50 (m, 4H), 2.48 - 2.42 (m, 2H), 2.39 (br d, *J*=6.2 Hz, 2H), 2.24 (s, 3H), 1.86 - 1.78 (m, 1H), 1.03 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ 638.

Example 731: N-[5-[l-(5-cyano-l,3-thiazol-2-yl)-2,3,6, 7-tetrahydroazepin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide

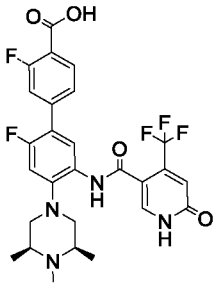


[001138] A procedure similar to that of Example 270 using 4-(difluoromethyl)-N-(4-fluoro-5-(2,3,6,7-tetrahydro-lH-azepin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide (30 mg, 0.060 mmol) and 2-bromo-5-cyanothiazole (11.26 mg, 0.060 mmol) afforded the title compound was collected as a white fluffy powder (32 mg, 0.050 mmol, 83 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 (s, 1H), 7.73 - 7.65 (m, 1H), 7.50 - 7.43 (m, 1H), 7.31 - 7.05 (m, 1H), 6.83 - 6.75 (m, 1H), 6.69 (s, 1H), 6.02 - 5.80 (m, 1H), 4.24 (br d, *J*=5.1 Hz, 1H), 3.85 - 3.71 (m, 3H), 2.90 (br d, *J*=ll.l Hz, 2H), 2.58 - 2.51 (m, 2H), 2.48 - 2.41 (m, 2H), 2.41 - 2.32 (m, 2H), 2.25 - 2.22 (m, 3H), 2.01 - 1.94 (m, 1H), 1.05 - 0.99 (m, 6H); LCMS $[M+H]^+$ 612.

Example 732: N-[5-[4-(cyclohexylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide

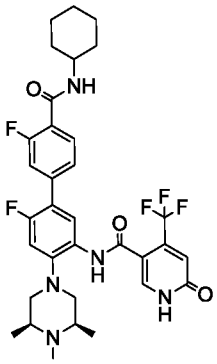


Step 1: 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l, 6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l ,l'-biphenyl]-4-carboxylic acid



[001139] The procedure followed was similar to Example 100 using N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinamide (300 mg, 0.495 mmol), 4-carboxy-3-fluorophenylboronic acid (137 mg, 0.743 mmol) to give, after deprotection of the silyloxy pyridyl intermediate, the title compound (193 mg, 88% yield) as a pale yellow powder. LCMS: [M+H]+ 565.2.

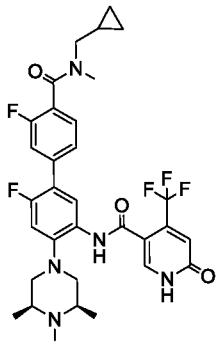
Step 2: N-[5-[4-(cyclohexylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-carboxamide



[001140] A 30 mL vial was charged with HATU (30.3 mg, 0.080 mmol) and cyclohexylamine (7.91 mg, 0.080 mmol). A stock solution of 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,l'-biphenyl]-4-carboxylic acid (30 mg, 0.053 mmol) in *N N*-dimethylformamide (2 ml) was added. The mixture was stirred at rt for 5 min upon which *N N*-diisopropylethylamine (0.037 ml, 0.213 mmol) was added via a syringe. The mixture was stirred at rt for 30 min, LCMS showed completion. The crude product was adsorbed on celite and dried and purified by reverse phase flash column chromatography (C18 13.3 g column, eluent: 10%, 10-70%, then 70% AcCN/water). The product fractions were concentrated under vacuum and lyophilized

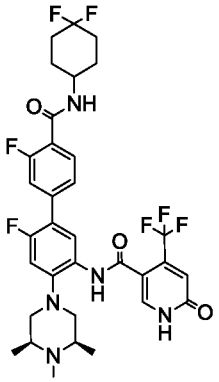
to afford the title compound as a white powder (4 mg, 5.89 μηιοϊ, 11.1 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.81 (m, 2H), 7.63 (t, *J*=7.8 Hz, IH), 7.37 (d, *J*=8.1 Hz, IH), 7.31 (d, *J*=12.0 Hz, IH), 6.98 (d, *J*=12.2 Hz, IH), 6.83 - 6.78 (m, IH), 3.85 - 3.75 (m, IH), 3.00 (br d, *J*=11.2 Hz, 2H), 2.56 - 2.50 (m, 2H), 2.47 (br d, *J*=5.0 Hz, 2H), 2.28 (s, 3H), 1.92 - 1.85 (m, 2H), 1.75 - 1.68 (m, 2H), 1.62 - 1.53 (m, IH), 1.39 - 1.12 (m, 6H), 1.07 (d, *J*=6.1 Hz, 6H); LCMS [M+H]$^+$ 646.

Example 733: N-[5-[4-[cyclopropylmethyl(methyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide



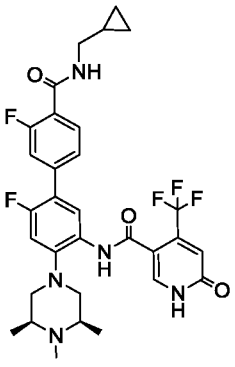
[001141] A procedure similar to Example 732 using 1-cyclopropyl-N-methylmethanamine (6.79 mg, 0.080 mmol) and 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,l'-biphenyl]-4-carboxylic acid (30 mg, 0.053 mmol) in Step 2 afforded the title compound as a white fluffy powder (4 mg, 6.02 μηιοϊ, 11.3 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.86 - 7.81 (m, 2H), 7.39 - 7.35 (m, IH), 7.33 (br d, *J*=8.1 Hz, IH), 7.30 (dd, *J*=1.5, 7.6 Hz, IH), 6.96 (d, *J*=12.2 Hz, IH), 6.79 - 6.76 (m, IH), 3.36 (d, *J*=7.1 Hz, IH), 3.08 (s, 2H), 3.06 - 3.02 (m, IH), 2.96 (br d, *J*=11.2 Hz, 2H), 2.94 - 2.89 (m, 2H), 2.53 - 2.46 (m, 2H), 2.45 - 2.36 (m, 2H), 2.24 (s, 3H), 1.04 (d, *J*=6.1 Hz, 6H), 0.90 - 0.80 (m, IH), 0.50 - 0.46 (m, IH), 0.44 - 0.39 (m, IH), 0.27 - 0.22 (m, IH), 0.02 - -0.04 (m, IH); LCMS [M+H]$^+$ 632.

Example 734: N-[5-[4-[(4, 4-difluorocyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)- 1H-pyridine-3-carboxamide



[001142] The procedure followed was similar to Example 732 using 4,4-difluorocyclohexylamine hydrochloride (13.68 mg, 0.080 mmol) and 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,l'-biphenyl]-4-carboxylic acid (30 mg, 0.053 mmol) in Step 2 to afford the title compound as an off-white fluffy powder (25.8 mg, 63.4 %yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.36 - 8.25 (m, IH), 7.89 - 7.85 (m, 2H), 7.63 (t, *J*=7.8 Hz, IH), 7.37 (d, *J*=8.1 Hz, IH), 7.32 (d, *J*=11.7 Hz, IH), 7.02 (d, *J*=12.1 Hz, IH), 6.84 - 6.80 (m, IH), 3.96 (br t, *J*=10.4 Hz, IH), 3.14 - 3.05 (m, 2H), 2.88 - 2.75 (m, 2H), 2.69 - 2.61 (m, 2H), 2.49 (s, 3H), 2.07 - 1.90 (m, 5H), 1.90 - 1.77 (m, 2H), 1.68 - 1.58 (m, 2H), 1.16 (d, *J*=6.4 Hz, 6H); LCMS $[M+H]^{+}$ 682.

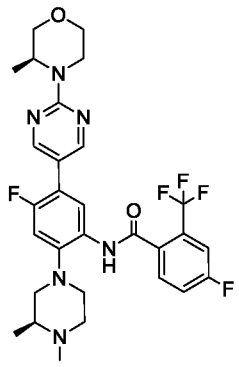
Example 735: N-[5-[4-(cyclopropylmethylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3A,5-trimethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluorom ethyl)-1H-pyridine-3-carboxamide



[001143] A similar procedure to that of Example 732 using aminomethylcyclopropane (5.67 mg, 0.080 mmol) and 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-

trimethylpiperazin-l-yl)-[l ,1'-biphenyl]-4-carboxylic acid (30 mg, 0.053 mmol) in Step 2 afforded the title compound as a white fluffy powder (1 mg, 2.4 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.83 (m, 2H), 7.69 (t, *J*=7.9 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 1H), 7.33 (br d, *J*=12.1 Hz, 1H), 6.98 (d, *J*=12.2 Hz, 1H), 6.83 - 6.78 (m, 1H), 3.00 (br d, *J*=ll.l Hz, 2H), 2.57 - 2.51 (m, 2H), 2.48 (br d, *J*=6.0 Hz, 2H), 2.28 (s, 3H), 1.07 (d, *J*=6.1 Hz, 6H), 1.04 - 0.97 (m, 1H), 0.47 - 0.42 (m, 2H), 0.23 - 0.17 (m, 2H); LCMS [M+H]$^+$ 618.

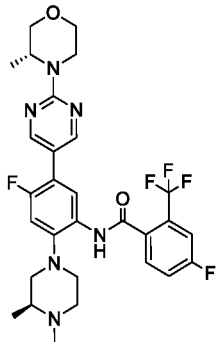
Example 736: 4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoro methyl)benzamide



[001144] To a 20 mL microwave vial charged with 5-bromo-2-chloropyrimidine (967 mg, 5 mmol) and (S)-3-methylmorpholine (0.62 mL, 5.5 mmol) was added EtOH (5 mL), followed by Eï$_3$N (1.40 mL, 10 mmol). The resulting mixture was heated in microwave at 120 °C for 1 h. Solvents were removed and the residue was dried to give the crude (S)-4-(5-bromopyrimidin-2-yl)-3-methylmorpholine as a light brown oil (1.152 g, 87%). LCMS [M + H]$^+$ 258.2. The title compound (formic acid salt, light yellow solid, 50.4 mg, 94% calcd. NMR purity, 37%) was prepared according to the second step described for the preparation of Example 660 using (S)-4-(5-bromopyrimidin-2-yl)-3-methylmorpholine in place of (S)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.56 (s, 2H), 8.39 (br s, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 7.80 (dd, *J*=5.3, 8.4 Hz, 1H), 7.65 (dd, *J*=2.4, 9.0 Hz, 1H), 7.56 (dt, *J*=2.5, 8.2 Hz, 1H), 7.17 (d, *J*=11.9 Hz, 1H), 4.78 - 4.72 (m, 1H), 4.38 (dd, *J*=2.6, 13.6 Hz, 1H), 3.98 (dd, *J*=3.7, 11.4 Hz, 1H), 3.79 (d, *J*=11.4 Hz, 1H), 3.71 (dd, *J*=3.1, 11.4 Hz, 1H), 3.56 (dt, *J*=3.1, 11.9 Hz, 1H), 3.38 - 3.32 (m, 2H),

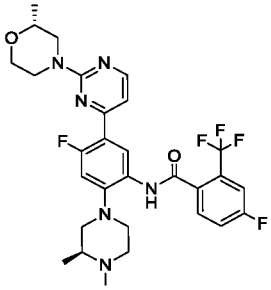
3.28 - 3.20 (m, 2H), 3.13 - 3.04 (m, IH), 3.01 (br d, *J*=9.2 Hz, 2H), 2.82 (dd, *J*=10.4, 12.5 Hz, IH), 2.71 (s, 3H), 1.34 - 1.28 (m, 6H); LCMS [M + H]$^+$ 591.3.

Example 737: 4-fluoro-N-[4-fluoro-2-[(3SJ-3,4-dimethylpiperazin-l -yl]-5-[2-[(3R)-3-methylmorpholin-4-ylJpyrimidin-5-ylJphenylJ-2-(trifluoromethyl)benzamide



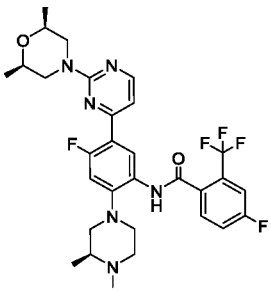
[001145] To a 20 mL microwave vial charged with 5-bromo-2-chloropyrimidine (967 mg, 5 mmol) and (R)-3-methylmorpholine (0.62 mL, 5.5 mmol) was added EtOH (5 mL), followed by EtsN (1.40 mL, 10 mmol). The resulting mixture was heated in microwave at 120 °C for 1 h. Solvents were removed and the residue was dried to give crude (R)-4-(5-bromopyrimidin-2-yl)-3-methylmo rpholine as a light brown oil (1.003 g, 74%). LCMS [M + H]$^+$ 258.2. The title compound (formic acid salt, light yellow solid, 36.5 mg, 89% calcd. NMR purity, 26%) was prepared according to the second step described above for the preparation of Example 736 using crude (R)-4-(5-bromopyrimidin-2-yl)-3-methylmorpholine in place of (S)-4-(5-bromopyrimidin-2-yl)-3-methylmorpholine. ¾ NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.46 (br s, IH), 8.05 (d, *J*=8.3 Hz, IH), 7.82 (dd, *J*=5.3, 8.5 Hz, IH), 7.67 (dd, *J*=2.4, 9.0 Hz, IH), 7.58 (dt, *J*=2.5, 8.2 Hz, IH), 7.18 (d, *J*=11.9 Hz, IH), 4.80 - 4.72 (m, IH), 4.40 (dd, *J*=2.6, 13.6 Hz, IH), 4.00 (dd, *J*=3.6, 11.3 Hz, IH), 3.81 (d, *J*=11.5 Hz, IH), 3.73 (dd, *J*=3.1, 11.5 Hz, IH), 3.58 (dt, *J*=3.0, 11.9 Hz, IH), 3.36 - 3.34 (m, IH), 3.28 - 3.17 (m, 3H), 3.07 (br t, *J*=10.9 Hz, IH), 2.94 - 2.84 (m, 2H), 2.81 - 2.74 (m, IH), 2.64 (s, 3H), 1.34 - 1.31 (m, 3H), 1.27 (d, *J*=6.4 Hz, 3H); LCMS [M+ H]$^+$ 591.3.

Example 738: 4-fluoro-N-[4-fluoro-2-[(3S)-3, 4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-ylJpyrimidin-4-ylJphenylJ-2-(trifluoromethyl)benzamide



[001146] The title compound (formic acid salt, pale beige solid, 68.8 mg, 53%) was prepared according to the second step described above for the preparation of Example 736 using (R)-4-(4-bromopyrimidin-2-yl)-2-methylmorpholine in place of (S)-4-(5-bromopyrimidin-2-yl)-3-methylmorpholine. ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.74 (d, *J*=8.2 Hz, IH), 8.41 (s, IH), 8.39 (s, IH), 7.77 (dd, *J=5.3,* 8.4 Hz, IH), 7.68 (dd, *J*=2.2, 9.0 Hz, IH), 7.58 (dt, *J*=2.2, 8.3 Hz, IH), 7.16 (d, *J*=5.8 Hz, IH), 7.12 - 7.08 (m, IH), 4.68 (br d, *J*=13.1 Hz, IH), 4.61 (br d, *J*=13.3 Hz, IH), 3.98 (dd, *J*=2.3, 11.5 Hz, IH), 3.71 - 3.59 (m, 2H), 3.40 - 3.34 (m, 2H), 3.17 - 2.97 (m, 4H), 2.92 - 2.81 (m, IH), 2.77 - 2.67 (m, 4H), 1.33 (d, *J*=6.4 Hz, 3H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 591.3.

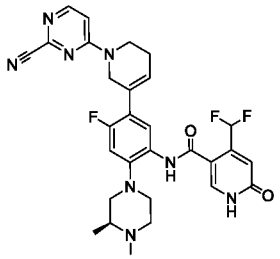
Example 739: 4-fluoro-N-[4-fluoro-5-[2-[(2R, 6S)-2, 6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R)-3,4^iimethylpiperazm-l-yl]phenyl]-2-(trifluoromethyl)benzam ide



[001147] The title compound (formic acid salt, pale beige solid, 74.3 mg, 57%) was prepared according to the second step described above for the preparation of example 736 using (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmo ϕ holine in place of (S)-4-(5-bromopyrirnidin-2-yl)-3-methylmorpholine. ¾ NMR (500MHz, METHANOL-d4) δ = 8.73 (d, *J*=8.3 Hz, IH), 8.45 (br s, IH), 8.38 (d, *J*=5.1 Hz, IH), 7.75 (dd, *J*=5.3, 8.3 Hz, IH), 7.67 (dd, *J*=2.1, 9.0 Hz, IH), 7.58 (dt, *J*=2.1, 8.2 Hz, IH), 7.15 (d, *J*=5.9 Hz, IH), 7.08 (d, *J*=13.1 Hz, IH), 4.74 - 4.64 (m, 2H), 3.74 - 3.62 (m, 2H), 3.39 - 3.23 (m, 3H),

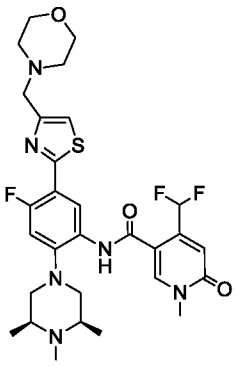
3.13 - 3.02 (m, 1H), 2.96 - 2.85 (m, 2H), 2.85 - 2.75 (m, 1H), 2.69 - 2.58 (m, 5H), 1.29 (d, *J*=6.2 Hz, 3H), 1.26 (d, *J*=6.2 Hz, 6H); LCMS [M+ H]$^+$ 605.3.

Example 740: N-[5-[l-(2-cyanopyrimidin-4-yl)-3, 6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide

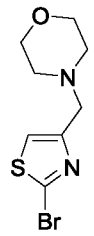


[001148] The procedure followed was similar to Example 270 using 4-bromopyrimidine-2-carbonitrile (10.64 mg, 0.058 mmol) and (S)-4-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(l,2,5,6-tetrahydropyridin-3-yl)phenyl)-6-oxo-l,6-dihydropyridine-3-carboxamide (25 mg, 0.053 mmol) to afford the title compound (17 mg, 53 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 8.13 - 8.05 (m, 1H), 7.93 - 7.87 (m, 1H), 7.64 - 7.57 (m, 1H), 7.33 - 7.08 (m, 1H), 6.92 - 6.83 (m, 2H), 6.74 - 6.67 (m, 1H), 6.13 - 6.05 (m, 1H), 4.52 - 4.16 (m, 2H), 3.98 - 3.66 (m, 2H), 3.03 - 2.96 (m, 1H), 2.96 - 2.90 (m, 1H), 2.84 - 2.77 (m, 2H), 2.46 - 2.39 (m, 2H), 2.38 - 2.33 (m, 2H), 2.32 - 2.25 (m, 4H), 1.03 - 0.99 (m, 3H); LCMS [M+H]+ 579.5.

Example 741: 4-(difluoromethyl)-N-[4-fluoro-5-[4-(morpholin-4-ylmethyl)-l, 3-thiazol-2-ylJ-2-[(3R5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



Step 1: 4-((2-bromothiazol-4-yl)methyl)morpholine



[001149] 2-Bromo-thiazole-4-carbaldehyde (0.15 g, 0.781 mmol), morpholine (0.14 niL, 1.6 mmol) and acetic acid (0.18 mL, 3.1 mmol) were mixed in anhydrous DCE (8 mL). After 5 min, sodium triacetoxyborohydride (0.50 g, 2.3 mmol) was added and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with DCM. The combined organic extracts were washed with a saturated brine solution and dried over magnesium sulfate. After removal of the inorganics by filtration the filtrate was concentrated in vacuo to afford 4-((2-bromothiazol-4-yl)methyl)morpholine (0.18 g, 47 %). LCMS [M+H]+: 263.1.

Step 2: 4-(Q-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-4-yl)methyl)morpholine

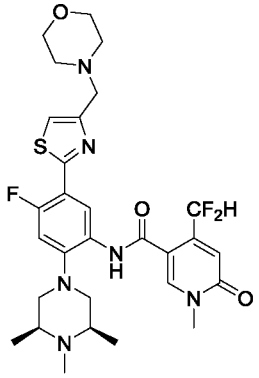
[001150] A reaction vial was charged with a mixture of 2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-methyl-l,3,6,2-dioxazaborocane-4,8-dione (0.075 g, 0.18 mmol), 6-bromo-l-methyl-lH-benzo[d]imidazole (0.056 g, 0.27 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.021 g, 0.018 mmol). The vial was sealed with a septum and evacuated and backfilled with nitrogen. 1,4-dioxane (5 mL) and 2 M aqueous sodium carbonate (0.5 mL) were added via syringe and the vial was evacuated and backfilled an additional time. The reaction was heated to 90 °C for 18 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash chromatography [0-10% MeOH/DCM + 0.1% NH_4OH] to

afford 4-((2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-4-yl)methyl)morpholine (0.090 g, 84 %). LCMS [M+H]+: 450.2.

Step 3: 4-fluoro-5-(4-(morpholinomethyl)thiazol-2-yl)-2-(cis-3,4,^-trimethylpiperazin-1-yl)aniline

[001151] A mixture of 4-((2-(2-fluoro-5-nitro-4-(cis-3,4,5-trimethylpiperazin-l-yl)phenyl)thiazol-4-yl)methyl)morpholine (0.090 g, 0.20 mmol) and tin chloride (0.11 g, 0.60 mmol) in EtOH (4 mL) was heated to 80 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated onto celite and purified by flash [0.5-10% MeOH/DCM + 0.5% NH_4OH] to afford 4-fluoro-5-(4-(morpholinomethyl)thiazol-2-yl)-2-(cis-3,4,5-trimethylpiperazin-l-yl)aniline (0.039 g, 46 %). LCMS [M+H]+: 420.4.

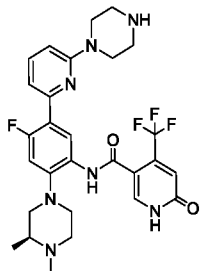
Step 4: 4-(difluoromethyl)-N-(4-fluoro-5-(4-(morpholinomethyl)thiazol-2-yl)-2-(cis-3,4,5-Mmethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide



[001152] 4-(Difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid (0.014 g, 0.068 mmol) was activated with HATU (0.026 g, 0.068 mmol) and N,N-diisopropylethylamine (0.012 mL, 0.068 mmol) in DMF (1 mL). After agitating for 5 min the solution of activated acid was added dropwise to a stirring solution of 4-fluoro-5-

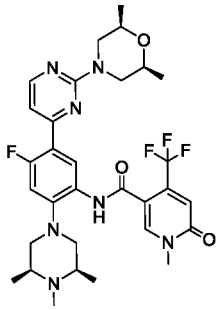
(4-(morpholinomethyl)thiazol-2-yl)-2-(cis-3,4,5-trimethylpiperazin-1-yl)aniline (0.019 g, 0.045 mmol) in DMF (1 mL) and the reaction warmed to 40 °C for 18 h. The reaction mixture was loaded onto celite and purified by flash chromatography [0.5-10% MeOH/DCM + 0.5% NH_4OH]. The product containing fractions were combined and concentrated onto celite and repurified by reverse phase chromatography [5-95% MeCN / 10 mM $NH4HCO_3$] to afford the title compound 4-(difluoromethyl)-N-(4-fluoro-5-(4-(morpholinomethyl)thiazol-2-yl)-2-(cis-3,4,5-trimethylpiperazin-1-yl)phenyl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (0.0089 g, 32%). ¾ NMR (500MHz, DMSO-d6) δ = 9.60 (s, 1H), 8.43 (s, 1H), 8.26 (d, *J*=8.2 Hz, 1H), 7.58 (s, 1H), 7.49 - 7.20 (m, 1H), 7.08 (d, *J*=13.2 Hz, 1H), 6.64 (s, 1H), 3.64 (s, 2H), 3.58 (t, *J*=4.5 Hz, 4H), 3.52 (s, 3H), 3.13 (br d, *J*=11.4 Hz, 2H), 2.47 (s, 1H), 2.44 (br s, 3H), 2.38 - 2.28 (m, 2H), 2.18 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 605.3.

Example 742: N-[4-fluoro-5-(5-piperazin-1-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide



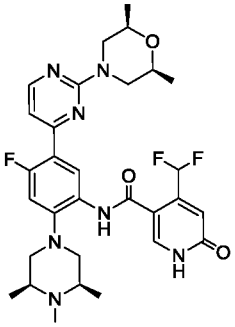
[001153] The title compound was prepared similar to the sequence described for the preparation of Example 698 using 4-Boc-1-(6-bromo-2-pyridyl)piperazine in place of (2S,6R)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine. ^1H NMR (500 MHz, MeOD) δ 8.55 (d, *J* = 8.6 Hz, 1H), 7.99 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.00 (d, *J* = 12.9 Hz, 1H), 6.84 (s, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 3.68 (dd, *J* = 6.2, 4.3 Hz, 4H), 3.16 - 3.12 (m, 1H), 3.10 (dt, *J* = 11.7, 2.7 Hz, 1H), 3.07 - 3.04 (m, 4H), 2.94 (td, *J* = 10.6, 2.8 Hz, 2H), 2.58 - 2.52 (m, 2H), 2.42 - 2.38 (m, 1H), 2.36 (s, 3H), 1.13 (d, *J* = 6.4 Hz, 3H); LCMS $[M+l]^+$ = 574.32.

Example 743: N-[4-fluoro-5-[2-[(2R,6SJ-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(Mfluoro methyl)pyridine-3-carboxamide



[001154] The title compound (25 mg, 26% yield) was prepared similar to the sequence described above for the preparation of Example 693 from N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide (113 mg, 0.155 mmol) and (2R,6S)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine (46.4 mg, 0.170 mmol). ^{1}H NMR (500 MHz, MeOD) δ 8.64 (d, *J* = 8.2 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.18 (s, 1H), 7.11 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.02 (d, *J* = 13.2 Hz, 1H), 6.94 (s, 1H), 4.68 (d, *J* = 12.9 Hz, 2H), 3.70 - 3.65 (m, 2H), 3.64 (s, 3H), 3.14 (d, *J* = 11.5 Hz, 2H), 2.65 - 2.58 (m, *J* = 13.4, 11.0 Hz, 4H), 2.53 (s, 2H), 2.36 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.17 (d, *J* = 6.2 Hz, 6H); LCMS HSS $[M+l]^+$ = 632.41.

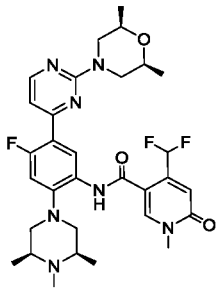
Example 744: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6SJ-2,6-dimethylmorpholin-4-ylJpyrimidin-4-ylJ-2-[(3S,5R)-3,4,5-trimethylpiperazm-l-ylJphenylJ-6 -oxo-1H-pyridine-3-carboxamide



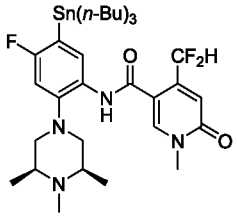
[001155] The title compound (26.2 mg, 29% yield) was prepared similar to the sequence described above for the preparation of Example 692 using 4-(difluoromethyl)-N-(4-fluoro-5-(tribu†ylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-6-(2-(trimethylsilyl)ethoxy Nicotinamide (111 mg, 0.139 mmol) and (2R,6S)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine (41.7 mg, 0.153 mmol).

^{1}H NMR (500 MHz, MeOD) δ 8.50 (d, ***J*** = 8.2 Hz, 1H), 8.35 (d, ***J*** = 5.2 Hz, 1H), 7.98 (s, 1H), 7.32 (t, ***J*** = 55.1 Hz, 1H), 7.10 (dd, ***J*** = 5.2, 1.9 Hz, 1H), 6.99 (d, ***J*** = 13.2 Hz, 1H), 6.81 (s, 1H), 4.67 (d, ***J*** = 12.4 Hz, 2H), 3.66 (ddd, ***J*** = 10.5, 6.3, 2.4 Hz, 2H), 3.16 (d, ***J*** = 11.3 Hz, 2H), 2.61 (dt, ***J*** = 13.1, 9.3 Hz, 4H), 2.55 - 2.50 (m, 2H), 2.36 (s, 3H), 1.23 (d, ***J*** = 6.2 Hz, 6H), 1.16 (d, ***J*** = 6.2 Hz, 6H); LCMS $[M+l]^+$ = 600.35.

Example 745: 4-(difluoromethyl)-N-[4-fluoro-5-[2-[(2R, 6SJ-2, 6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-l-m ethyl-6-oxopyridine-3-carboxamide



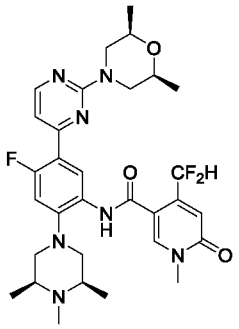
Step 1: 4-(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-Mmethylpiperazin-l-yl)phenyl)-l-methyl-6 -oxo-l,6-dihy dropyridine-3-carboxamide



[001156] To a stirred solution of N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-4-(difluoromethyl)- 1-methyl-6-oxo- 1,6-dihydropyridine-3-carboxamide (6 g, 12.0 mmol, leq, prepared as described in Example 416) in toluene: DMF (60:5mL) degassed with argon for 15min, then hexabutylditin (12.22mL, 24.0mmol, 2eq) was added, followed by $Pd_2(dppf)_2Cl_2$ (0.97g, 1.2mmol, O.leq) and after that heated to reflux under argon atmosphere for 24h. TLC analysis indicated formation of less polar spots. The reaction mixture was filtered through celite bed washed with EtOAc; the filtrate was evaporated under reduced pressure. The crude compound was purified by column chromatography (neutral alumina) using 0-50% EtOAc in pet ether as an eluent to afford ***4-***(difluoromethyl)-N-(4-fluoro-5-(tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-

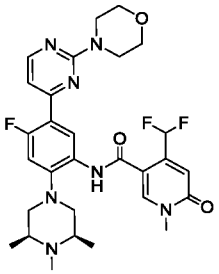
l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (4.3 g, 50%) as an off white solid. LCMS: [M+H]+ 713.46.

Step 2: 4-(difluoromethyl)-N-(5-(2-((2S, 6R)-2, 6-dimethylmorpholino)pyrimidin-4-yl)-4-fluoro-2-(ʻ3S, 5R)-3, 4, 5-trimethylpiperazin-l -yl)phenyl)-l -methyl-6-oxo-l, 6-dihydropyridine-3-carboxamide



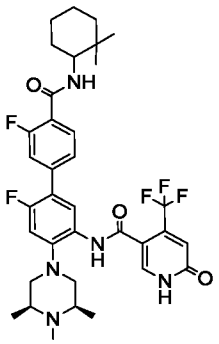
[001157] In N,N-dimethylformamide (DMF) (635 μï) was dissolved 4-(difluoromethyl)-N-(4-fluoro-5-(tribu†ylstamyl)-2-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (113 mg, 0.159 mmol). To the solution was added (2R,6S)-4-(4-bromopyrimidin-2-yl)-2,6-dimethylmorpholine (47.5 mg, 0.175 mmol), lithium chloride (20.20 mg, 0.476 mmol) and bis(triphenylphosphine)palladium(II) dichloride (6.13 mg, 8.74 μηιοï) at room temperature and then it was microwaved at the temperature of 120 °C for 3 hours. To the reaction mixture was added water and then it was extracted with DCM. The organic layer was separated, concentrated and purified by column chromatography on silica gel (0-100%, 89% CH_2Cl_2, 10% MeOH, 1% NH_4Ac/CH_2Cl_2) the fractions were concentrated and freeze dried for 2 days to afford the product as a white powder. ^{1}H NMR (500 MHz, MeOD) δ 8.47 (d, *J* = 8.1 Hz, 1H), 8.35 (d, *J* = 5.4 Hz, 1H), 8.26 (s, 1H), 7.29 (t, *J* = 55.2 Hz, 1H), 7.09 (dd, *J* = 5.1, 2.2 Hz, 1H), 7.00 (d, *J* = 13.2 Hz, 1H), 6.82 (s, 1H), 4.66 (dd, *J* = 13.4, 2.2 Hz, 2H), 3.66 (ddd, *J* = 6.8, 5.3, 2.4 Hz, 2H), 3.64 (s, 3H), 3.16 (d, *J* = 11.7 Hz, 2H), 2.64 - 2.57 (m, 4H), 2.50 (ddd, *J* = 10.8, 6.7, 3.4 Hz, 2H), 2.35 (s, 3H), 1.23 (d, *J* = 6.1 Hz, 6H), 1.15 (d, *J* = 6.1 Hz, 6H); LCMS [M+l] $^+$ = 614.35.

Example 746: 4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]pheriyl]-l-methy l-6-oxopyridine-3-carboxamide



[001158] The title compound (19.7 mg, 22% yield) was prepared similar to the sequence described above for the preparation of Example 745 using 4-(difluoromethyl)-N-(4-fluoro-5<tributylstannyl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxamide (111 mg, 0.156 mmol) and 4-(4-bromopyrimidin-2-yl)morpholine (38.1 mg, 0.156 mmol). 'H NMR (500 MHz, MeOD) δ 8.41 (d, *J* = 8.2 Hz, IH), 8.37 (d, *J* = 5.2 Hz, IH), 8.29 (s, IH), 7.28 (t, *J* = 55.2 Hz, IH), 7.12 (dd, *J* = 5.2, 2.0 Hz, IH), 6.99 (d, *J* = 13.3 Hz, IH), 6.81 (s, IH), 3.84 - 3.82 (m, 4H), 3.76 - 3.74 (m, 4H), 3.63 (s, 3H), 3.16 (d, *J* = 11.8 Hz, 2H), 2.61 (t, *J* = 11.2 Hz, 2H), 2.50 (s, 2H), 2.34 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 6H); LCMS $[M+l]^+$ = 586.36.

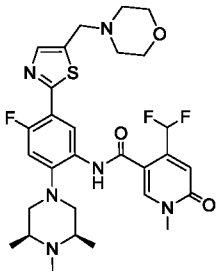
Example 747: N-[5-[4-[(2,2-dimethylcyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]pheriyl]-6^xo-4-(Mflw romethyl)-1H-pyridine-3-carboxamide



[001159] A procedure similar to that of Example 732 using 2,2-dimethylcyclohexanamine (10.14 mg, 0.080 mmol) and 2',3-difluoro-5'-(6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamido)-4'-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l,l'-biphenyl]-4-carboxylic acid (30 mg, 0.053 mmol) afforded the title compound as an off-white fluffy powder (15.4 mg, 38.2 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.89 - 7.81 (m, 3H), 7.64 (t, *J*=7.9 Hz, IH), 7.38 (d, *J*=8.1 Hz, IH), 7.33 (d, *J*=11.9 Hz, IH), 7.01 (d, *J*=12.1 Hz, IH), 6.83 (s,

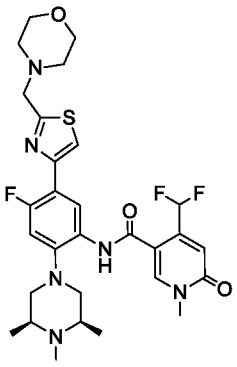
IH), 3.85 - 3.77 (m, IH), 3.06 (br d, J=11.9 Hz, 2H), 2.67 (br s, 2H), 2.63 - 2.57 (m, 2H), 2.41 (s, 3H), 1.72 - 1.64 (m, IH), 1.62 - 1.56 (m, IH), 1.52 - 1.41 (m, 3H), 1.40 - 1.23 (m, 3H), 1.13 (d, J=6.1 Hz, 6H), 0.91 (s, 3H), 0.87 (s, 3H); LCMS [M+H]$^+$ 674.

Example 748: 4-(difluoromethyl)-N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)-l, 3-thiazol-2-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001160] The title compound was prepared similar to the procedure described above for the preparation of Example 741 using 2-bromo-5-formylthiazole in place of 2-bromo-thiazole-4-carbaldehyde in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.57 (s, IH), 8.38 (s, IH), 8.32 (br d, J=8.1 Hz, IH), 7.78 (s, IH), 7.53 - 7.19 (m, IH), 7.09 (br d, J=12.7 Hz, IH), 6.64 (s, IH), 3.78 (s, 2H), 3.58 (br t, J=4.3 Hz, 4H), 3.52 (s, 3H), 3.14 (br d, J=9.9 Hz, 2H), 2.42 (br s, 4H), 2.38 - 2.27 (m, 2H), 2.18 (br s, 3H), 1.01 (br s, 6H); LCMS [M+H]+: 605.1.

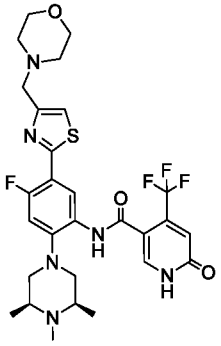
Example 749: 4-(difluoromethyl)-N-[4-fluoro-5-[2-(morpholin-4-ylmethyl)-l, 3-thiazol-4-ylJ-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-ylJphenylJ-l-methyl-6-oxopyridine-3-carboxamide



[001161] The title compound was prepared similar to the procedure described above for the preparation of Example 741 using 4-bromo-2-formylthiazole in place of

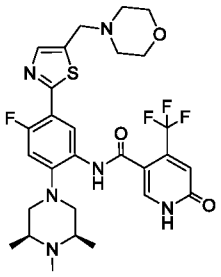
2-bromo-thiazole-4-carbaldehyde in Step 1. ^{1}H NMR (500MHz, DMSO-d6) δ = 9.49 (s, IH), 8.42 (s, IH), 8.21 (d, *J*=8.3 Hz, IH), 7.83 (d, *J*=2.3 Hz, IH), 7.51 - 7.19 (m, IH), 7.02 (d, *J*=13.2 Hz, IH), 6.64 (s, IH), 3.87 (s, 2H), 3.65 - 3.58 (m, 4H), 3.52 (s, 3H), 3.06 (br d, *J*=ll.l Hz, 2H), 2.53 (br s, 4H), 2.46 - 2.46 (m, IH), 2.47 - 2.42 (m, IH), 2.35 - 2.28 (m, 2H), 2.18 (s, 3H), 0.99 (d, *J*=6.0 Hz, 6H); LCMS [M+H]+: 605.3.

Example 750: N-[4-fluoro-5-[4-(morpholin-4-ylmethyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



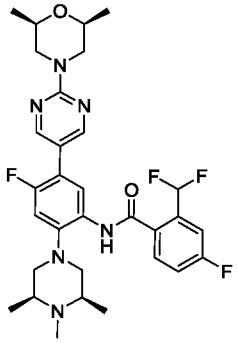
[001162] The title compound was prepared similar to the procedure described above for the preparation of Example 741 using 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in place of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in Step 4. ¾ NMR (500MHz, DMSO-d6) δ = 9.60 (s, IH), 8.35 (d, *J*=8.1 Hz, IH), 7.97 (s, IH), 7.58 (s, IH), 7.07 (d, *J*=13.1 Hz, IH), 6.81 (s, IH), 3.65 (s, 2H), 3.58 (t, *J*=4.5 Hz, 4H), 3.11 (br d, *J*=11.4 Hz, 2H), 2.48 (br s, IH), 2.45 (br d, *J*=4.9 Hz, 4H), 2.39 - 2.31 (m, 2H), 2.19 (s, 3H), 1.00 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 609.3.

Example 751: N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-Mmethylpiperazin-l-yl]phenyl]-6<>xo-4-(Mfluoromethyl)-lH-pyridine-3-car^ oxamide



[001163] The title compound was prepared similar to the procedure described above for the preparation of Example 748 using 4-(trifluoromethyl)-6-(2-(trimethylsilyl)ethoxy)nicotinic acid in place of 4-(difluoromethyl)-l-methyl-6-oxo-l,6-dihydropyridine-3-carboxylic acid in Step 4. ¾ NMR (500MHz, DMSO-d6) δ = 12.77 - 12.17 (m, 1H), 9.55 (s, 1H), 8.42 (d, *J*=8.2 Hz, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 7.07 (d, *J*=13.1 Hz, 1H), 6.78 (s, 1H), 3.78 (s, 2H), 3.58 (br t, *J*=4.3 Hz, 4H), 3.11 (br d, *J*=ll.l Hz, 2H), 2.49 - 2.46 (m, 2H), 2.42 (br s, 4H), 2.39 - 2.31 (m, 2H), 2.19 (s, 3H), 1.01 (d, *J*=6.1 Hz, 6H); LCMS [M+H]+: 609.2.

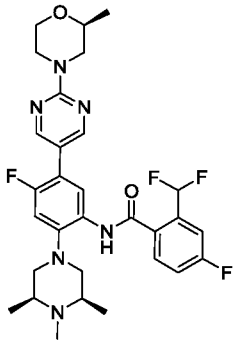
Example 752: 2-(difluoromethyl)-N-(5-(2-((2S, 6R)-2, 6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-(⁽3S,5R)-3, 4,5-trimethylpiperazin-l-yl)phenyl)-4-fluorobenzamide



[001164] A mixture of 2-(difluoromethyl)-4-fiuorobenzoic acid (171 mg, 0.9 mmol), HATU (342 mg, 0.9 mmol) and N,N-diisopropylethylamine (0.21 ml, 1.2 mmol) in DMF (2 mL) was heated at 70 °C for 1 min to afford a clear solution before 5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)aniline (190 mg, 0.6 mmol) was added in one portion. The resulting mixture was heated at 70 °C for 2 h. It was diluted with EtOAc (20 mL) and washed with **H_20** (30 mL x 2), concentrated and purified by flash chromatography (EtOAc/hex 0-100%, then MeOH/DCM 0-5%) to give crude N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-2-(difluoromethyl)-4-fluorobenzamide as a dark brown (416 mg, 70% assuming full conversion). LCMS $[M + H]^+$ 488.0. It was redissolved in dioxane (12 mL) and divided equally into 3 portions (each 4 mL, 0.2 mmol). The title compound (formic acid salt, white solid, 26.7 mg, 21%) was prepared according to a procedure similar to Example 31 using (2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)boronic acid (71 mg, 0.3 mmol) and crude N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-2-(difluoromethyl)-4-fluorobenzamide in dioxane (0.2 mmol). ^{1}H NMR

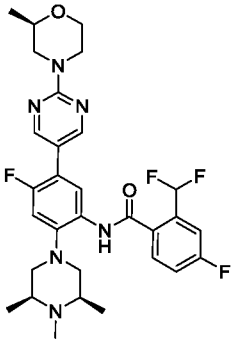
(500MHz, METHANOL-d4) δ = 8.54 (br s, 2H), 8.35 (br s, IH), 7.95 (br d, *J*=8.1 Hz, IH), 7.90 - 7.83 (m, IH), 7.54 (br d, *J*=9.2 Hz, IH), 7.48 - 7.24 (m, 2H), 7.19 (d, *J*=11.9 Hz, IH), 4.63 (br d, *J*=13.0 Hz, 2H), 3.68 - 3.61 (m, 2H), 3.42 - 3.33 (m, 2H), 3.30 - 3.24 (m, 2H), 2.94 (br d, *J*=10.8 Hz, 2H), 2.84 (br s, 3H), 2.65 - 2.57 (m, 2H), 1.38 (br d, *J*=6.2 Hz, 6H), 1.23 (br d, *J*=6.1 Hz, 6H); LCMS [M+ H]$^+$ 601.4.

Example 753: 2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((S)-2-methylmorpholino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-Mmethylpiperazin-l-yl)phenyl)benzamide



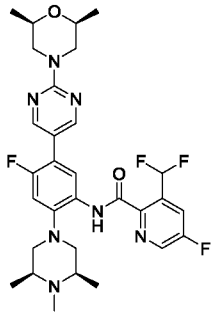
[001165] The title compound (formic acid salt, white solid, 36.5 mg, 29%) was prepared by a procedure similar to Example 31 using crude (S)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.6 mmol) and crude N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-2-(difluoromethyl)-4-fluorobenzamide (preparation described in Example 752) in dioxane (0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.37 (br s, IH), 7.97 (br d, *J*=8.2 Hz, IH), 7.91 - 7.82 (m, IH), 7.56 (dd, *J*=2.1, 9.2 Hz, IH), 7.50 - 7.26 (m, 2H), 7.20 (d, *J*=11.9 Hz, IH), 4.65 - 4.52 (m, 2H), 3.99 (dd, *J*=2.6, 11.5 Hz, IH), 3.67 - 3.57 (m, 2H), 3.32 - 3.24 (m, 4H), 3.13 - 3.02 (m, IH), 2.93 (br t, *J*=12.3 Hz, 2H), 2.83 (s, 3H), 2.74 (dd, *J*=10.5, 13.2 Hz, IH), 1.38 (d, *J*=6.4 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS [M + H]$^+$ 587.3.

Example 754: 2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-Mmethylpiperazin-l-yl)phenyl)benzamide



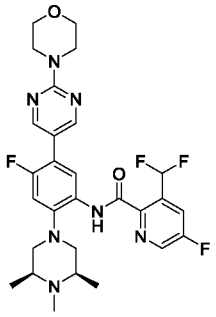
[001166] The title compound (formic acid salt, white solid, 12.3 mg, 89% calcd. NMR purity, 9%) was prepared according to a procedure similar to Example 31 using crude (R)-(2-(2-methylmo rpholino)pyrimidin-5-yl)boronic acid (0.6 mmol + 0.3 mmol) and crude N-(5-bromo-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)-2-(difluoromethyl)-4-fluorobenzamide in dioxane (0.2 mmol). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.57 (s, 2H), 8.42 (br s, IH), 7.97 (br d, *J*=8.1 Hz, IH), 7.88 (br dd, *J*=5.5, 7.9 Hz, IH), 7.56 (dd, *J*=2.4, 9.3 Hz, IH), 7.51 - 7.26 (m, 2H), 7.18 (d, *J*=12.0 Hz, IH), 4.66 - 4.55 (m, 2H), 3.99 (dd, *J*=2.4, 11.6 Hz, IH), 3.69 - 3.58 (m, 2H), 3.27 (br d, *J*=12.3 Hz, 2H), 3.15 - 3.03 (m, 3H), 2.84 (br t, *J*=11.8 Hz, 2H), 2.77 - 2.68 (m, 4H), 1.33 (d, *J*=6.4 Hz, 6H), 1.25 (d, *J*=6.2 Hz, 3H); LCMS $[M + H]^{+}$ 587.4.

Example 755: 3-(difluoromethyl)-N-(5-(2-((2S, 6R)-2, 6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluo ropicolinamide



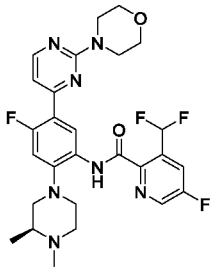
[001167] The title compound was collected as a yellow fluffy powder (41.5 mg, 0.066 mmol, 69.7 % yield). ^{1}HNMR (500MHz, METHANOL-d4) δ = 8.78 (br s, IH), 8.58 (s, 2H), 8.55 (br d, *J*=8.2 Hz, IH), 8.17 (br d, *J*=8.3 Hz, IH), 8.14 - 7.90 (m, IH), 7.14 (br d, *J*=11.7 Hz, IH), 4.66 (br d, *J*=13.0 Hz, 2H), 3.74 - 3.63 (m, 2H), 3.06 (br d, *J*=8.9 Hz, 2H), 2.76 - 2.63 (m, 6H), 2.46 (s, 3H), 1.26 (br d, *J*=6.1 Hz, 6H), 1.19 (br d, *J*=5.0 Hz, 6H); LCMS $[M+H]^{+}$ 602.

Example 756: 3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin- -5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide



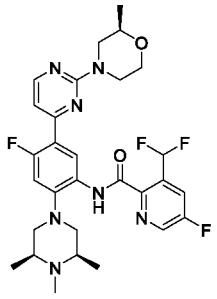
[001168] The title compound was collected as a tan fluffy powder (36 mg, 0.058 mmol, 70.6 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 8.66 (d, *J*=2.6 Hz, IH), 8.47 (d, *J*=l.l Hz, 2H), 8.42 (d, *J*=8.3 Hz, IH), 8.04 (dd, *J*=2.4, 8.9 Hz, IH), 8.01-7.78 (m, IH), 7.05 - 6.98 (m, IH), 3.77 - 3.72 (m, 4H), 3.69 - 3.62 (m, 4H), 2.96 - 2.91 (m, 2H), 2.62 - 2.52 (m, 4H), 2.34 (s, 3H), 1.07 (d, *J*=5.7 Hz, 6H); LCMS $[M+H]^+$ 574.

Example 757: (S)-3-(difluoromethyl)-N-(2-(3, 4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrimidin-4-yl)phenyl)-5-fluoropicolinamide



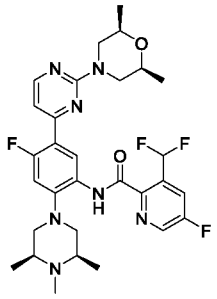
[001169] The title compound was collected as a beige fluffy powder (25 mg, 0.042 mmol, 40.6 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.04 (d, *J*=8.2 Hz, IH), 8.67 (d, *J*=2.6 Hz, IH), 8.29 (d, *J*=5.3 Hz, IH), 8.05 (dd, *J*=2.5, 8.9 Hz, IH), 8.02- 7.79 (m, IH), 7.03 - 6.98 (m, 2H), 3.81 - 3.78 (m, 4H), 3.71 - 3.68 (m, 4H), 3.05 - 2.99 (m, 2H), 2.92 - 2.86 (m, 2H), 2.60 - 2.42 (m, 4H), 2.33 (s, 3H), 1.04 (d, *J*=6.1 Hz, 3H); LCMS $[M+H]^+$ 560.

Example 758: 3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyrimidin-4-yl)-2-((3S, 5R)-3,4,5-trimethylpiperazin-l -yl)phenyl)picolinamide



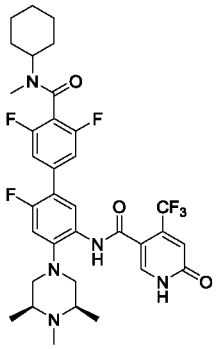
[001170] The title compound was collected as a tan fluffy powder (56 mg, 0.091 mmol, 63.1 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.14 (d, *J*=8.3 Hz, IH), 8.63 (d, *J*=2.6 Hz, IH), 8.26 (d, *J*=5.1 Hz, IH), 8.03 (dd, *J*=2.4, 8.8 Hz, IH), 8.00-7.76 (m, IH), 7.01 (dd, *J*=*l.9,* 5.2 Hz, IH), 6.93 (d, *J*=12.8 Hz, IH), 4.64 (br d, *J*=13.0 Hz, IH), 4.50 (br d, *J*=13.3 Hz, IH), 3.88 (dd, *J*=2.6, 11.5 Hz, IH), 3.59 - 3.51 (m, 2H), 3.02 - 2.96 (m, 3H), 2.63 (dd, *J*=10.5, 13.2 Hz, IH), 2.59 - 2.51 (m, 4H), 2.33 (s, 3H), 1.17 (d, *J*=6.2 Hz, 3H), 1.06 (d, *J*=5.6 Hz, 6H); LCMS [M+H]$^+$ 588.

Example 759: 3-(difluoromethyl)-N-(5-(2-((2S, 6R)-2, 6-dimethylmorpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide



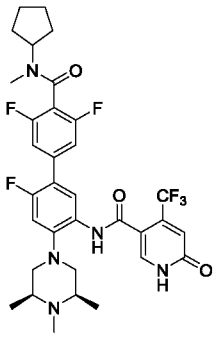
[001171] The title compound was collected as a dark beige fluffy powder (39 mg, 0.062 mmol, 42.9 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 9.24 (br d, *J*=8.1 Hz, IH), 8.65 (br s, IH), 8.26 (br d, *J*=4.9 Hz, IH), 8.04 (br d, *J*=7.9 Hz, IH), 8.01 - 7.77 (m, IH), 7.02 (br d, *J*=3.8 Hz, IH), 6.95 (br d, *J*=12.8 Hz, IH), 4.64 (br d, *J*=12.8 Hz, 2H), 3.59 (br s, 2H), 3.02 (br d, *J*=9.4 Hz, 2H), 2.62 -2.52 (m, 7H), 2.34 (s, 3H), 1.17 (br d, *J*=6.0 Hz, 6H), 1.07 (br d, *J*=5.0 Hz, 6H); LCMS [M+H]$^+$ 602.

Example 760: N-(4 '-(cyclohexyl(methyl)carbamoyl)-3 ',5',6-trifluoro-4-((*3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide*



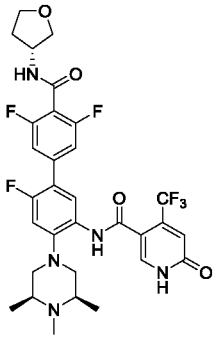
[001172] The title compound was collected as an off-white fluffy powder (13.9 mg, 0.019 mmol, 29.1 % yield). IH NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.82 (m, 2H), 7.22 (dd, *J*=8.6, 11.4 Hz, 2H), 6.99 (dd, *J*=4.3, 12.4 Hz, IH), 6.83 - 6.79 (m, IH), 4.39 (tt, *J*=3.7, 12.0 Hz, IH), 3.00 (br d, *J*=ll.l Hz, 2H), 2.94 (s, 2H), 2.78 (s, IH), 2.56 - 2.50 (m, 2H), 2.48 - 2.39 (m, 2H), 2.27 (s, 3H), 1.80 (br d, *J*=13.3 Hz, IH), 1.75 - 1.67 (m, 2H), 1.64 - 1.56 (m, 3H), 1.51 (dt, *J*=3.1, 12.3 Hz, 2H), 1.42 - 1.32 (m, IH), 1.06 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ 678.

Example 761: N-(4'-(cyclopentyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



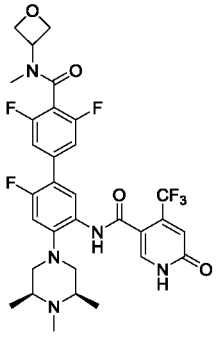
[001173] The title compound was collected as an off-white fluffy powder (19.7 mg, 0.028 mmol, 54.8 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.86 (s, IH), 7.85 - 7.83 (m, IH), 7.22 (br d, *J*=8.3 Hz, 2H), 7.00 (d, *J*=12.3 Hz, IH), 6.84 - 6.81 (m, IH), 3.96 (quin, *J*=7.8 Hz, IH), 3.05 - 2.97 (m, 2H), 2.94 (s, 2H), 2.79 (s, IH), 2.61 - 2.49 (m, 4H), 2.33 (s, 3H), 1.91 - 1.83 (m, IH), 1.78 - 1.69 (m, 2H), 1.68 - 1.56 (m, 4H), 1.43 (br s, IH), 1.09 (br d, *J*=5.5 Hz, 6H); LCMS $[M+H]^+$ 664.

Example 762: 6-oxo-N-(3',5\ 6-trifluoro-4'-(((R)-tetrahydrofuran-3-yl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



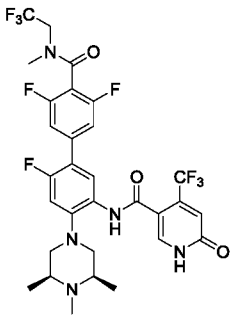
[001174] The title compound was collected as a white fluffy powder (15.7 mg, 0.023 mmol, 44.4 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.86 (s, IH), 7.83 (d, *J*=8.2 Hz, IH), 7.17 (d, *J*=8.4 Hz, 2H), 6.98 (d, *J*=12.3 Hz, IH), 6.83 - 6.80 (m,lH), 4.54 . 4.45 (m, IH), 3.89 - 3.81 (m, 2H), 3.74 (dt, *J*=5.5, 8.4 Hz, IH), 3.64 (dd, *J*=3.4, 9.3 Hz, IH), 3.00 (br d, *J*=ll.l Hz, 2H), 2.57 - 2.42 (m, 4H), 2.29 (s, 3H), 2.21 (qd, *J*=7.7, 13.0 Hz, IH), 1.90 - 1.82 (m, IH), 1.07 (d, *J*=6.1 Hz, 6H); LCMS $[M+H]^+$ 652.

Example 763: 6-oxo-N-(3',5\ 6-trifluoro-4'-(methyl(oxetan-3-yl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



[001175] The title compound was collected as a white fluffy powder (14 mg, 0.020 mmol, 32.1 % yield). ¾ NMR (500MHz, METHANOL-d4) δ = 7.88 - 7.83 (m, 2H), 7.24 (t, *J*=7.6 Hz, 2H), 7.00 (d, *J*=12.2 Hz, IH), 6.83 - 6.81 (m, IH), 5.37 (quin, *J*=7.2 Hz, IH), 4.96 - 4.86 (m, IH), 3.32 (s, 2H), 3.03 (s, 2H), 3.01 (s, IH), 2.59 - 2.43 (m, 5H), 2.30 (s, 3H), 1.08 (d, *J*=5.9 Hz, 6H); LCMS $[M+H]^+$ 652.

Example 764: 6-oxo-N-(3',5',6-trifluoro-4'-(methyl(2,2,2-trifluoroethyl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)-[l, 1'-biphenyl]-3-yl)-4-(trifluoromethyl)-l ,6-dihydropyridine-3-carboxamide



[001176] The title compound was collected as a white fluffy powder (16.9 mg, 0.024 mmol, 46.0 % yield). ^{1}H NMR (500MHz, METHANOL-d4) δ = 7.87 (t, *J*=4.0 Hz, 2H), 7.28 - 7.22 (m, 2H), 7.03 (d, *J*=12.2 Hz, 1H), 6.83 (s, 1H), 4.27 (q, *J*=9.1 Hz, 2H), 4.03 - 3.97 (m, 1H), 3.09 (br d, *J*=12.0 Hz, 2H), 3.03 (s, 3H), 2.76 (br d, *J*=2.3 Hz, 2H), 2.67 - 2.58 (m, 2H), 2.46 (br s, 3H), 1.15 (d, *J*=6.2 Hz, 6H); LCMS $[M+H]^+$ 678.

C. Biological Assays

[001177] Compounds of the present application displayed inhibition of the binding between WDR5 and its binding partners as evidenced in the following assays:

(i) Surface Plasmon Resonance (SPR) Assay

Protocol

[001178] Exemplary compounds of the application were dissolved in 100% DMSO at lOmM, assayed fresh, and then stored at -20°C for repeat studies and other experiments. Full length WDR5 with an N-terminal His tag and C-terminal AviTag (Avidity Inc.) was expressed in E. coli with coexpression of BirA to biotin labelled protein *in vivo.* Purification of the protein was performed using Ni-NTA. The purified WDR5 protein has a molecular weight of 41976 Da.

[001179] SPR studies were performed using a Biacore™ T200 instrument (GE Health Sciences Inc.). Biotinylated WDR5 protein (approximately 3000RU) was stably captured to streptavidin coupled SA chips according to the manufacture's

protocol (GE Health Sciences Inc.). The running buffer used was HBS-EP (20mM Hepes pH 7.4, 150mM NaCl, 3mM EDTA, 0.05% P-20) plus 5% DMSO with a flow rate of 40μl/min. For SPR analysis, 5 different concentrations of each exemplary compound of the application were sprayed into 96 or 384 well plates using an HP D300 digital dispenser. The concentration ranged from about 195nM to about 12nM in a two-fold series. Concentration ranges were adjusted higher or lower for weaker or more potent compounds respectively when necessary. For the K_D determinations, single cycle kinetic analysis was performed with an on time of 60 seconds, and an off time of 300 or 600 seconds. Curve fitting and K_D calculations were performed with the Biacore T200 Evaluation software (GE Health Sciences Inc).

Results

[001180] Table 1 shows the binding affinity values (K_D) of exemplary compounds of the application for the WDR5 protein. The exemplary compounds of the application have binding affinities which range in the nanomolar concentrations.

(ii) MLL1-WRAD2 Enzyme Assay

[001181] Compound potency was assessed through incorporation of 3H-SAM into oligonucleosomes purified from HeLa cells. Specifically, recombinant human MLL1 (aa 3745-3969, GenBank Accession No. NM_005933), WDR5 (aa 22-334, GenBank Accession No. NM_017588), RbBP5 (aa 1-538, GenBank Accession No. NM_005057), Ash2L (aa 2-534, GenBank Accession No. NM_001 105214), and DPY-30 (aa 1-99, GenBank Accession No. NM_0325742), all with N-terminal His tag, were expressed in E. coli and mixed at a molar ratio of 1:1:1:1:2. 10 nM of the assembled MLL1-WRAD2 complex was mixed with 100 nM WRAD2 to enhance complex formation before incubation with 0.05 mg/ml nucleosome substrate and exemplary compounds of the application (as 10 point duplicate dose response titrations) for 15 min in a buffer consisting of 50 mM Tris (pH 8.5), 5 mM $MgCl_2$, 50 mM NaCl, 1 mM DTT, 0.01% Brij-35, and 1% DMSO. Reaction was initiated with 1 μM 3H-SAM and incubated for 1 hour at 30°C. Reaction mixture was transferred to P81 filter-paper and washed with PBS before detection.

Results

[001182] Table 2 shows the inhibitory activity of representative of compounds of the invention in the *in vitro* methyl transferase assay (MLL1-WRAD2 assay).

(iii) Detection of in-cell H3K4 Dimethylation

[001183] T24 cells were seeded into a 96-well plate at 400 cells/well in 150 µï medium (McCoy 5A containing 10% FBS, 100 µg/ml Normocin, and 50 µg/ml Gentamycin, Invitrogen). A HP D300 digital dispenser was used to dose cells with DMSO or test compounds across a 10-point range of concentrations (high dose of 10 µM), and cultures were grown in a humidified 5% $C0_2$ incubator at 37°C. After five days, plates were removed from incubator, media was aspirated, and the cells washed in PBS. Cell lysis, histone extraction, and detection of H3K4 dimethylation (H3K4me2) were performed using an AlphaLisa kit according to the manufacturer's instructions (Perkin Elmer). Signal was measured using an Envision plate reader.

Results

[001184] Exemplary compounds of the application significantly inhibit the demethylation of H3K4 in T24 cells as shown in **Table 3.**

(iv) Cell Proliferation Assay

[001185] MV4-11 cells were seeded into a 96-well plate at 1,000 cells/well in 150 µï medium (Alpha-MEM containing 10% FBS, 100 µg/ml Normocin, and 50 µg/ml Gentamycin, Invitrogen). A HP D300 digital dispenser was used to dose cells with DMSO or test compounds across a 10-point range of concentrations (high dose of 10 µM), and cultures were grown in a humidified 5% $C0_2$ incubator at 37°C. After five days, plates were removed from the incubator and equilibrated to room temperature. An equal volume of ATPlite assay reagent was added to each well, and samples were processed according to manufacturer's instructions (Perkin Elmer). Luminescent signal was measured using an Envision plate reader equipped with a US-Luminescence detector.

Results

[001186] Table 4 illustrates the anti-proliferative activity of exemplary compounds of the invention,

(v) Residency Time

[001187] Biochemical and cellular assays of drug interactions with their target macromolecules have traditionally been based on measures of drug-target binding affinity under thermodynamic equilibrium conditions. Equilibrium binding metrics such as the half-maximal inhibitory concentration (IC_{50}), the effector concentration for half-maximal response (EC_{50}), the equilibrium dissociation constant (K_D) and the inhibition constant (K_i), all pertain to *in vitro* assays run under closed system conditions, in which the drug molecule and target are present at invariant concentrations throughout the time course of the experiment *[Nat. Rev. Drug Discov.* **2006,** 5, 730-739; *Biochemistry* **2008,** 47, 5481-5492; *Expert Opin. Drug Discov.* **2010,** 5, 305-310]. In living organisms, the concentration of drug available for interaction with a localized protein target is in constant flux because of various physiological processes. Such processes include gastrointestinal absorption, hepatic and renal metabolism, and tissue distribution. Hence, equilibrium measures of drug-target interactions are not entirely valid in the context of the open, non-equilibrium conditions of *in vivo* pharmacology. It has been suggested that the key determinant of *in vivo* pharmacological activity and duration is not the binding affinity of a drug for its intended target but the lifetime, or residence time, of the binary drug-target complex. Pharmacological activity typically depends on the binding of the drug to its intended target, and pharmacological activity will usually only persist while the drug remains bound. As soon as a drug dissociates from its target, that target protein is then free to resume its pathophysiological function, which is presumably the molecular progenitor of disease.

[001188] The lifetime of a drug on its target is determined by two rate constants: the association rate constant (k_{on}) and the dissociation rate constant (k_0s). In principle, the lifetime of the binary drug- target complex is thus extended by a rapid rate of drug binding and/or a slow rate of drug-target complex dissociation. The *in vivo* lifetime of a drug-target complex is most critically dependent on the value of the k_{0ff} *[Nat. Rev. Drug Discov.* **2006,** 5, 730-739; *Biochemistry* **2008,** 47, 5481-5492; *Expert Opin. Drug Discov.* **2010,** 5, 305-310]. Drug-target residence time is defined as the reciprocal of k_os ($\tau = 1/k_{0ff}$), making the residence time a parameter that is easily measured by routine *in vitro* assay methods. Moreover, residence time contributes to

the multiple, critical parameters that influence *in vivo* pharmacodynamics *[Anal. Biochem.* **2014,** 468, 42-49].

[001189] The potency of drug- target binding interactions (as measured by the K_D) and residence time are distinct parameters, they are nevertheless interdependent. This interdependency is clear from the mathematical definitions of the K_D for various modalities of binding (see below). The simplest binding interaction is a 1:1 binding reaction in which one molecule of ligand (L, in this case a drug molecule) interacts with one molecule of the protein target (R, the target of pharmacological intervention), that is held in a single conformational state. The association of ligand and target occurs in a single kinetic step, defined by the k_{on}; similarly, binary complex dissociation occurs in a single kinetic step, defined by the k_{0ff}. For this binding mode, the K_D is defined by equation shown below.

$$K_D = k_{off} / k_{on}$$

Hence, from this model, the K_D would be expected to be directly related to the $k_o s$ and inversely related to both the residence time ($1/k_{0ff}$) and the k_{on}. However, in many cases of high-potency ligand binding to protein targets, one finds that the value of k_{on} is invariant over a series of chemically related ligands (for example, a pharmacophore series) binding to a protein target, or for a specific ligand binding to variants of a protein target.

[001190] The drug-target residence time model was formulated on the basis of a foundation of experimental data suggesting that slow binding and particularly slow drug- target complex dissociation might be a critical molecular antecedent of durable pharmacological activity *in vivo [Proc. Natl Acad. Sci. USA* **1994,** 91, 11202-11206; *J. Am. Chem. Soc. USA* **1996,** 118, 2359-2365; *Proc. Natl Acad. Sci. USA* **2006**, **103**, 7625-7630]. The mathematical basis for analyzing slow binding and dissociating enzyme inhibition kinetics was developed in the seminal work of Morrison and Walsh *[Adv. Enzymol. Relat. Areas Mol. Biol.* **1988,** 61, 201-299]. The advent of surface plasmon resonance (SPR) methods led to the ability to measure, and therefore renewed interest in, protein-ligand association and dissociation kinetics *[Future Med. Chem.* **2009,** 1, 1399-1414].

[001191] Based on a number of experimental studies, the drug-target residence time model predicts that durable pharmacodynamics can be achieved by developing drug molecules with long residence times on their intended target. If the residence time of the drug on its target exceeds the pharmacokinetic half-life of the drug in systemic circulation, one could even achieve the seemingly paradoxical situation of sustained pharmacodynamics activity, even after the bulk of drug has been cleared from the body *[Nat. Rev. Drug Discov.* **2006,** 5, 730-739; *Biochemistry* **2008,** 47, 5481-5492; *Drug Discov. Today* **2013,** 18: 697-707 (2013). Indeed, numerous examples of long-residence-time drugs that exhibit this unexpected pharmacokinetics-pharmacodynamics temporal relationship now exist *[Curr. Opin. Drug Discov.* **2009**,**12** 488-496; *Curr. Opin. Chem. Biol.* **2010,** 14, 467-474]. The ability to sustain durable pharmacodynamics after the clearance of bulk drug from the circulation can provide important advantages in terms of convenient dosing schedules for patients and avoiding off-target mediated toxicities *[Nat Rev Drug Discov.* **2016,** 15(2): 87-95].

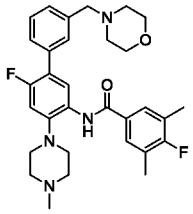
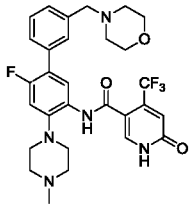
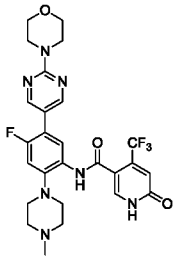
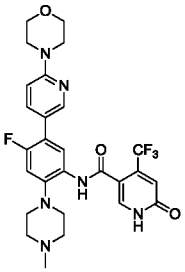
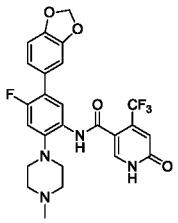
[001192] Over the past 10 years, the drug-target residence time model has been further refined and applied to drug discovery and development efforts. We have discovered a novel class of compounds which inhibit the WDR5 protein-protein binding. In addition, structure-activity relationship studies demonstrated that specific chemical features contribute to longer residence times. WDR5 inhibitors with longer residence times has demonstrated increased inhibition of MLL1 catalytic activity resulting in significantly improved growth inhibition observed in hematologic and solid tumors (Table 5 and 6).

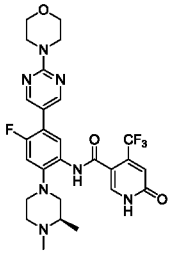
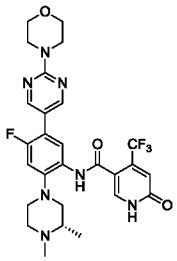
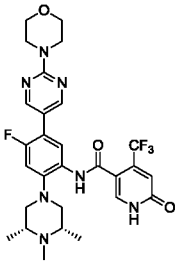
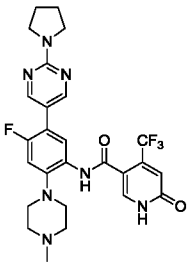
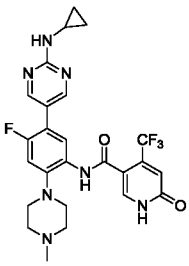
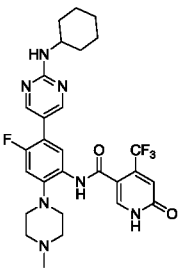
[001193] While the present application has been described with reference to examples, it is to be understood that the scope of the claims should not be limited by the embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

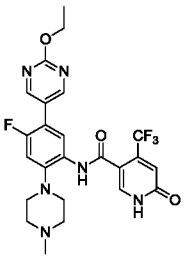
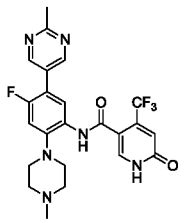
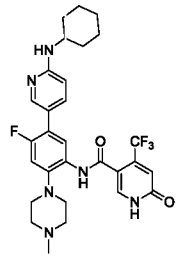
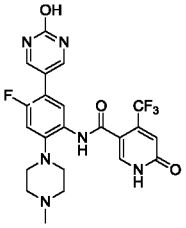
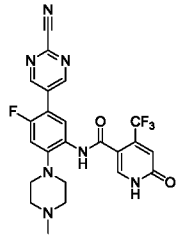
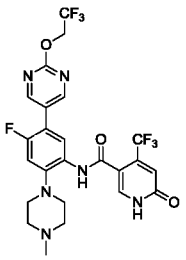
[001194] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is

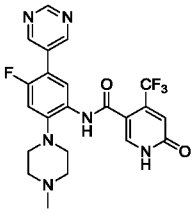
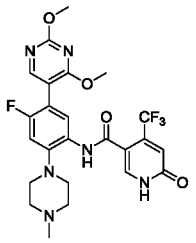
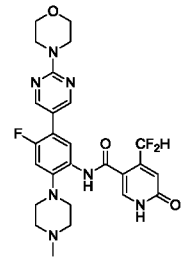
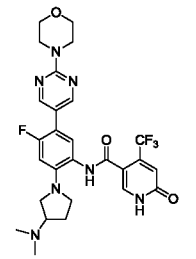
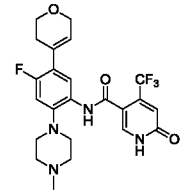
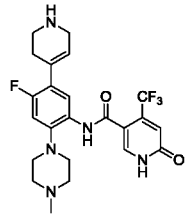
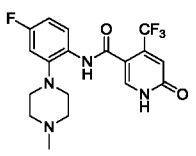
found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

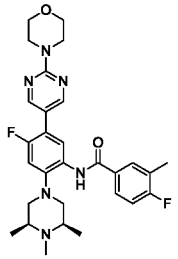
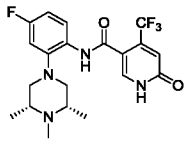
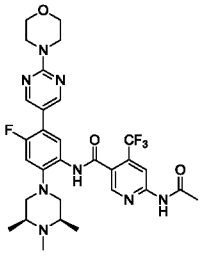
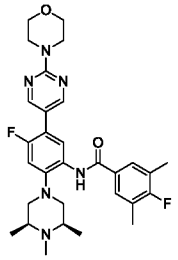
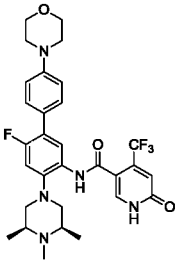
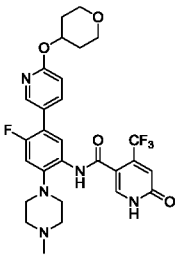
Table 1: Binding affinities (K_D) derived from surface plasmon resonance (SPR) assays

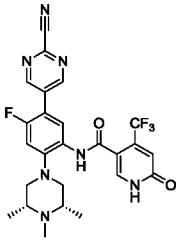
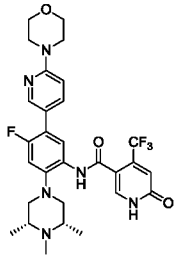
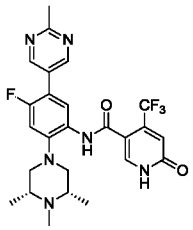
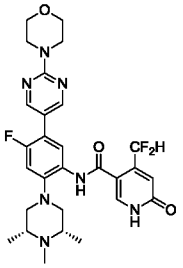
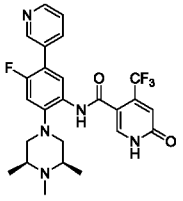
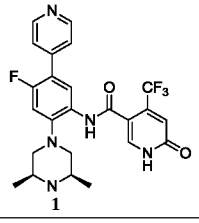
Example No.	Structure	IUPAC Name	WDR5 binding affinity (K_D, μM)
1		4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide	0.084
2		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.011
3		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.002
4		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(6-morpholin-4-ylpyridin-3-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.004
5		N-[5-(1,3-benzodioxol-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.033

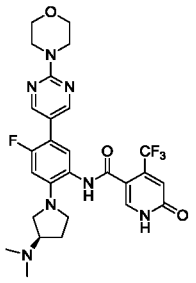
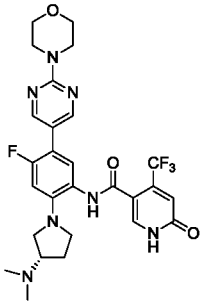
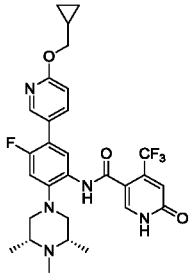
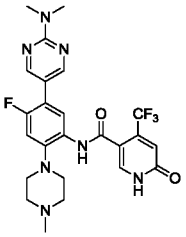
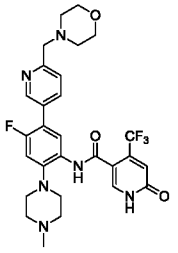
6		N-[2-[(3R)-3,4-dimethylpiperazin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.003
7		N-[2-[(3S)-3,4-dimethylpiperazin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00006
8		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0003
9		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.005
10		N-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.013
11		N-[5-[2-(cyclohexylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.005

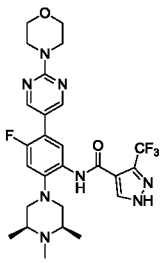
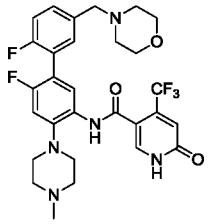
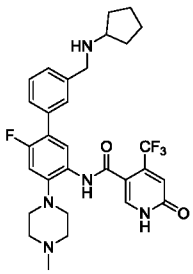
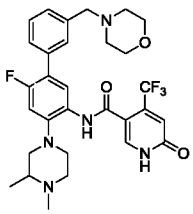
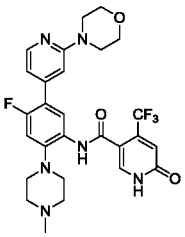
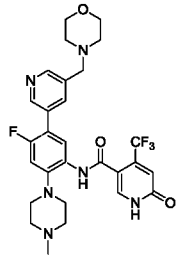
12		N-[5-(2-ethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.005
13		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-methylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.004
14		N-[5-[6-(cyclohexylamino)pyridin-3-yl]-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.005
15		N-[4-fluoro-5-(2-hydroxypyrimidin-5-yl)-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.026
16		N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.002
17		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[2-(2,2,2-trifluoroethoxy)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.006

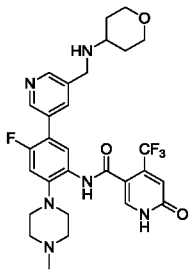
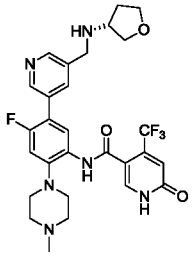
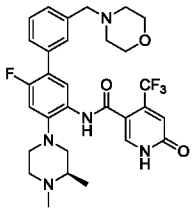
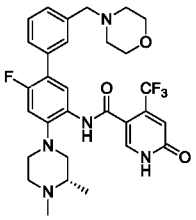
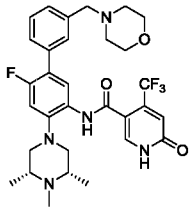
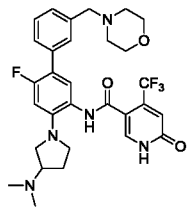
18		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-pyrimidin-5-ylphenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.009
19		N-[5-(2,4-dimethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.004
20		4-(difluoromethyl)-N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.002
21		N-[2-[3-(dimethylamino)pyrrolidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0009
22		N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0076
23		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0171
24		N-[4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0756

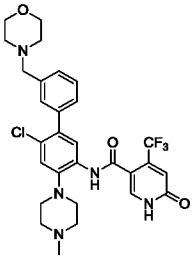
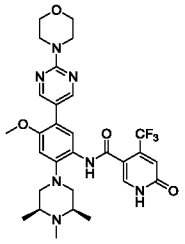
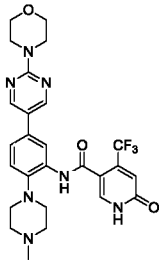
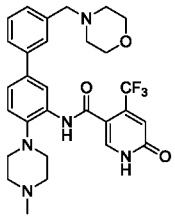
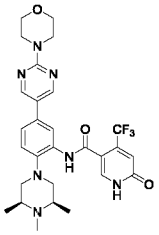
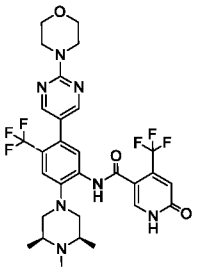
25		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methylbenzamide	0.0085
26		N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0425
27		6-acetamido-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)pyridine-3-carboxamide	0.2940
28		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,5-dimethylbenzamide	0.0015
29		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0009
30		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[6-(oxan-4-yloxy)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0032

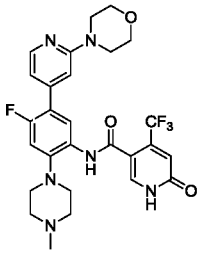
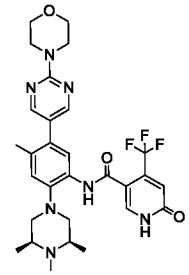
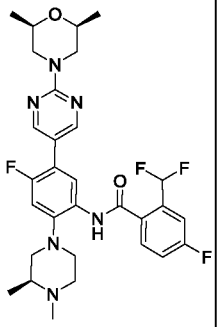
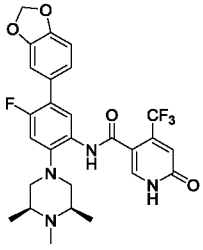
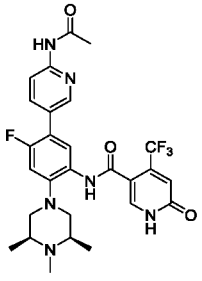
31		N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0014
32		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0004
33		N-[4-fluoro-5-(2-methylpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0005
34		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.0001
35		N-[4-fluoro-5-pyridin-3-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0026
36		N-[4-fluoro-5-pyridin-4-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0022

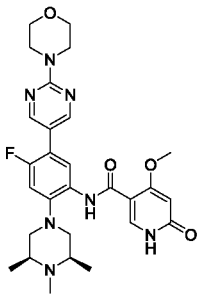
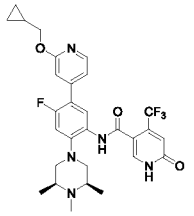
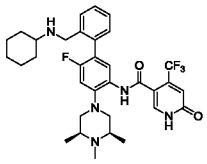
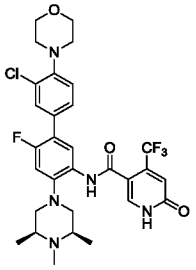
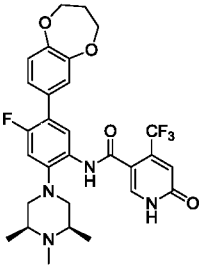
37		N-[2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0002
38		N-[2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0038
39		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0003
40		N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0078
41		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[6-(morpholin-4-ylmethyl)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0086

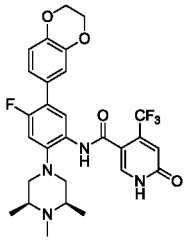
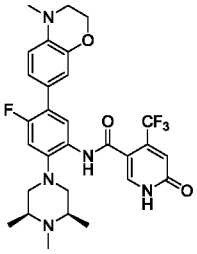
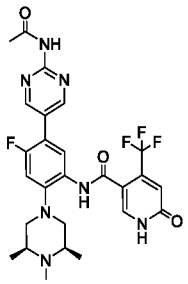
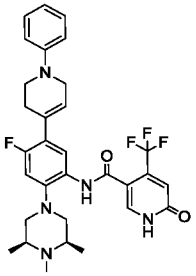
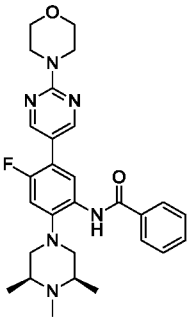
42		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	0.009
43		N-(2',6-difluoro-4-(4-methylpiperazin-1-yl)-5'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.020
44		N-(3'-((cyclopentylamino)methyl)-6-fluoro-4-(4-methylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.005
45		N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.009
46		N-(4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-morpholinopyridin-4-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.005
47		N-(4-fluoro-2-(4-methylpiperazin-1-yl)-5-(5-(morpholinomethyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.019

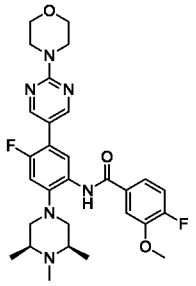
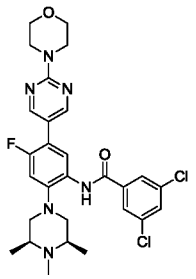
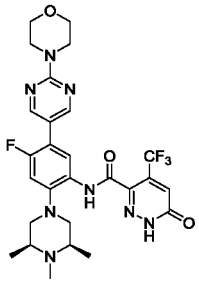
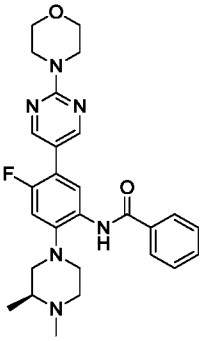
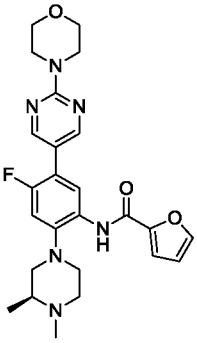
48		N-(4-fluoro-2-(4-methylpiperazin-1-yl)-5-(5-(((tetrahydro-2H-pyran-4-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.015
49		(R)-N-(4-fluoro-2-(4-methylpiperazin-1-yl)-5-(5-(((tetrahydrofuran-3-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.014
50		(R)-N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.012
51		(S)-N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.007
52		N-(6-fluoro-3'-(morpholinomethyl)-4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.006
53		N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0057

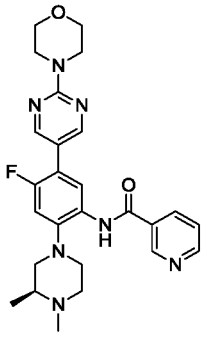
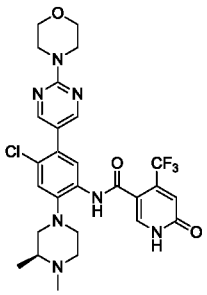
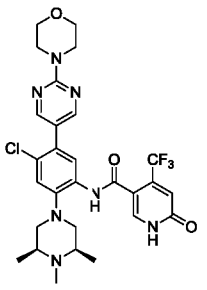
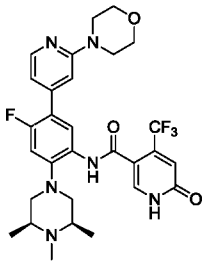
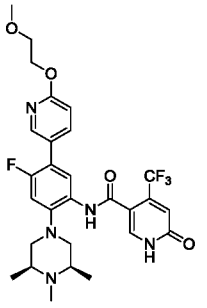
54		N-(6-chloro-4-(4-methylpiperazin-1-yl)-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0510
55 (Comparative Ex.)		N-[4-methoxy-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	>0.200
56		N-(2-(4-methylpiperazin-1-yl)-5-(2-morpholinopyrimidin-5-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0175
57		N-[2-(4-methylpiperazin-1-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.036
58		N-(5-(2-morpholinopyrimidin-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0035
59 (Comparative Ex.)		N-[5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-4-(trifluoromethyl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	>0.200

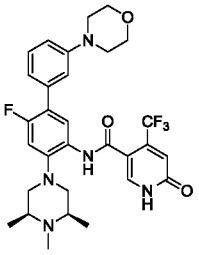
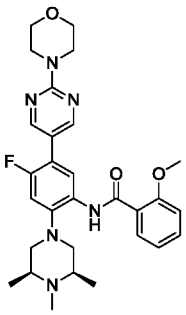
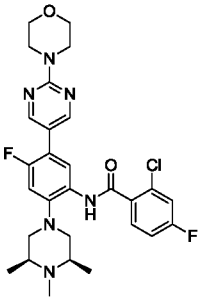
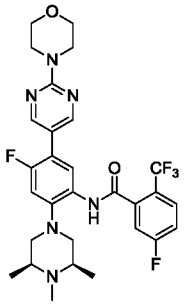
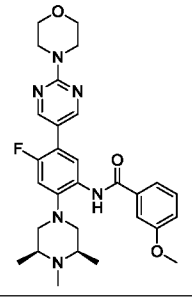
60		N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-(2-morpholin-4-ylpyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00479
61 (Comparative Ex.)		N-[4-methyl-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.026
62		2-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-((S)-3,4-dimethylpiperazin-1-yl)-4-fluorophenyl)-4-fluorobenzamide	XXX
63		N-[5-(1,3-benzodioxol-5-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000694
64		N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000199

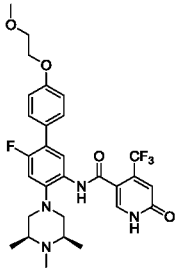
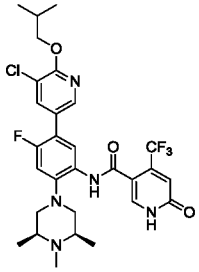
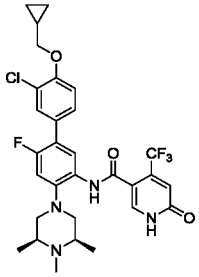
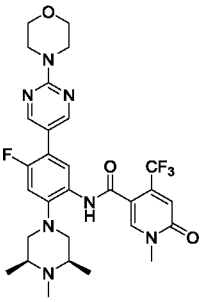
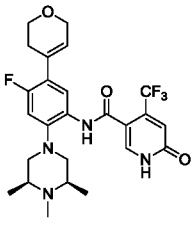
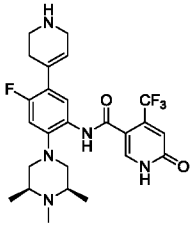
65		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-methoxy-6-oxo-1H-pyridine-3-carboxamide	0.0572
66		N-[5-[2-(cyclopropylmethoxy)pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00116
67		N-[5-[2-[(cyclohexylamino)methyl]phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00482
68		N-[5-(3-chloro-4-morpholin-4-ylphenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00134
69		N-[5-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000225

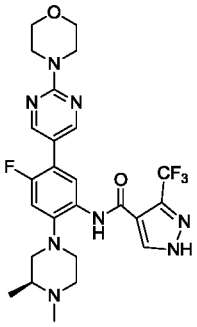
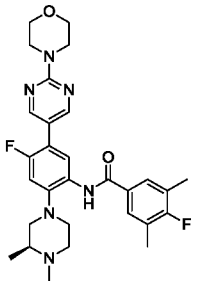
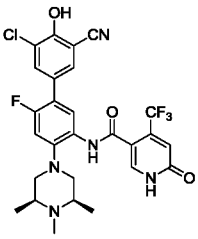
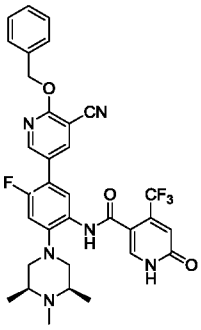
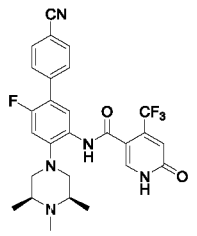
70		N-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000429
71		N-[4-fluoro-5-(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000623
72		N-[5-(2-acetamidopyrimidin-5-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000823
73		N-[4-fluoro-5-(1-phenyl-3,6-dihydro-2H-pyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00363
74		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.253

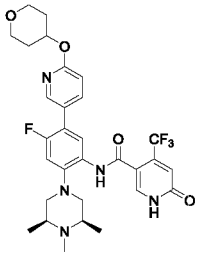
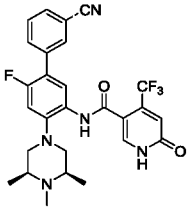
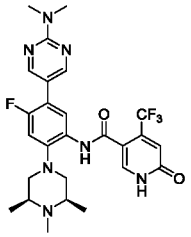
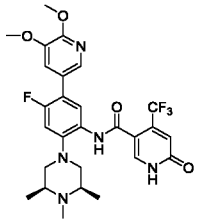
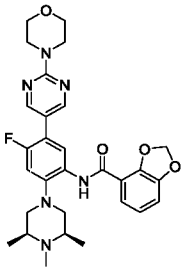
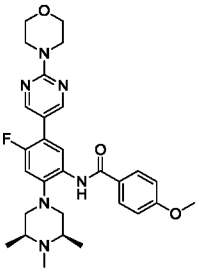
75		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methoxybenzamide	0.0409
76		3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00207
77		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridazine-3-carboxamide	0.00443
78		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.0179
79		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]furan-2-carboxamide	>0.200

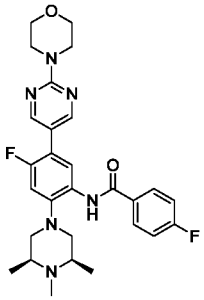
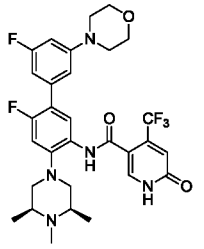
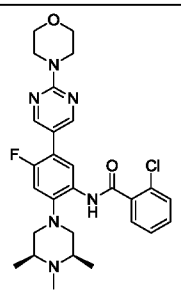
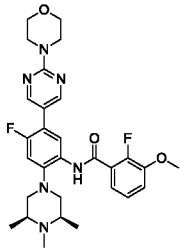
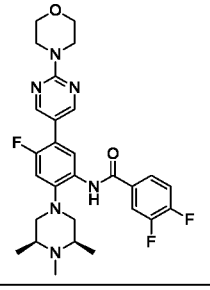
80		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]pyridine-3-carboxamide	>0.200
81 (Comparative Ex.)		N-[4-chloro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0111
82 (Comparative Ex.)		N-[4-chloro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0106
83		N-[4-fluoro-5-(2-morpholin-4-ylpyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000391
84		N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000338

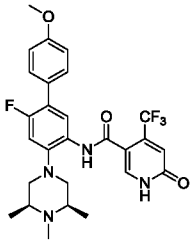
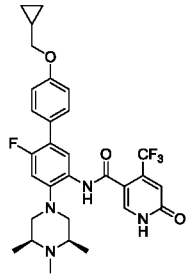
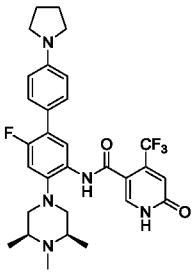
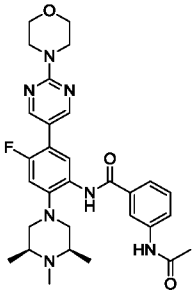
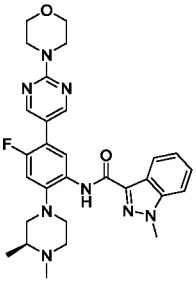
85		N-[4-fluoro-5-(3-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000703
86		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-methoxybenzamide	0.204
87		2-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00821
88		5-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0241
89		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methoxybenzamide	0.0338

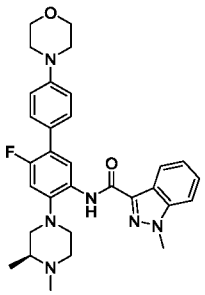
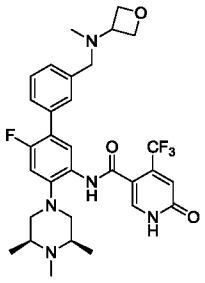
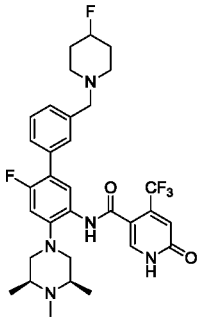
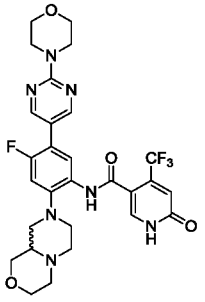
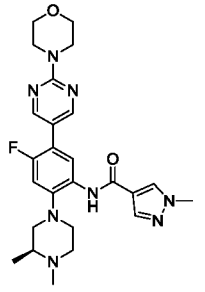
90		N-[4-fluoro-5-[4-(2-methoxyethoxy)phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000441
91		N-[5-[5-chloro-6-(2-methylpropoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00447
92		N-[5-[3-chloro-4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0109
93		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00217
94		N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00406
95		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-	0.00718

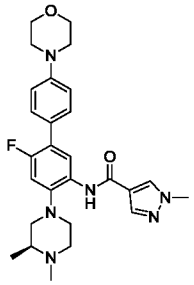
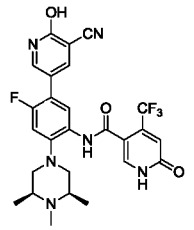
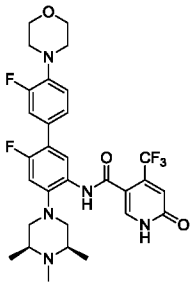
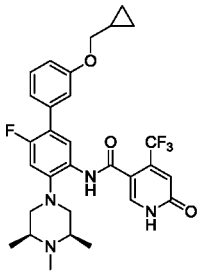
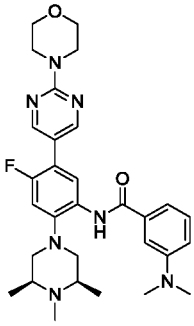
		pyridine-3-carboxamide	
96		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	0.00771
97		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,5-dimethylbenzamide	0.00221
98		N-[5-(3-chloro-5-cyano-4-hydroxyphenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0195
99		N-[5-(5-cyano-6-phenylmethoxypyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0111
100		N-[5-(4-cyanophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000508

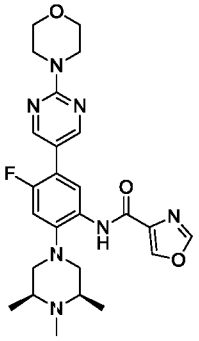
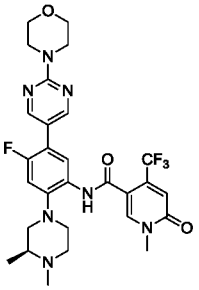
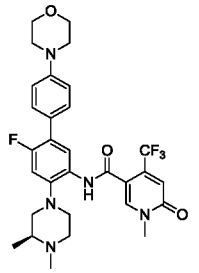
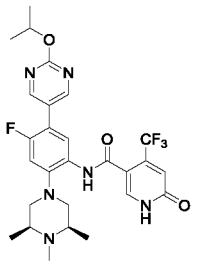
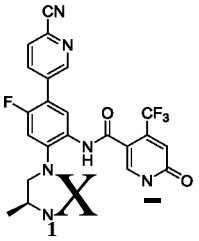
101		N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00032
102		N-[5-(3-cyanophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00208
103		N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000168
104		N-[5-(5,6-dimethoxypyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00241
105		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-benzodioxole-4-carboxamide	0.466
106		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-methoxybenzamide	5.4

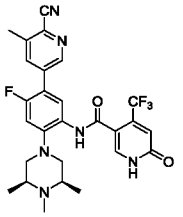
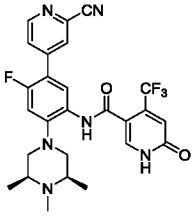
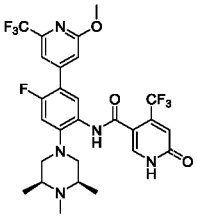
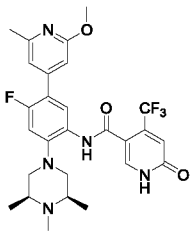
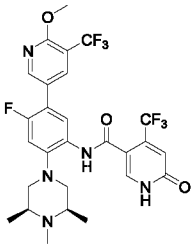
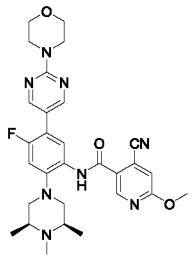
107		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.137
108		N-[4-fluoro-5-(3-fluoro-5-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00391
109		2-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.175
110		2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-methoxybenzamide	1.73
111		3,4-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0706

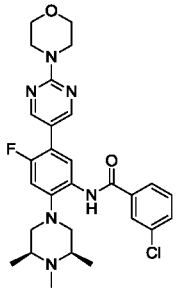
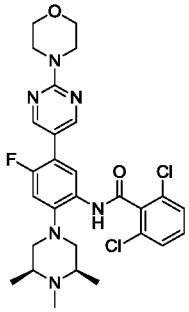
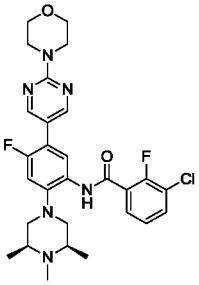
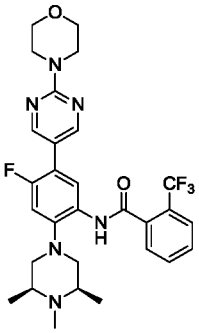
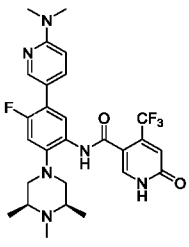
112		N-[4-fluoro-5-(4-methoxyphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00244
113		N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000858
114		N-[4-fluoro-5-(4-pyrrolidin-1-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00406
115		3-acetamido-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	>0.200
116		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methylindazole-3-carboxamide	0.0768

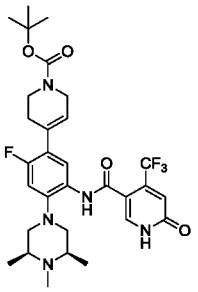
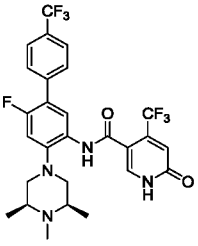
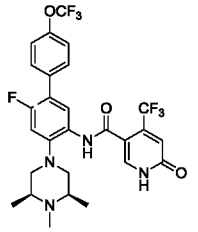
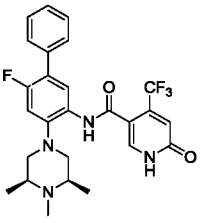
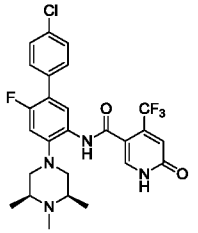
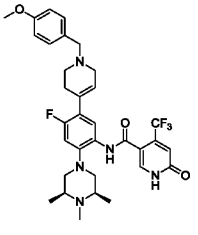
117		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methylindazole-3-carboxamide	0.0428
118		N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00453
119		N-[4-fluoro-5-[3-[(4-fluoropiperidin-1-yl)methyl]phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00512
120		N-[2-(3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl)-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	>0.200
121		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methylpyrazole-4-carboxamide	0.0334

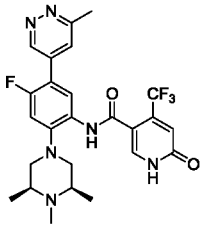
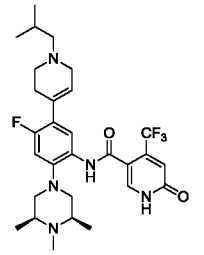
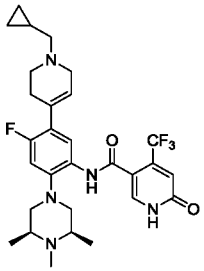
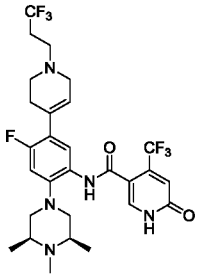
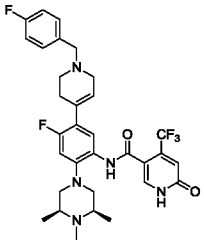
122		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methylpyrazole-4-carboxamide	0.0702
123		N-[5-(5-cyano-6-hydroxypyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00988
124		N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000439
125		N-[5-[3-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0109
126		3-(dimethylamino)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	3.5

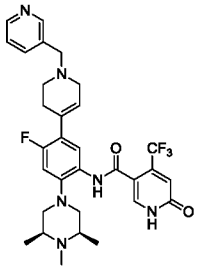
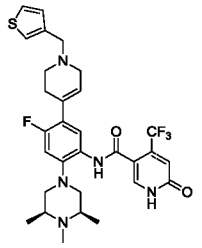
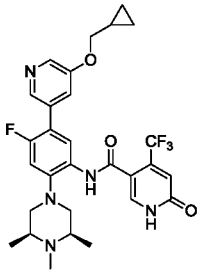
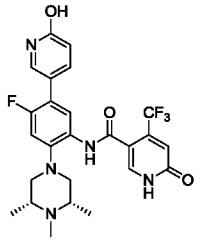
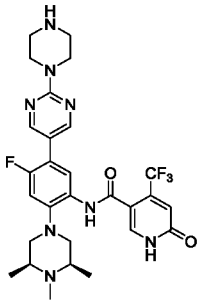
127		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-oxazole-4-carboxamide	>0.200
128		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00636
129		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0129
130		N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000656
131		N-[5-(6-cyanopyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00243

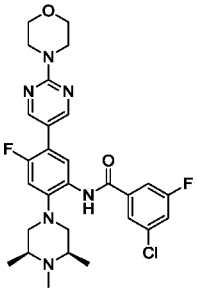
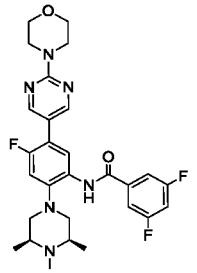
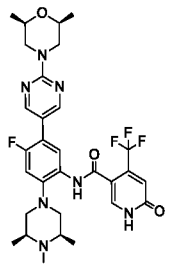
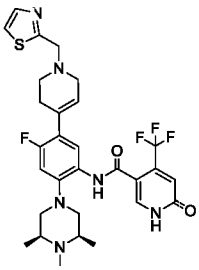
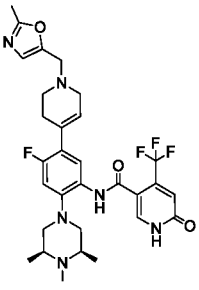
132		N-[5-(6-cyano-5-methylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0014
133		N-[5-(2-cyanopyridin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00133
134		N-[4-fluoro-5-[2-methoxy-6-(trifluoromethyl)pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00101
135		N-[4-fluoro-5-(2-methoxy-6-methylpyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00281
136		N-[4-fluoro-5-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000463
137		4-cyano-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-methoxypyridine-3-carboxamide	0.0197

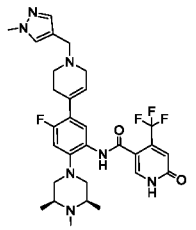
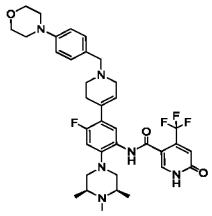
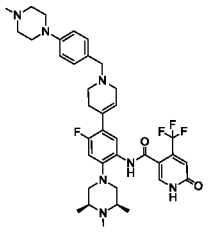
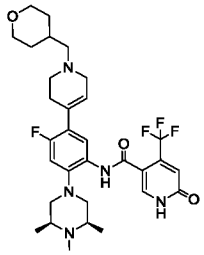
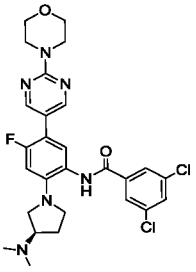
138		3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0113
139		2,6-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00586
140		3-chloro-2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0188
141		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0162
142		N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000985

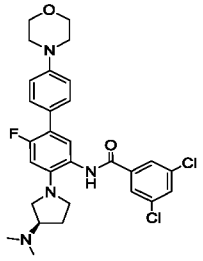
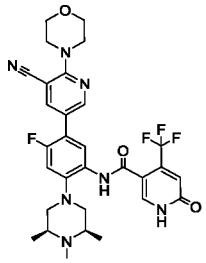
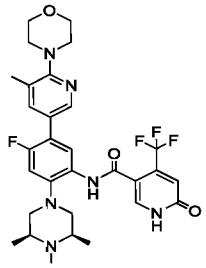
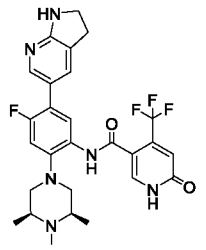
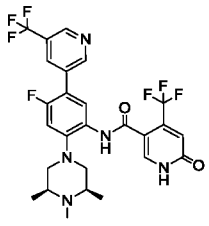
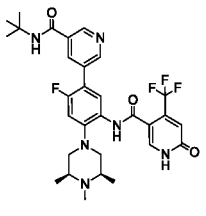
143		tert-butyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00124
144		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[4-(trifluoromethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00606
145		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[4-(trifluoromethoxy)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00683
146		N-[4-fluoro-5-phenyl-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00602
147		N-[5-(4-chlorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00444
148		N-[4-fluoro-5-[1-[(4-methoxyphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00054

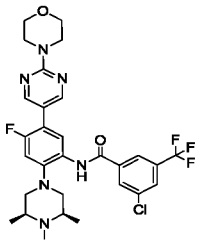
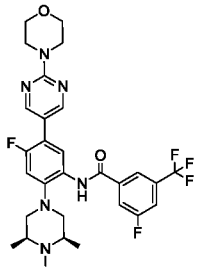
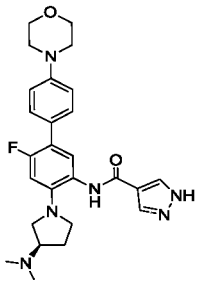
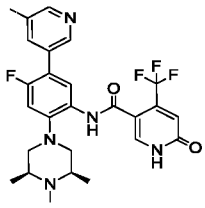
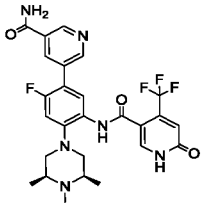
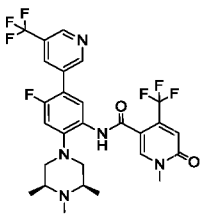
149		N-[4-fluoro-5-(6-methylpyridazin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00465
150		N-[4-fluoro-5-[1-(2-methylpropyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.009
151		N-[5-[1-(cyclopropylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00746
152		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[1-(3,3,3-trifluoropropyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00633
153		N-[4-fluoro-5-[1-[(4-fluorophenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00108

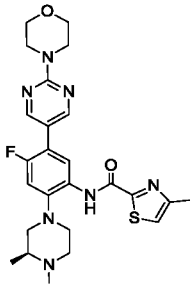
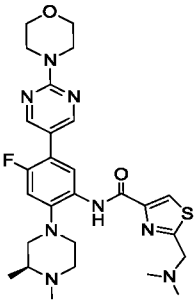
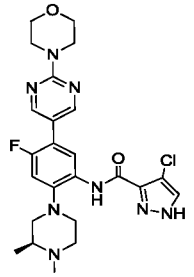
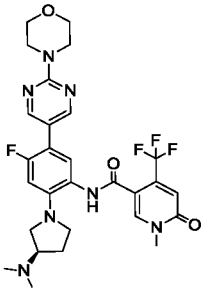
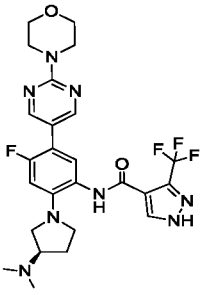
154		N-[4-fluoro-5-[1-(pyridin-3-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00546
155		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[1-(thiophen-3-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00476
156		N-[5-[5-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00861
157		N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00216
158		N-[4-fluoro-5-(2-piperazin-1-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000345

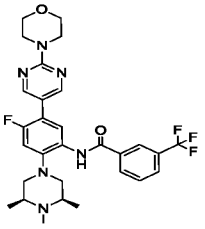
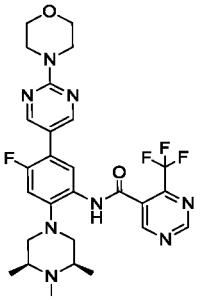
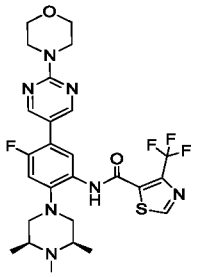
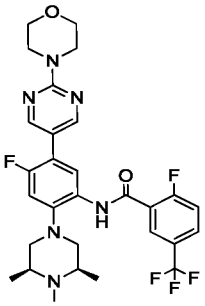
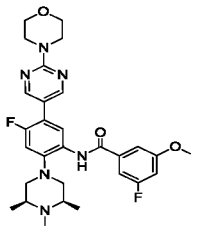
159		3-chloro-5-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.029
160		3,5-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0268
161		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.001
162		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[1-(1,3-thiazol-2-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00283
163		N-[4-fluoro-5-[1-[(2-methyl-1,3-oxazol-5-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00405

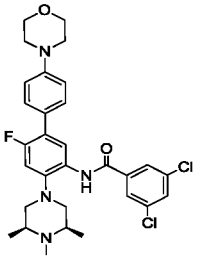
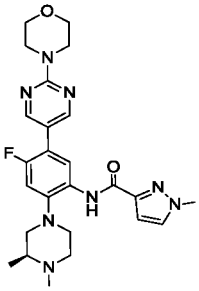
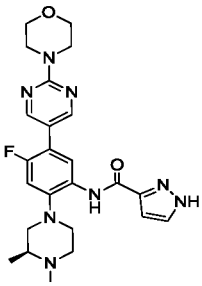
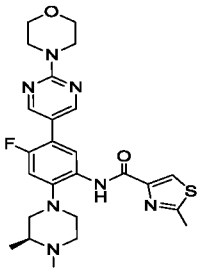
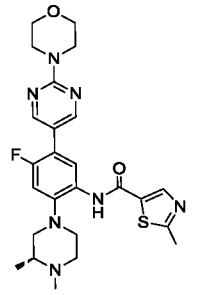
164		N-[4-fluoro-5-[1-[(1-methylpyrazol-4-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00143
165		N-[4-fluoro-5-[1-[(4-morpholin-4-ylphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00628
166		N-[4-fluoro-5-[1-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00023
167		N-[4-fluoro-5-[1-(oxan-4-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00576
168		3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]benzamide	0.03

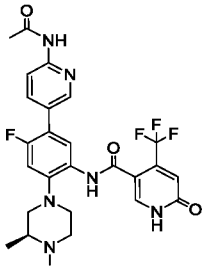
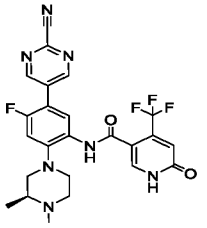
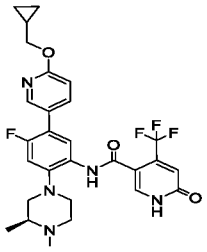
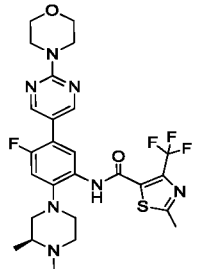
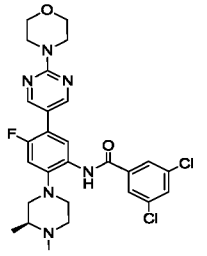
169		3,5-dichloro-N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]benzamide	0.122
170		N-[5-(5-cyano-6-morpholin-4-ylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00117
171		N-[4-fluoro-5-(5-methyl-6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0025
172		N-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0103
173		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[5-(trifluoromethyl)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00278
174		N-[5-[5-(tert-butylcarbamoyl)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-	0.00153

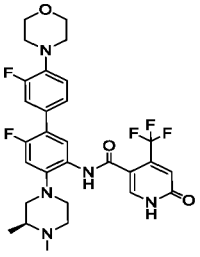
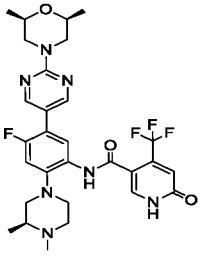
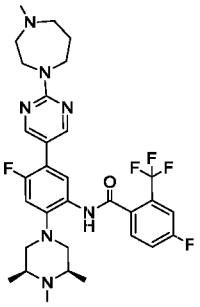
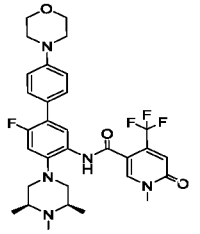
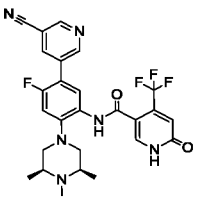
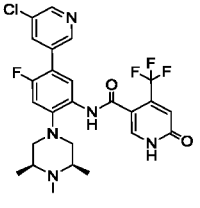
		pyridine-3-carboxamide	
175		3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-(trifluoromethyl)benzamide	0.0206
176		3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-(trifluoromethyl)benzamide	0.0509
177		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-1H-pyrazole-4-carboxamide	>0.200
178		N-[4-fluoro-5-(5-methylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0065
179		N-[5-(5-carbamoylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0115
180		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[5-(trifluoromethyl)pyridin-3-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-	0.0354

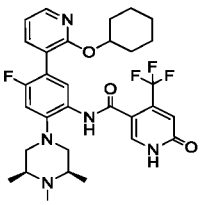
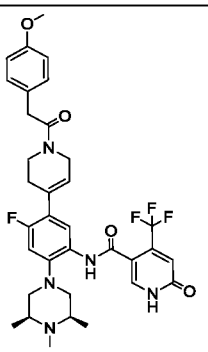
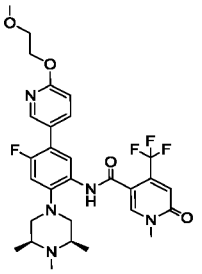
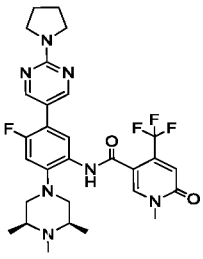
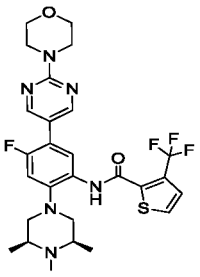
		3-carboxamide	
181		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-methyl-1,3-thiazole-2-carboxamide	>0.200
182		2-[(dimethylamino)methyl]-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1,3-thiazole-4-carboxamide	>0.200
183		4-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1H-pyrazole-3-carboxamide	0.113
184		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0098
185		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	0.0298

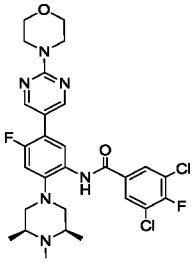
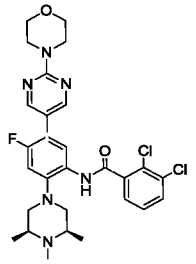
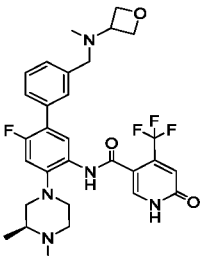
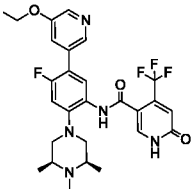
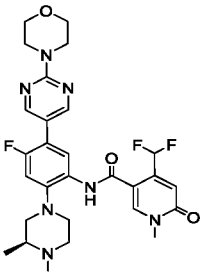
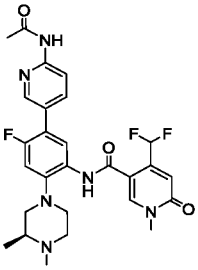
186		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)benzamide	0.0402
187		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide	0.209
188		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide	0.0932
189		2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-(trifluoromethyl)benzamide	0.442
190		3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-methoxybenzamide	0.0147

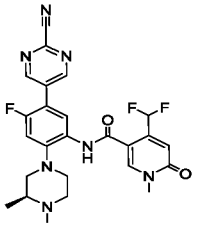
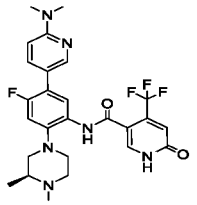
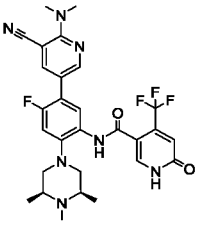
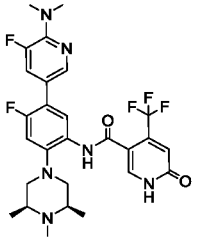
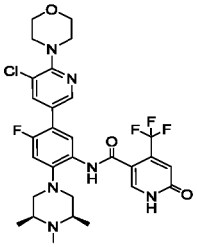
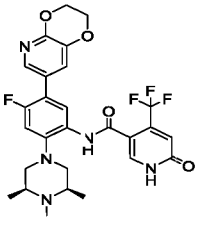
191		3,5-dichloro-N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0215
192		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methylpyrazole-3-carboxamide	1.26
193		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1H-pyrazole-3-carboxamide	0.592
194		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-methyl-1,3-thiazole-4-carboxamide	0.113
195		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-methyl-1,3-thiazole-5-carboxamide	0.106

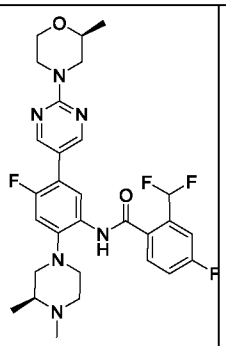
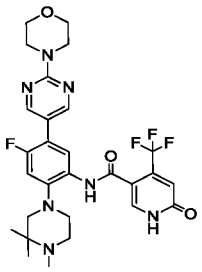
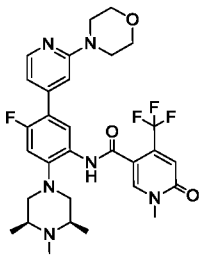
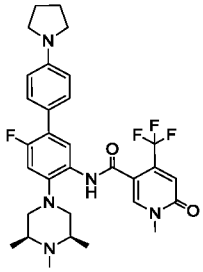
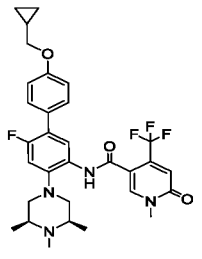
196		N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00024
197		N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000681
198		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000666
199		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-methyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide	0.0234
200		3,5-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.0097

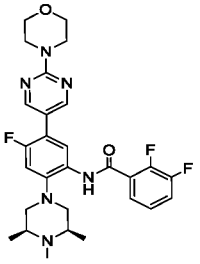
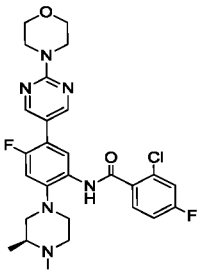
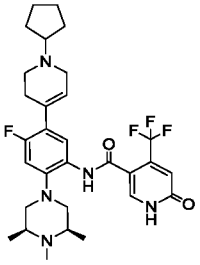
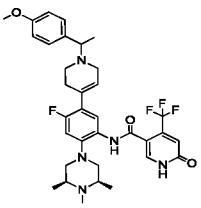
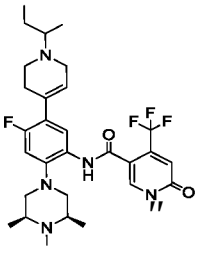
201		N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000466
202		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000434
203		4-fluoro-N-[4-fluoro-5-[2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00166
204		N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0138
205		N-[5-(5-cyanopyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00815
206		N-[5-(5-chloropyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00385

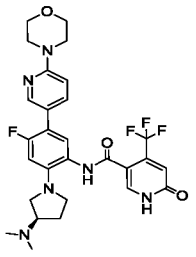
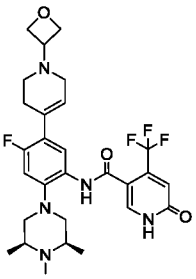
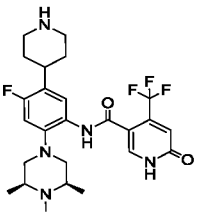
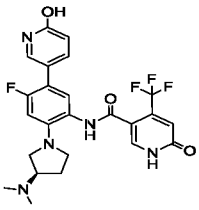
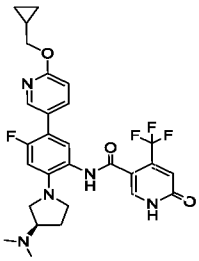
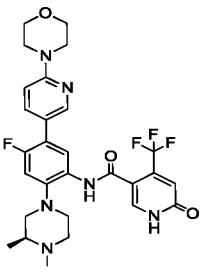
207		N-[5-(2-cyclohexyloxypyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00669
208		N-[4-fluoro-5-[1-[2-(4-methoxyphenyl)acetyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00057
209		N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00953
210		N-[4-fluoro-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00386
211		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)thiophene-2-carboxamide	0.12

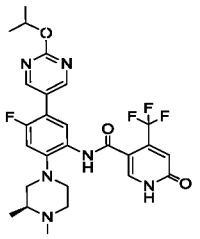
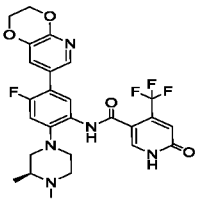
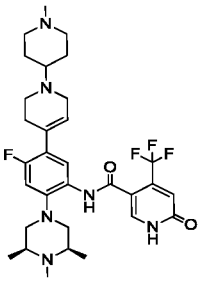
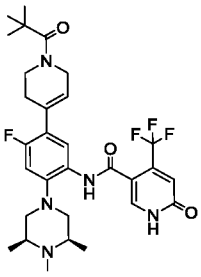
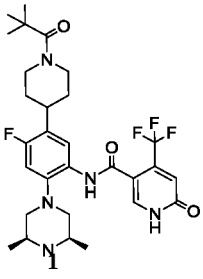
212		3,5-dichloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00271
213		2,3-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00691
214		N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00215
215		N-[5-(5-ethoxypyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00576
216		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00271
217		N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.00432

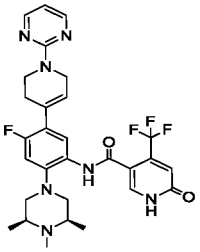
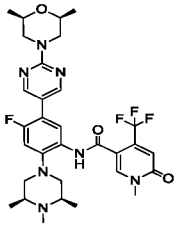
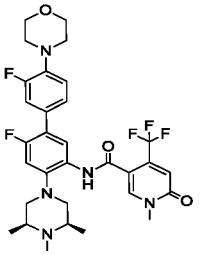
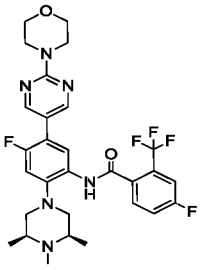
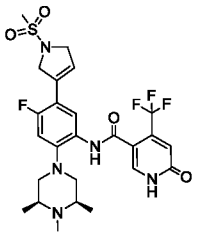
218		N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.00318
219		N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0014
220		N-[5-[5-cyano-6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00225
221		N-[5-[6-(dimethylamino)-5-fluoropyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000769
222		N-[5-(5-chloro-6-morpholin-4-ylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00134
223		N-[5-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00163

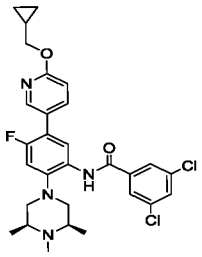
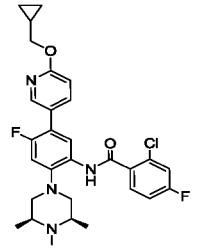
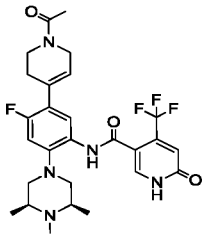
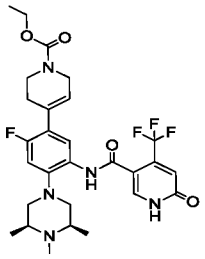
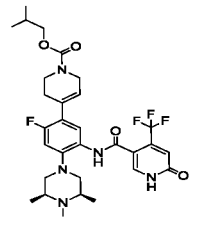
224		2-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-1-yl)-4-fluoro-5-(2-((S)-2-methylmorpholino)pyrimidin-5-yl)phenyl)-4-fluorobenzamide	
225		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-(3,3,4-trimethylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	3
226		N-[4-fluoro-5-(2-morpholin-4-ylpyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00799
227		N-[4-fluoro-5-(4-pyrrolidin-1-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00914
228		N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00726

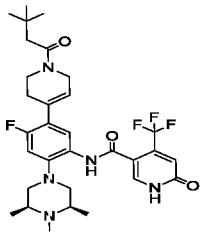
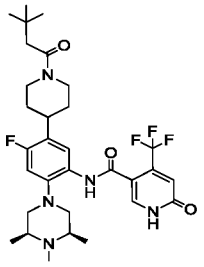
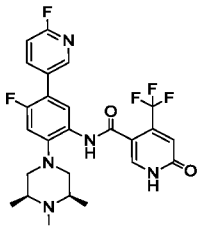
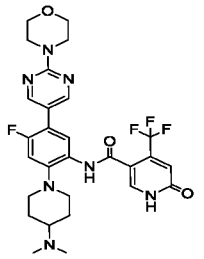
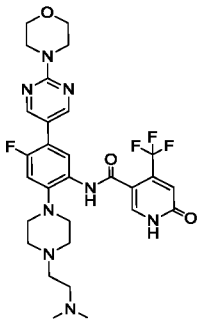
229		2,3-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.083
230		2-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.00895
231		N-[5-(1-cyclopentyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00251
232		N-[4-fluoro-5-[1-[1-(4-methoxyphenyl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00272
233		N-[5-(1-butan-2-yl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00389

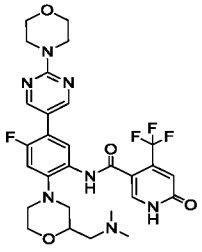
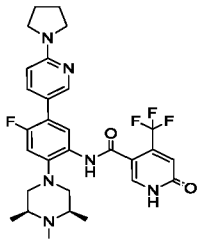
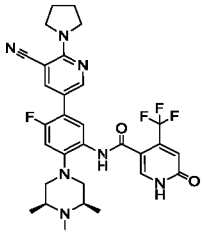
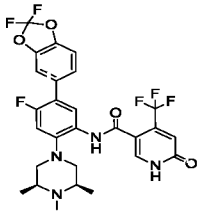
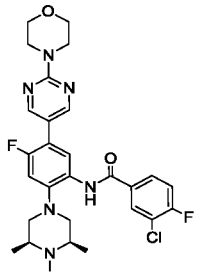
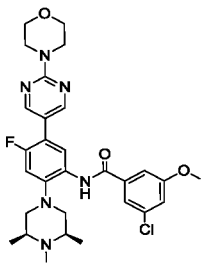
234		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00186
235		N-[4-fluoro-5-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000943
236		N-[4-fluoro-5-piperidin-4-yl-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0311
237		N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00933
238		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00511
239		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00107

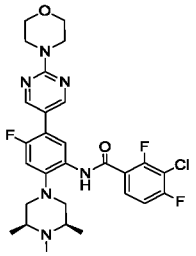
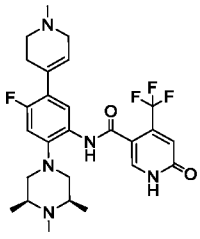
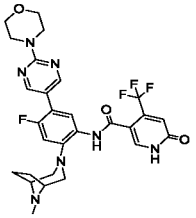
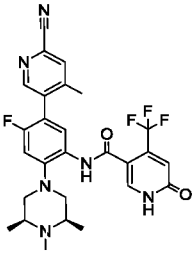
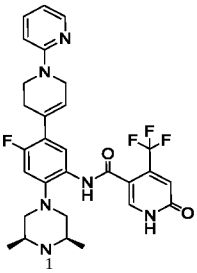
240		N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00223
241		N-[5-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00282
242		N-[4-fluoro-5-[1-(1-methylpiperidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00349
243		N-[5-[1-(2,2-dimethylpropanoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00216
244		N-[5-[1-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0197

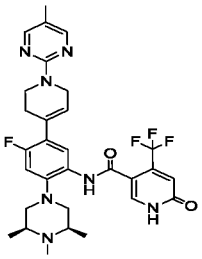
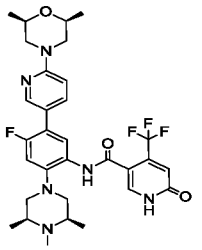
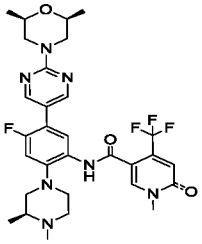
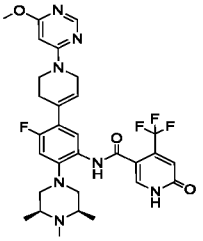
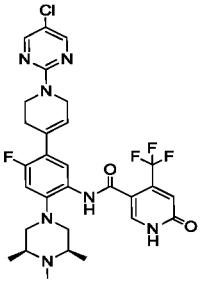
245		N-[4-fluoro-5-(1-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00139
246		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00251
247		N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00516
248		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00133
249		N-[4-fluoro-5-(1-methylsulfonyl-2,5-dihydropyrrol-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000665

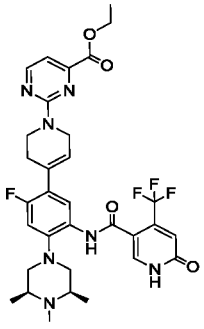
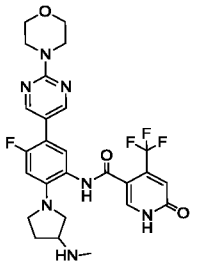
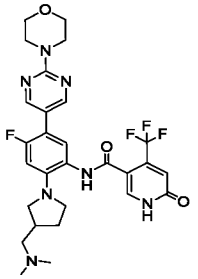
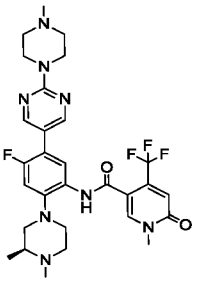
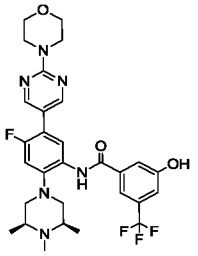
250		3,5-dichloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0769
251		2-chloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluorobenzamide	0.0156
252		N-[5-(1-acetyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00279
253		ethyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.0033
254		2-methylpropyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00334

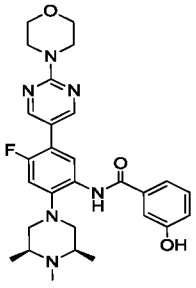
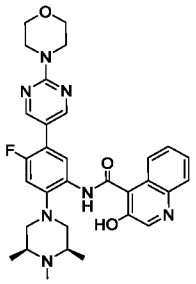
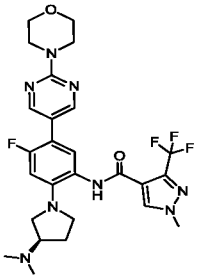
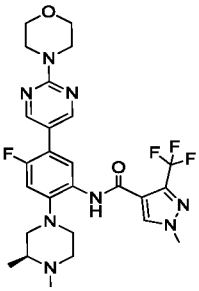
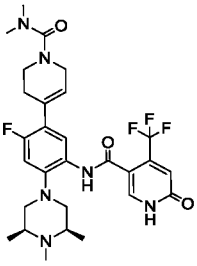
255		N-[5-[1-(3,3-dimethylbutanoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00198
256		N-[5-[1-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0118
257		N-[4-fluoro-5-(6-fluoropyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0017
258		N-[2-[4-(dimethylamino)piperidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0661
259		N-[2-[4-[2-(dimethylamino)ethyl]piperazin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-

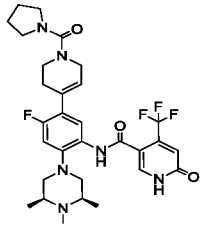
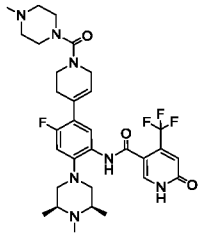
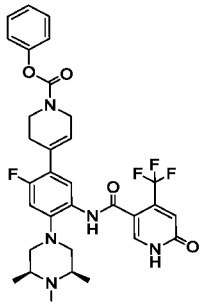
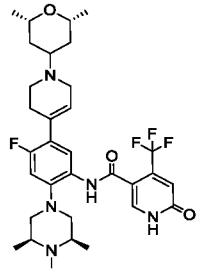
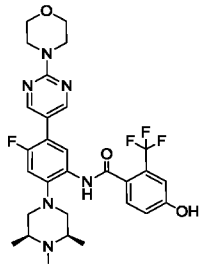
260		N-[2-[2-[(dimethylamino)methyl]morpholin-4-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
261		N-[4-fluoro-5-(6-pyrrolidin-1-ylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00164
262		N-[5-(5-cyano-6-pyrrolidin-1-ylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
263		N-[5-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
264		3-chloro-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00294
265		3-chloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-methoxybenzamide	0.0283

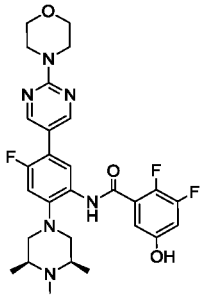
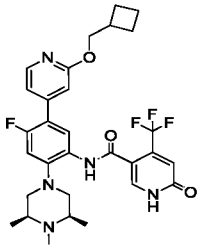
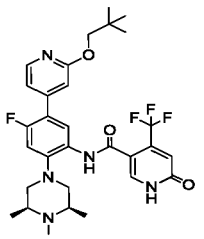
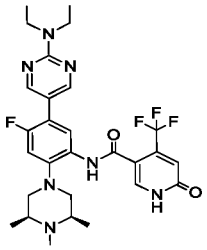
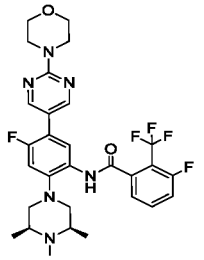
266		3-chloro-2,4-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0137
267		N-[4-fluoro-5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0107
268		N-[4-fluoro-2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
269		N-[5-(6-cyano-4-methylpyridin-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00874
270		N-[4-fluoro-5-(1-pyridin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000938

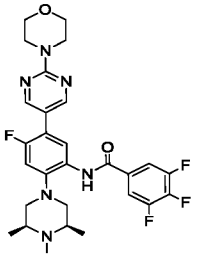
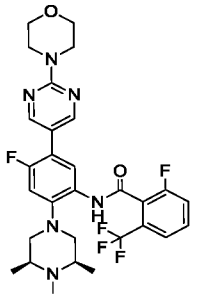
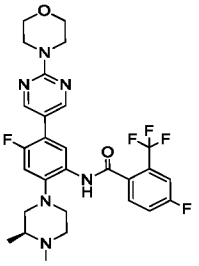
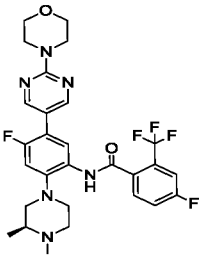
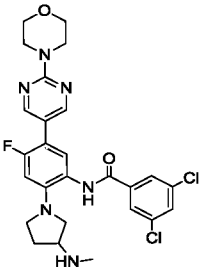
271		N-[4-fluoro-5-[1-(5-methylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000499
272		N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000532
273		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00211
274		N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00129
275		N-[5-[1-(5-chloropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00154

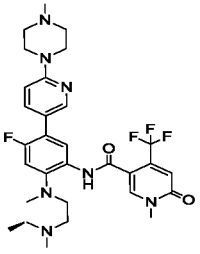
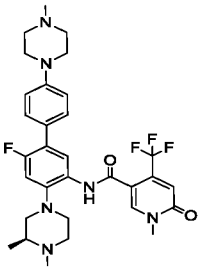
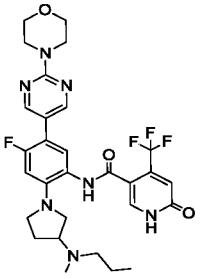
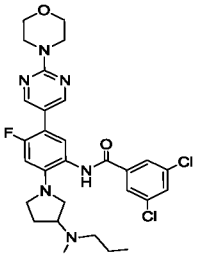
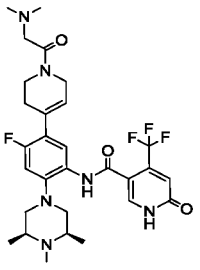
276		ethyl 2-[4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridin-1-yl]pyrimidine-4-carboxylate	0.00167
277		N-[4-fluoro-2-[3-(methylamino)pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0149
278		N-[2-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
279		N-[4-fluoro-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00208
280		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-hydroxy-5-(trifluoromethyl)benzamide	0.00312

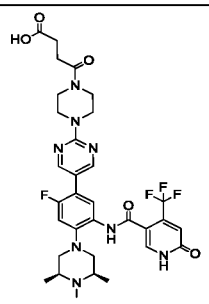
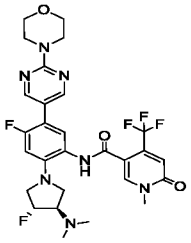
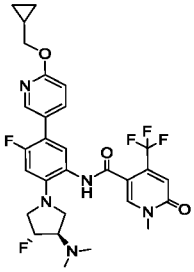
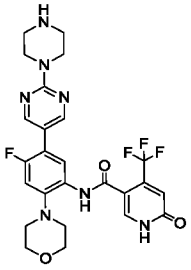
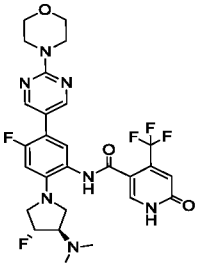
281		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-hydroxybenzamide	0.0291
282		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-hydroxyquinoline-4-carboxamide	0.00198
283		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide	0.0148
284		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide	0.00813
285		N-[5-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00101

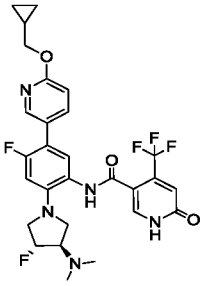
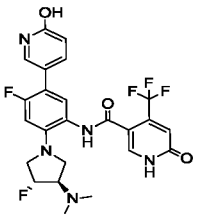
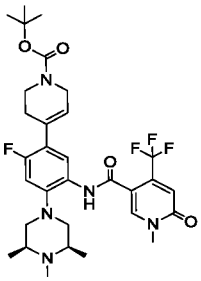
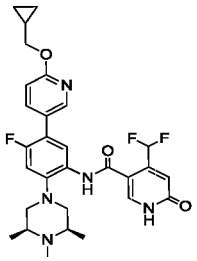
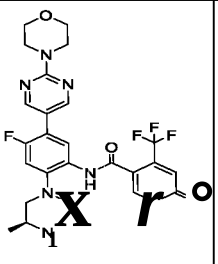
286		N-[4-fluoro-5-[1-(pyrrolidine-1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00118
287		N-[4-fluoro-5-[1-(4-methylpiperazine-1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00139
288		phenyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00111
289		N-[4-fluoro-5-[1-[rac-(2R,6S)-2,6-dimethyloxan-4-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00374
290		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-hydroxy-2-(trifluoromethyl)benzamide	0.0089

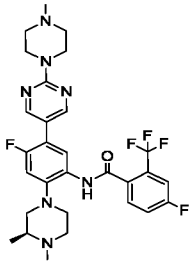
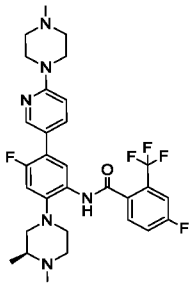
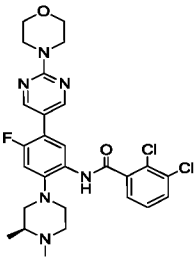
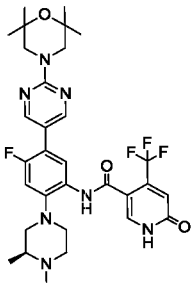
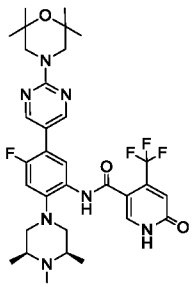
291		2,3-difluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-hydroxybenzamide	0.00421
292		N-[5-[2-(cyclobutylmethoxy)pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00432
293		N-[5-[2-(2,2-dimethylpropoxy)pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.003
294		N-[5-[2-(diethylamino)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00224
295		3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0111

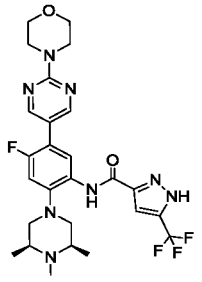
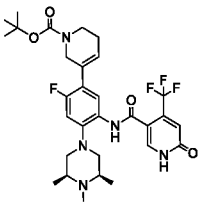
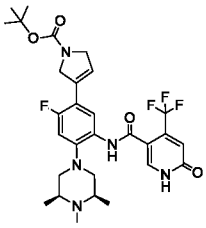
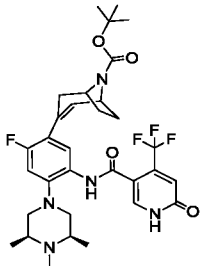
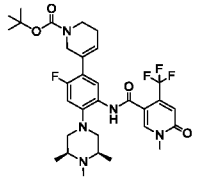
296		3,4,5-trifluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0212
297		2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-(trifluoromethyl)benzamide	0.0229
298		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00422
299		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000569
300		3,5-dichloro-N-[4-fluoro-2-[3-(methylamino)pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide	-

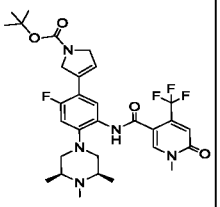
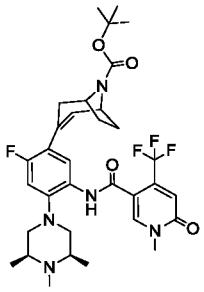
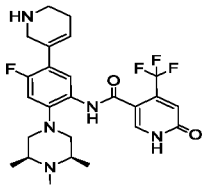
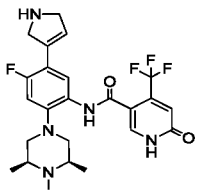
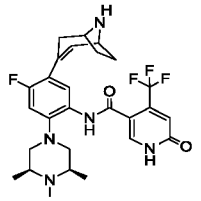
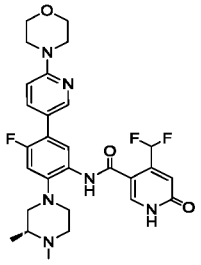
301		N-[4-fluoro-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00526
302		N-[4-fluoro-5-[4-(4-methylpiperazin-1-yl)phenyl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00537
303		N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00168
304		3,5-dichloro-N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide	-
305		N-[5-[1-[2-(dimethylamino)acetyl]-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00261

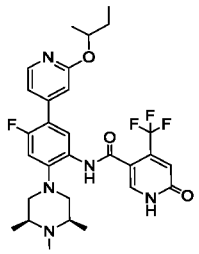
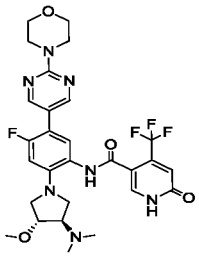
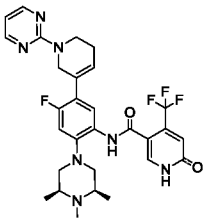
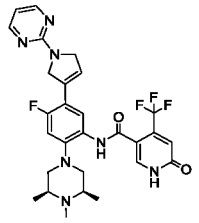
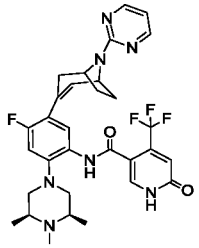
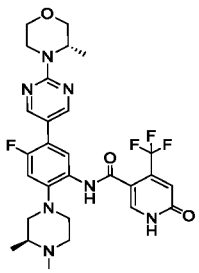
306		4-[4-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]pyrimidin-2-yl]piperazin-1-yl]-4-oxobutanoic acid	0.000789
307		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-
308		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-
309		N-[4-fluoro-2-morpholin-4-yl-5-(2-piperazin-1-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
310		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-

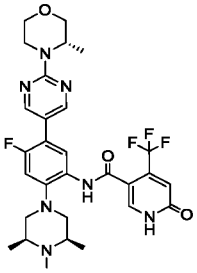
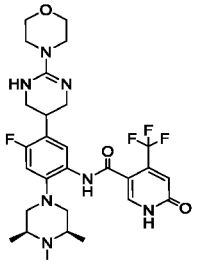
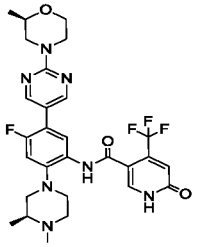
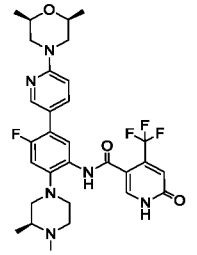
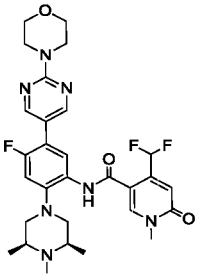
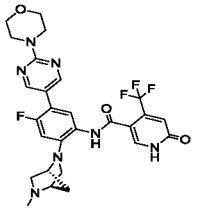
311		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
312		N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[rac-(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
313		tert-butyl 4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.0031
314		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00167
315		1-ethyl-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00849

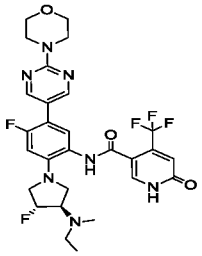
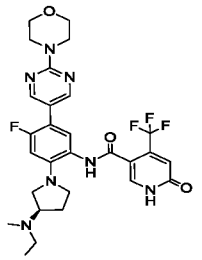
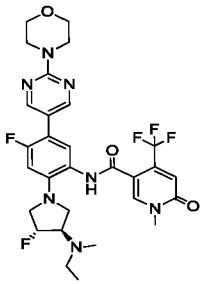
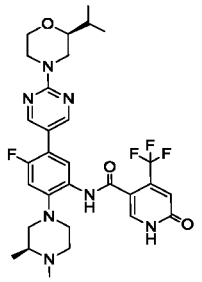
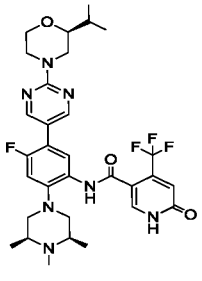
316		4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000989
317		4-fluoro-N-[4-fluoro-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00554
318		2,3-dichloro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.00668
319		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-(2,2,6,6-tetramethylmorpholin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00161
320		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[2-(2,2,6,6-tetramethylmorpholin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000722

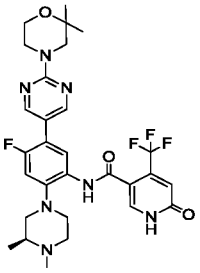
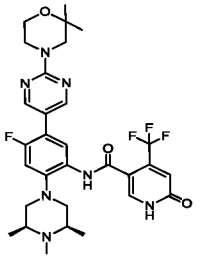
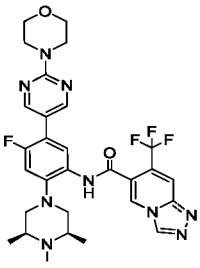
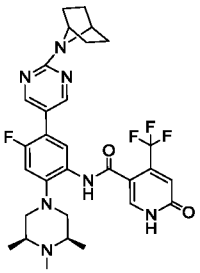
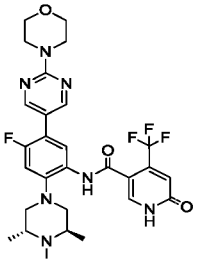
321		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide	0.0631
322		tert-butyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00136
323		tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-carboxylate	0.00248
324		tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate	0.0152
325		tert-butyl 5-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.0073

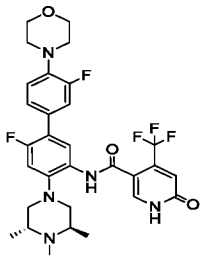
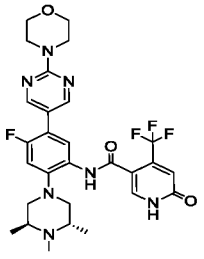
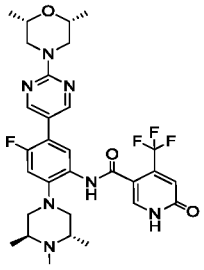
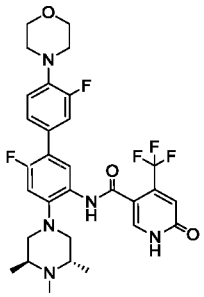
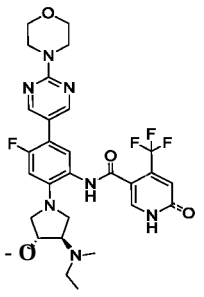
326		tert-butyl 3-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-carboxylate	0.00305
327		tert-butyl 3-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate	0.123
328		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-(1,2,3,6-tetrahydropyridin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00189
329		N-[5-(2,5-dihydro-1H-pyrrol-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00405
330		N-[5-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00574
331		4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00201

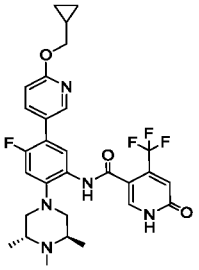
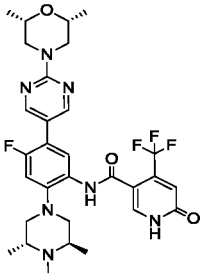
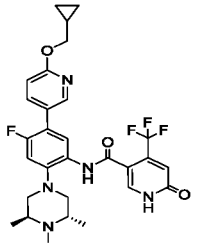
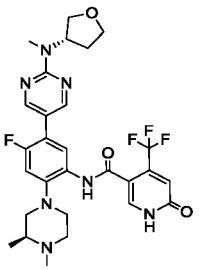
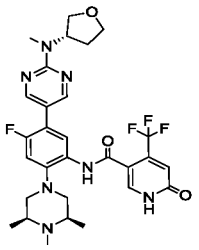
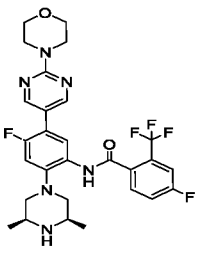
332		N-[5-(2-butan-2-yloxypyridin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
333		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-(dimethylamino)-4-methoxypyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
334		N-[4-fluoro-5-(1-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	9.5e-05
335		N-[4-fluoro-5-(1-pyrimidin-2-yl-2,5-dihydropyrrol-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00256
336		N-[4-fluoro-5-(8-pyrimidin-2-yl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0125
337		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00116

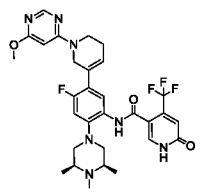
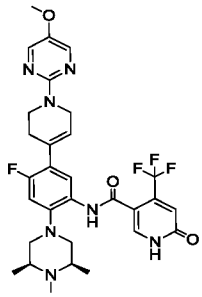
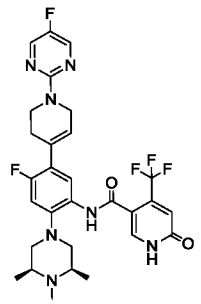
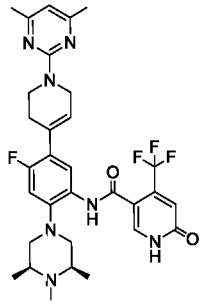
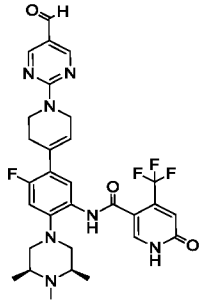
338		N-[4-fluoro-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00208
339		N-[4-fluoro-5-(2-morpholin-4-yl-1,4,5,6-tetrahydropyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.275
340		N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000551
341		N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00197
342		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00687
343		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-	-

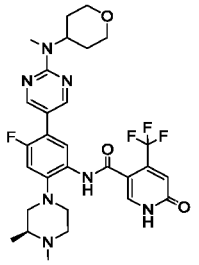
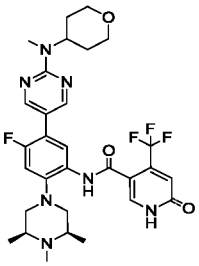
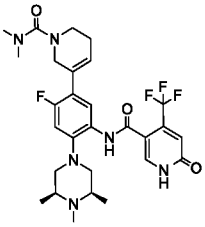
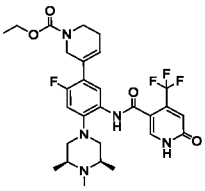
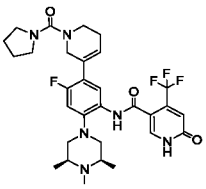
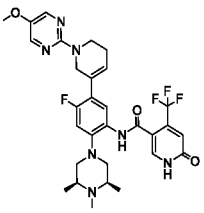
		pyridine-3-carboxamide	
344		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-[ethyl(methyl)amino]-4-fluoropyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0124
345		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[ethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0012
346		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-[ethyl(methyl)amino]-4-fluoropyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-
347		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-propan-2-ylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000606
348		N-[4-fluoro-5-[2-[rac-(2R)-2-propan-2-ylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-**pyridine-3-carboxamide**	0.00228

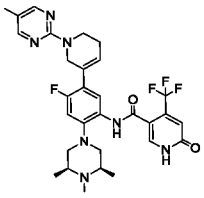
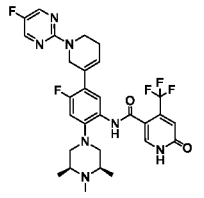
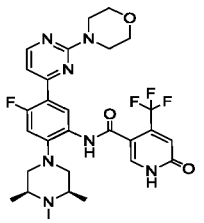
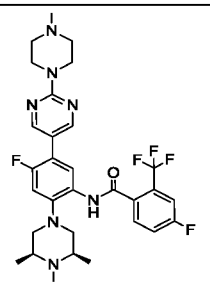
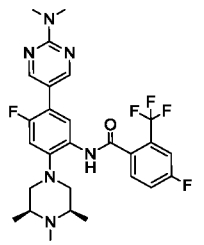
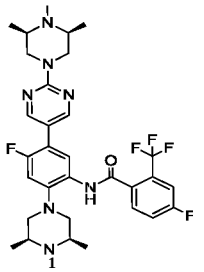
349		N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00235
350		N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00142
351		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide	-
352		N-[5-[2-(7-azabicyclo[2.2.1]heptan-7-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00273
353		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-

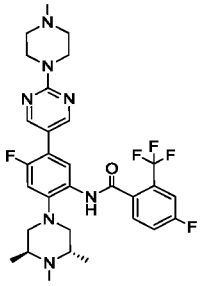
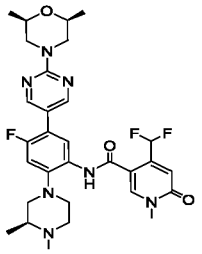
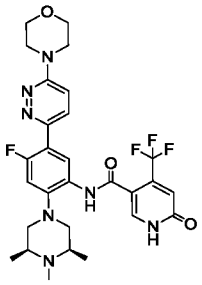
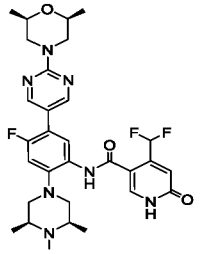
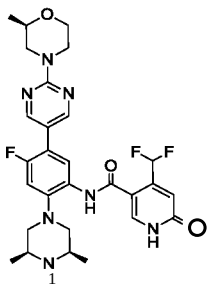
354		N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
355		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0379
356		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0199
357		N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.133
358		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-[ethyl(methyl)amino]-4-methoxypyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-

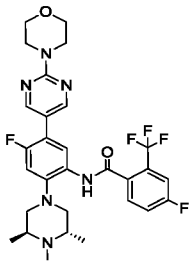
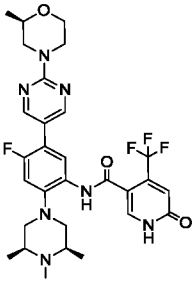
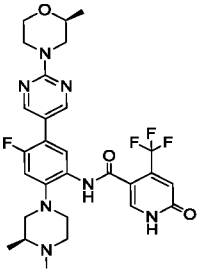
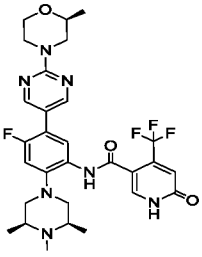
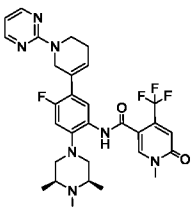
359		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
360		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
361		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0483
362		N-[4-fluoro-5-[2-[methyl-[rac-(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000244
363		N-[4-fluoro-5-[2-[methyl-[rac-(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000634
364		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,5-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00587

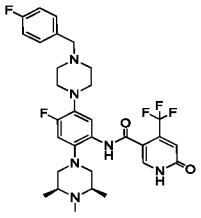
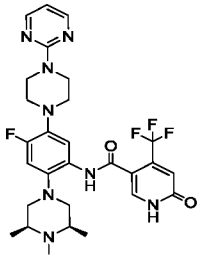
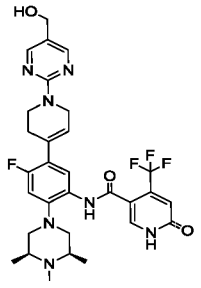
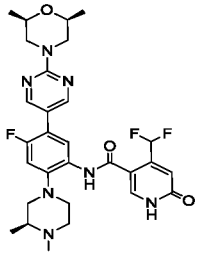
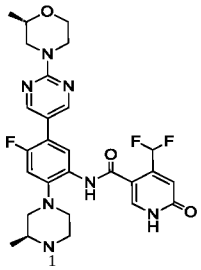
365		N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000246
366		N-[4-fluoro-5-[1-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00176
367		N-[4-fluoro-5-[1-(5-fluoropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00104
368		N-[5-[1-(4,6-dimethylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0023
369		N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000685

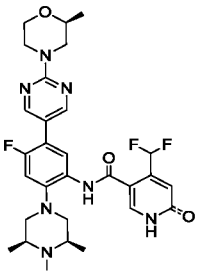
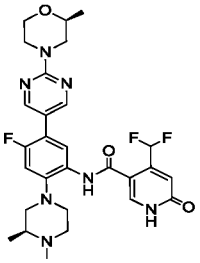
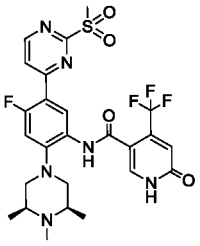
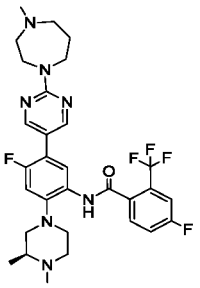
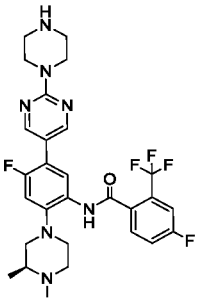
370		N-[4-fluoro-5-[2-[methyl(oxan-4-yl)amino]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000866
371		N-[4-fluoro-5-[2-[methyl(oxan-4-yl)amino]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00059
372		N-[5-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00175
373		ethyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.000808
374		N-[4-fluoro-5-[1-(pyrrolidine-1-carbonyl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00115
375		N-[4-fluoro-5-[1-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000688

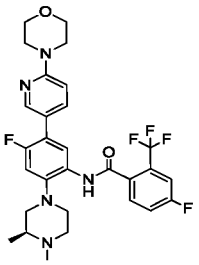
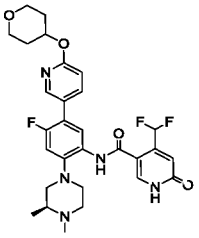
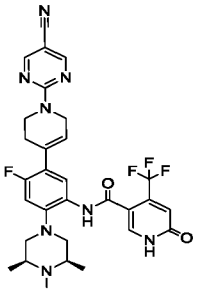
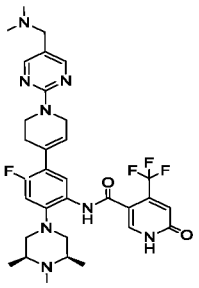
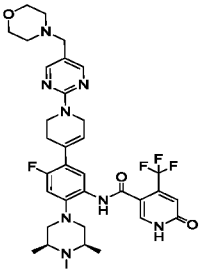
376		N-[4-fluoro-5-[1-(5-methylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000673
377		N-[4-fluoro-5-[1-(5-fluoropyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0013
378		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000877
379		4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000933
380		N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.0017
381		4-fluoro-N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-[2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00031

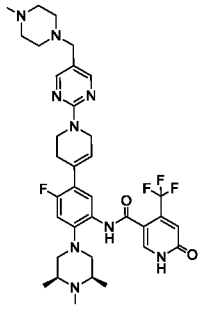
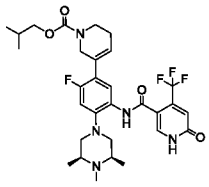
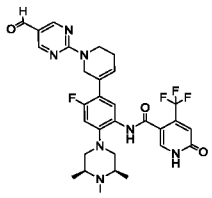
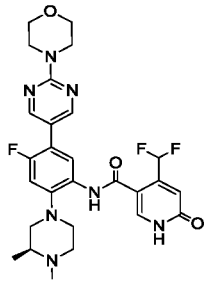
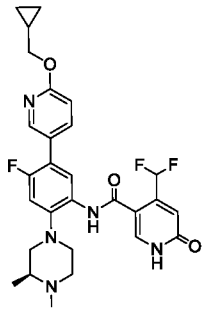
382		4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.117
383		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00119
384		N-[4-fluoro-5-(6-morpholin-4-ylpyridazin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00153
385		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00072
386		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00149

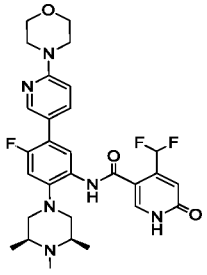
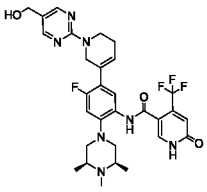
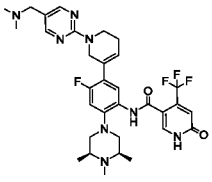
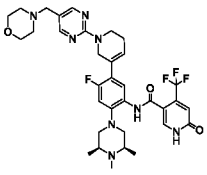
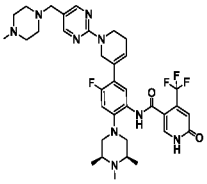
387		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0835
388		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000788
389		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000522
390		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000634
391		N-[4-fluoro-5-(1-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00427

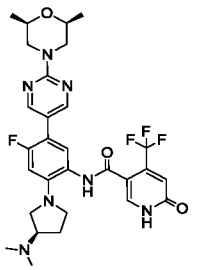
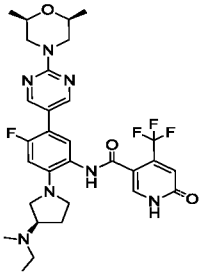
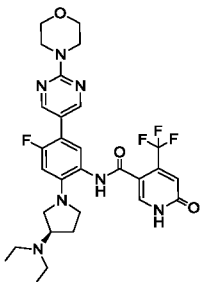
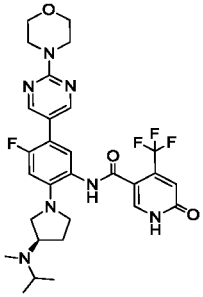
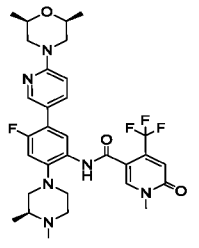
392		N-[4-fluoro-5-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00808
393		N-[4-fluoro-5-(4-pyrimidin-2-ylpiperazin-1-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0133
394		N-[4-fluoro-5-[1-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000775
395		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000152
396		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000564

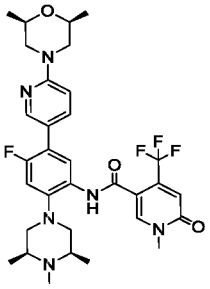
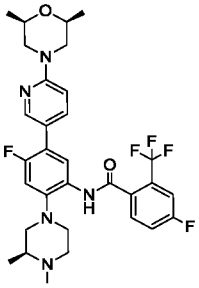
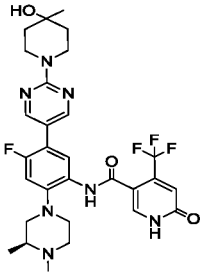
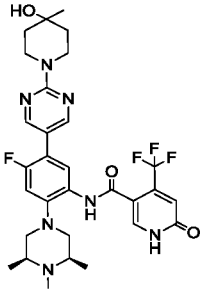
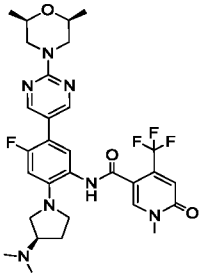
397		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00068
398		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000899
399		N-[4-fluoro-5-(2-methylsulfonylpyrimidin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00458
400		4-fluoro-N-[4-fluoro-5-[2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00147
401		4-fluoro-N-[4-fluoro-5-(2-piperazin-1-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00111

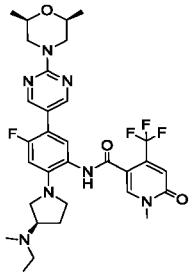
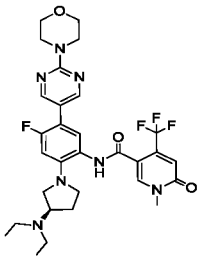
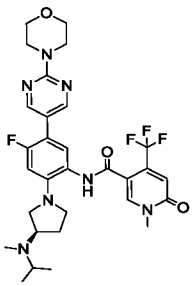
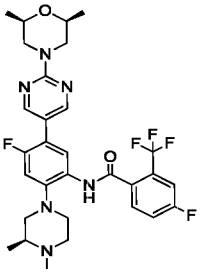
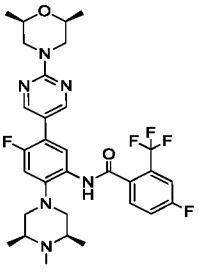
402		4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0037
403		4-(difluoromethyl)-N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00116
404		N-[5-[1-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.001
405		N-[5-[1-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	9.5e-05
406		N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000457

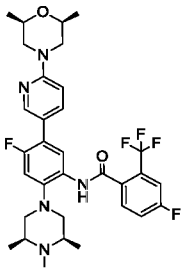
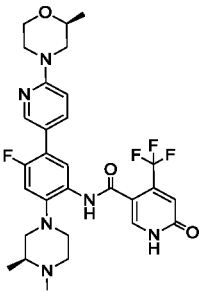
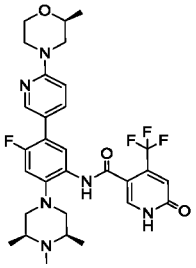
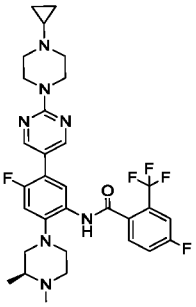
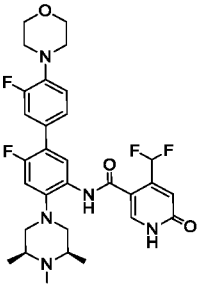
407		N-[4-fluoro-5-[1-[5-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000231
408		2-methylpropyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00275
409		N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000229
410		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00084
411		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00229

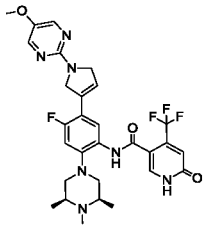
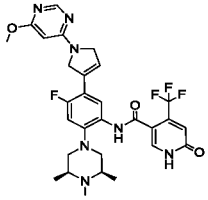
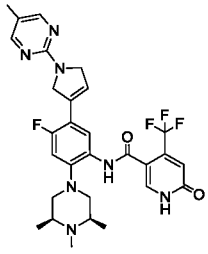
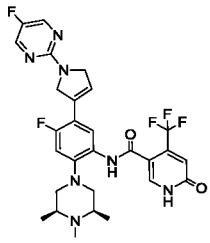
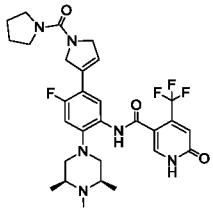
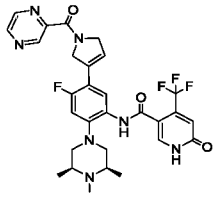
412		4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000962
413		N-[4-fluoro-5-[1-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000302
414		N-[5-[1-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000658
415		N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0011
416		N-[4-fluoro-5-[1-[5-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000108

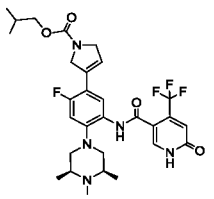
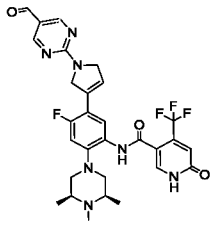
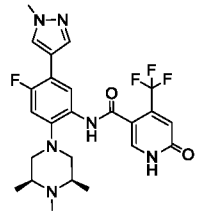
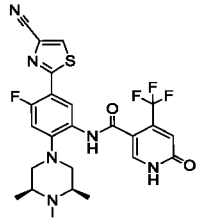
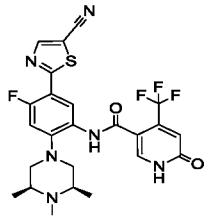
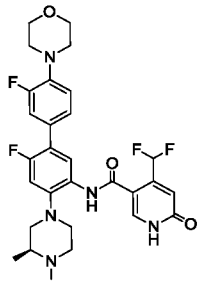
417		N-[4-fluoro-2-[rac-(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00141
418		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S)-3-[ethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00105
419		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00537
420		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.172
421		N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00196

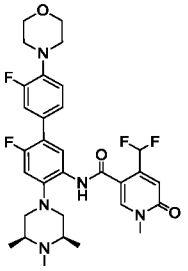
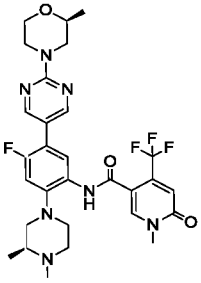
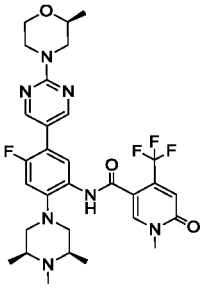
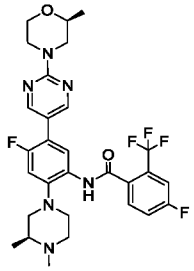
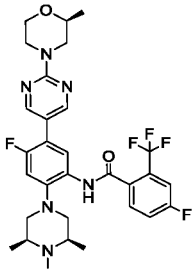
422		N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00243
423		4-fluoro-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00193
424		N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000609
425		N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00106
426		N-[4-fluoro-2-[rac-(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0109

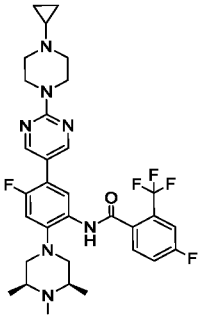
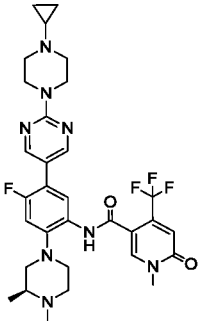
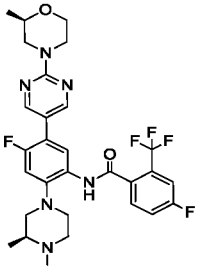
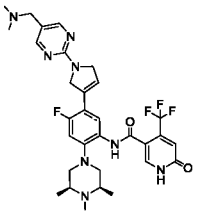
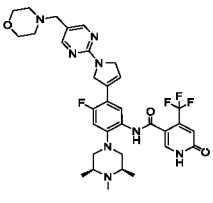
427		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S)-3-[ethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00559
428		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.145
429		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[methyl(propan-2-yl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-
430		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000296
431		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000649

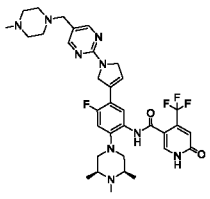
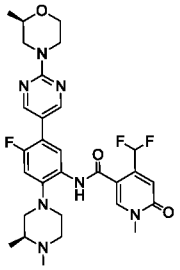
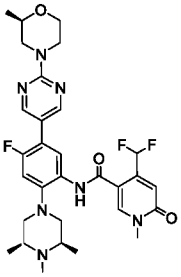
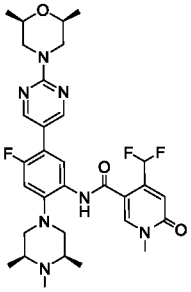
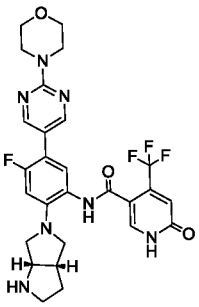
432		4-fluoro-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00231
433		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00284
434		N-[4-fluoro-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000617
435		N-[5-[2-(4-cyclopropylpiperazin-1-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00147
436		4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00139

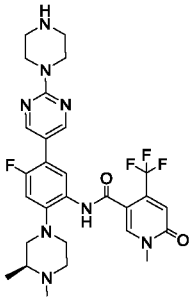
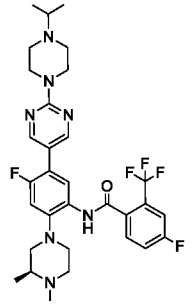
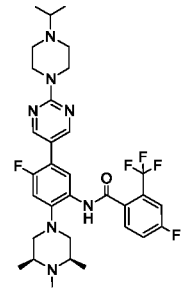
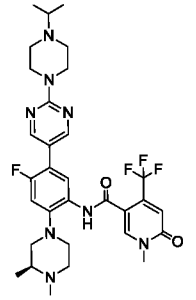
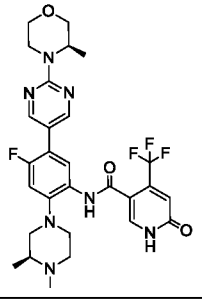
437		N-[4-fluoro-5-[1-(5-methoxypyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000721
438		N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00199
439		N-[4-fluoro-5-[1-(5-methylpyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00245
440		N-[4-fluoro-5-[1-(5-fluoropyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00288
441		N-[4-fluoro-5-[1-(pyrrolidine-1-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00191
442		N-[4-fluoro-5-[1-(pyrazine-2-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00367

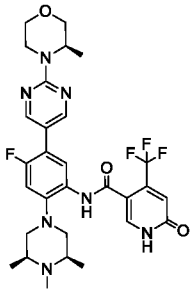
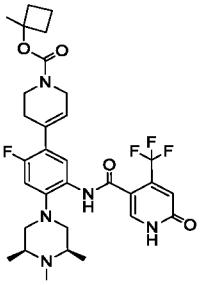
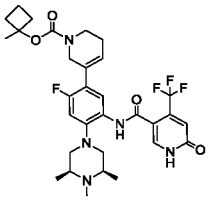
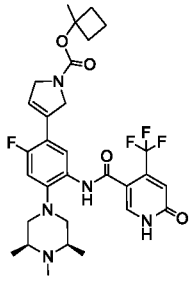
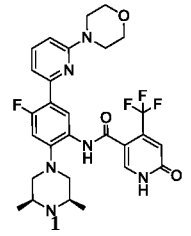
443		2-methylpropyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-carboxylate	0.00237
444		N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00296
445		N-[4-fluoro-5-(1-methylpyrazol-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00195
446		N-[5-(4-cyano-1,3-thiazol-2-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00294
447		N-[5-(5-cyano-1,3-thiazol-2-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00288
448		4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00101

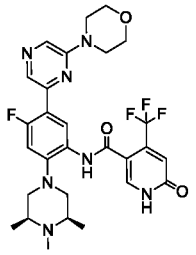
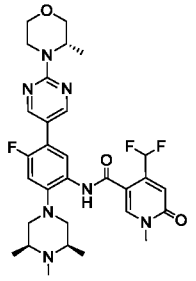
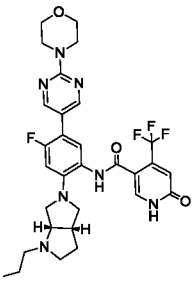
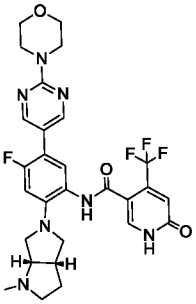
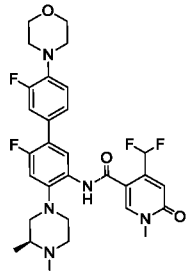
449		4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00903
450		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00102
451		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00172
452		4-fluoro-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000493
453		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000822

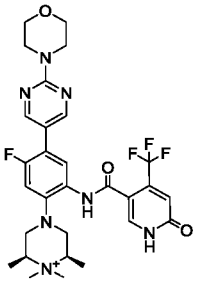
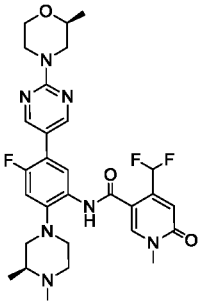
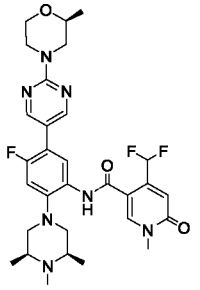
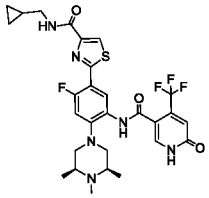
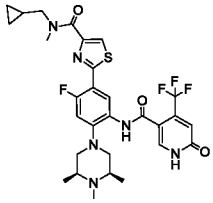
454		N-[5-[2-(4-cyclopropylpiperazin-1-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00405
455		N-[5-[2-(4-cyclopropylpiperazin-1-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00198
456		4-fluoro-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00108
457		N-[5-[1-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00257
458		N-[4-fluoro-5-[1-[5-(morpholin-4-ylmethyl)pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000474

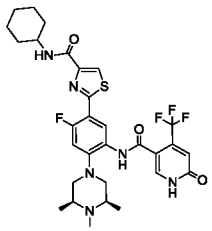
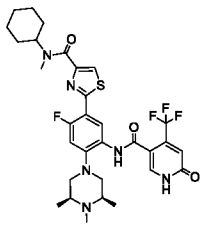
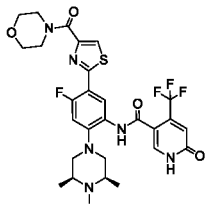
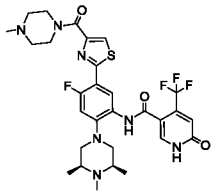
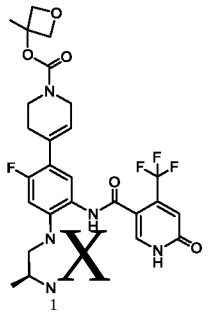
459		N-[4-fluoro-5-[1-[5-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000392
460		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00343
461		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00493
462		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.0037
463		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3aR,6aR)-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.168

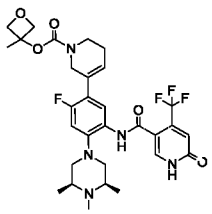
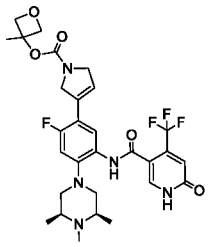
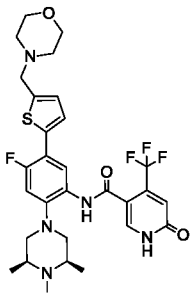
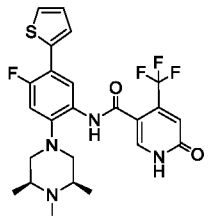
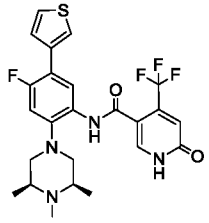
464		N-[4-fluoro-5-(2-piperazin-1-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00221
465		4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00177
466		4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00228
467		N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00254
468		N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00228

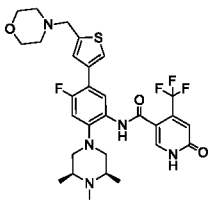
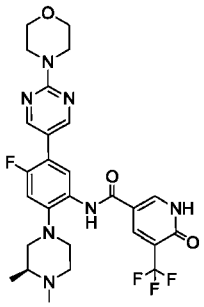
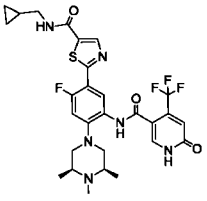
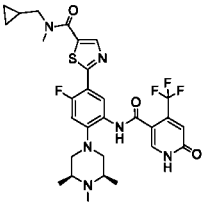
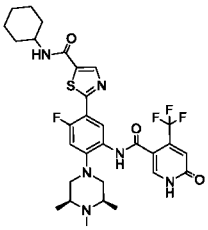
469		N-[4-fluoro-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00564
470		(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00427
471		(1-methylcyclobutyl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.000494
472		(1-methylcyclobutyl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-carboxylate	0.000407
473		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000533

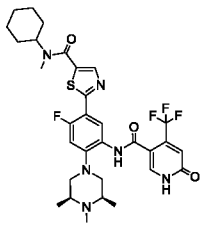
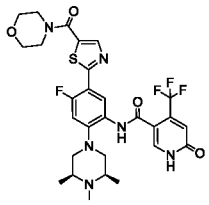
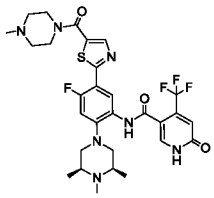
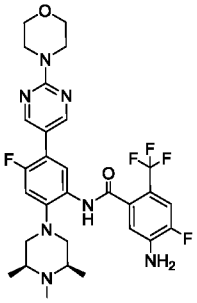
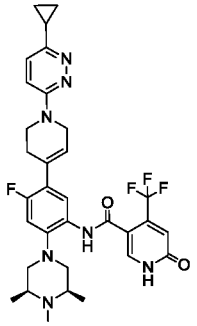
474		N-[4-fluoro-5-(6-morpholin-4-ylpyrazin-2-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0012
475		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00352
476		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3aR,6aR)-1-propyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00971
477		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3aR,6aR)-1-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0242
478		4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-morpholin-4-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00532

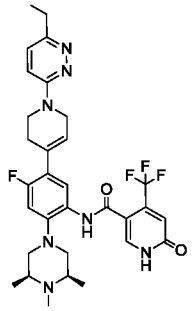
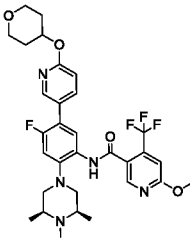
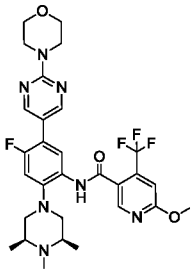
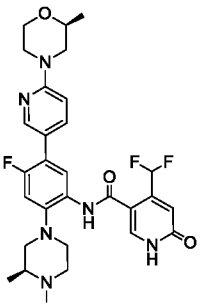
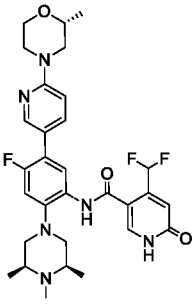
479		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,4,5-tetramethylpiperazin-4-ium-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00354
480		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00215
481		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00489
482		N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-4-carboxamide	0.00175
483		N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-4-carboxamide	0.00397

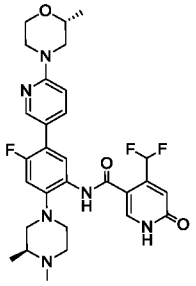
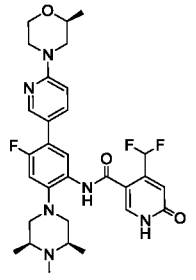
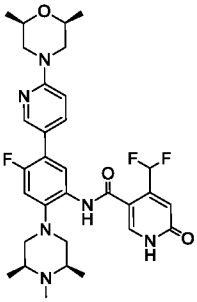
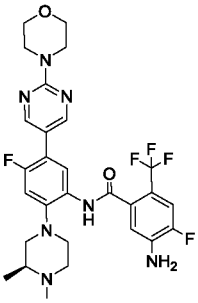
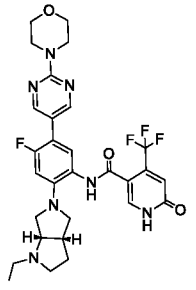
484		N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-4-carboxamide	0.00307
485		N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-4-carboxamide	0.00221
486		N-[4-fluoro-5-[4-(morpholine-4-carbonyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00244
487		N-[4-fluoro-5-[4-(4-methylpiperazine-1-carbonyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00281
488		(3-methyloxetan-3-yl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00487

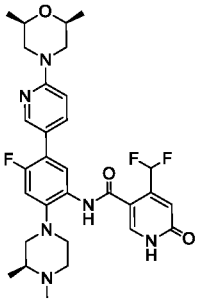
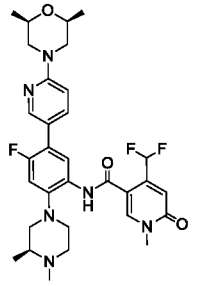
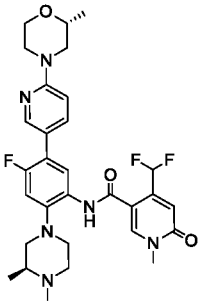
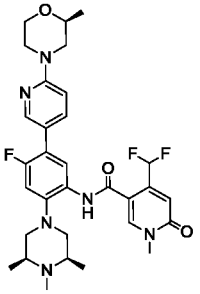
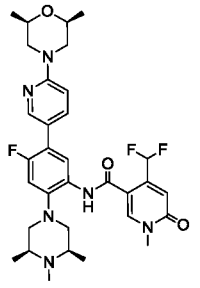
489		(3-methyloxetan-3-yl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00274
490		(3-methyloxetan-3-yl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-carboxylate	0.00324
491		N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00359
492		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-thiophen-2-ylphenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00335
493		N-[4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]-5-thiophen-3-ylphenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00286

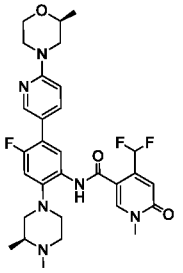
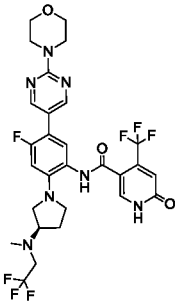
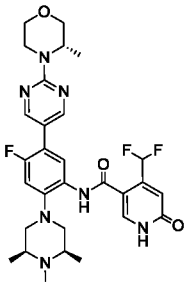
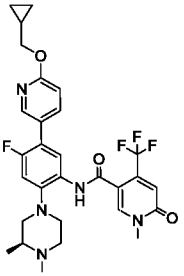
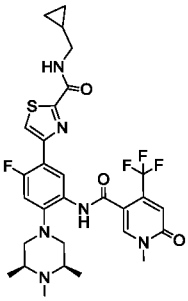
494		N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)thiophen-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00301
495		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-5-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0249
496		N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-5-carboxamide	0.00303
497		N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-5-carboxamide	0.00259
498		N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-5-carboxamide	0.00147

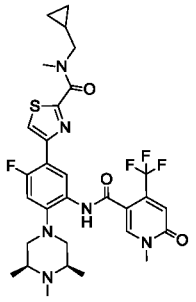
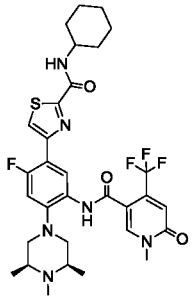
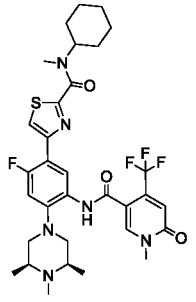
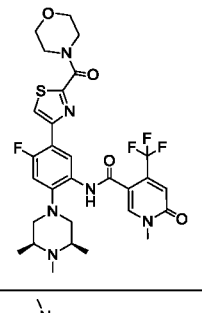
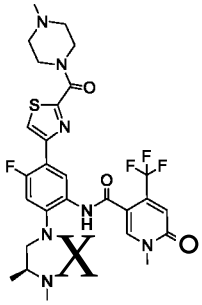
499		N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-5-carboxamide	0.0034
500		N-[4-fluoro-5-[5-(morpholine-4-carbonyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00185
501		N-[4-fluoro-5-[5-(4-methylpiperazine-1-carbonyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00344
502		5-amino-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00115
503		N-[5-[1-(6-cyclopropylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00244

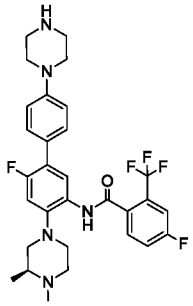
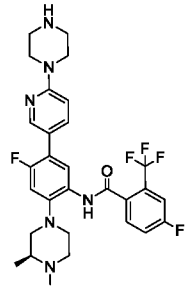
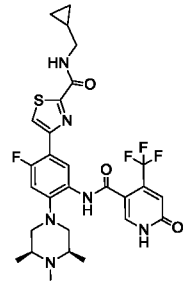
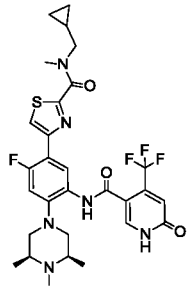
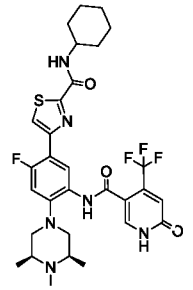
504		N-[5-[1-(6-ethylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00244
505		N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide	-
506		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide	0.354
507		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00176
508		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00266

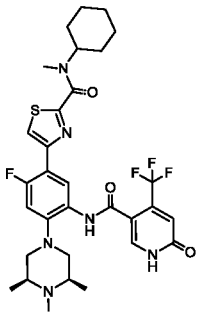
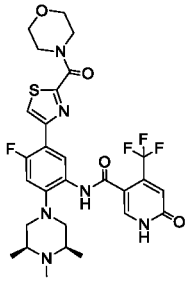
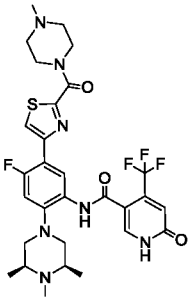
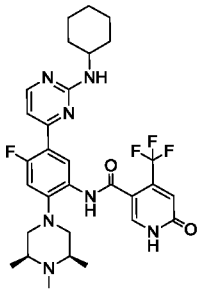
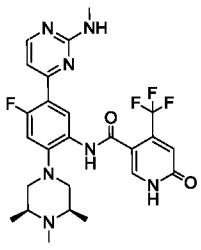
509		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000947
510		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000623
511		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000779
512		5-amino-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000711
513		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3aR,6aR)-1-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0099

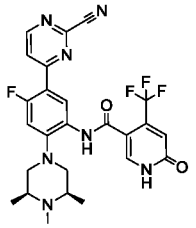
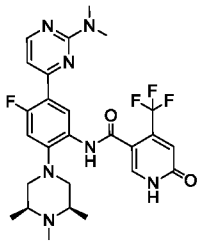
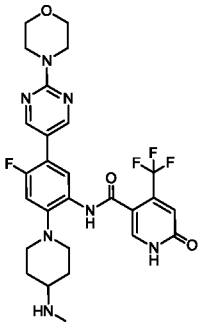
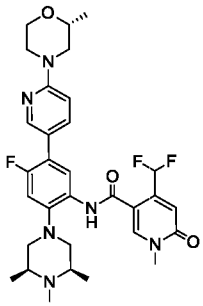
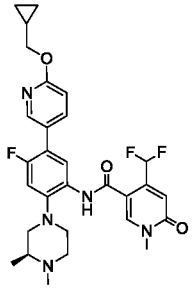
514		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000959
515		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00409
516		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.004
517		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00597
518		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00341

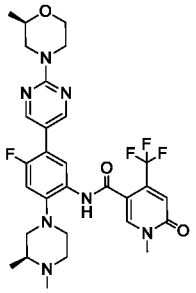
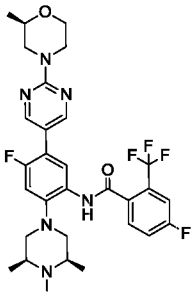
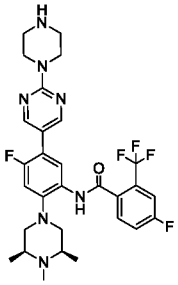
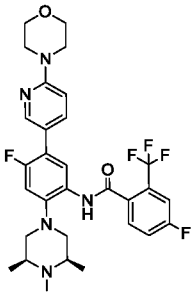
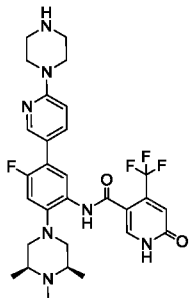
519		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00339
520		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[methyl(2,2,2-trifluoroethyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
521		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000579
522		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00562
523		N-(cyclopropylmethyl)-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-2-carboxamide	0.00459

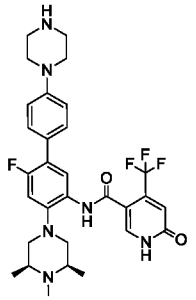
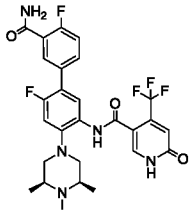
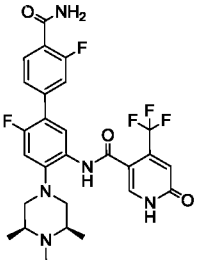
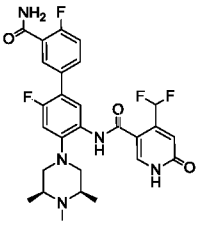
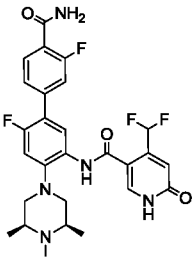
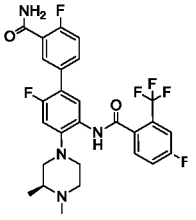
524		N-(cyclopropylmethyl)-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide	0.00503
525		N-cyclohexyl-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-2-carboxamide	0.00542
526		N-cyclohexyl-4-[2-fluoro-5-[[1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide	0.00489
527		N-[4-fluoro-5-[2-(morpholine-4-carbonyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00566
528		N-[4-fluoro-5-[2-(4-methylpiperazine-1-carbonyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00405

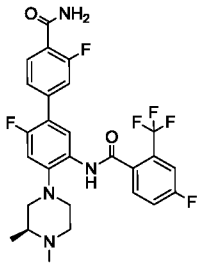
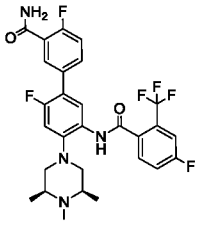
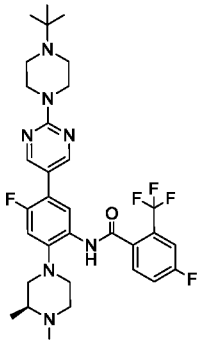
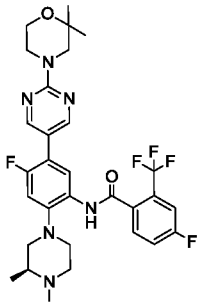
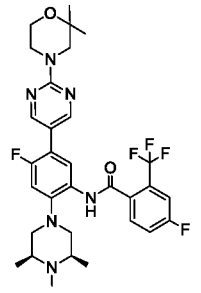
529		4-fluoro-N-[4-fluoro-5-(4-piperazin-1-ylphenyl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00292
530		4-fluoro-N-[4-fluoro-5-(6-piperazin-1-ylpyridin-3-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00216
531		N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-2-carboxamide	0.00106
532		N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide	0.000694
533		N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1,3-thiazole-2-carboxamide	0.00198

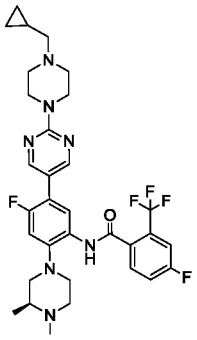
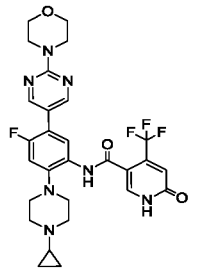
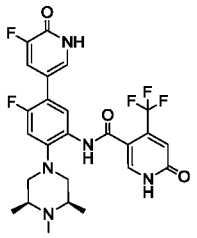
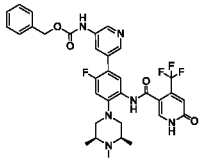
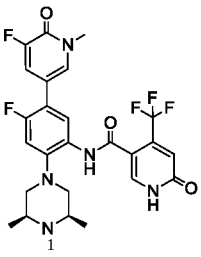
534		N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-methyl-1,3-thiazole-2-carboxamide	0.00131
535		N-[4-fluoro-5-[2-(morpholine-4-carbonyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0028
536		N-[4-fluoro-5-[2-(4-methylpiperazine-1-carbonyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00103
537		N-[5-[2-(cyclohexylamino)pyrimidin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000944
538		N-[4-fluoro-5-[2-(methylamino)pyrimidin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00302

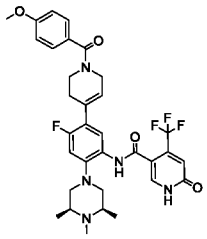
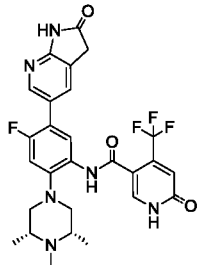
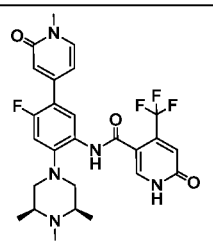
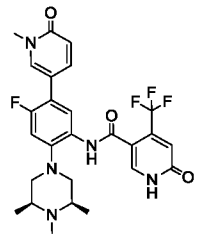
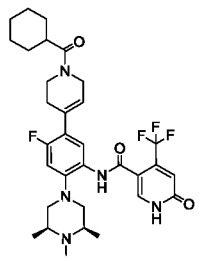
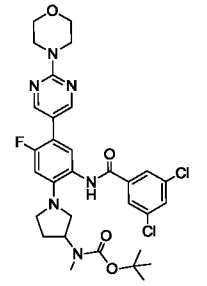
539		N-[5-(2-cyanopyrimidin-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00256
540		N-[5-[2-(dimethylamino)pyrimidin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0011
541		N-[4-fluoro-2-[4-(methylamino)piperidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00744
542		4-(difluoromethyl)-N-[4-fluoro-5-[6-[rac-(2R)-2-methylmorpholin-4-yl]pyridin-3-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00553
543		N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.00821

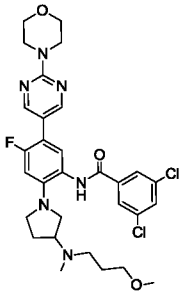
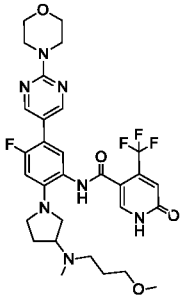
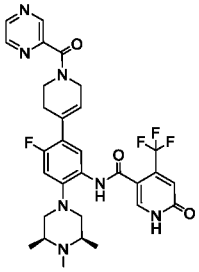
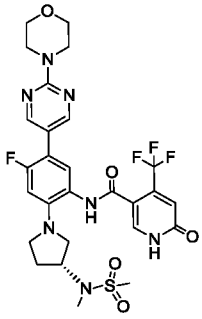
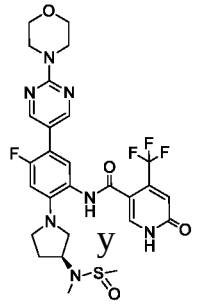
544		N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0018
545		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0034
546		4-fluoro-N-[4-fluoro-5-(2-piperazin-1-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0021
547		4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.0015
548		N-[4-fluoro-5-(6-piperazin-1-ylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0005

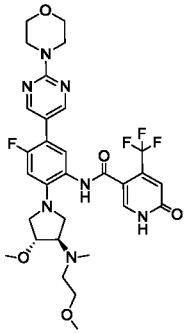
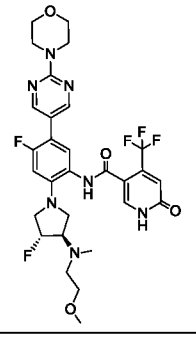
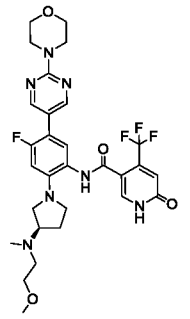
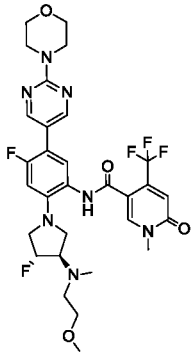
549		N-[4-fluoro-5-(4-piperazin-1-ylphenyl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0008
550		N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0025
551		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0006
552		N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.0031
553		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.001
554		2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.0053

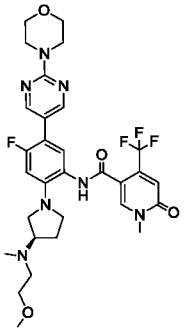
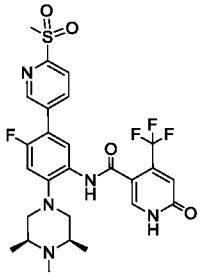
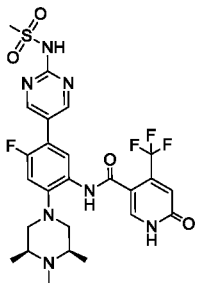
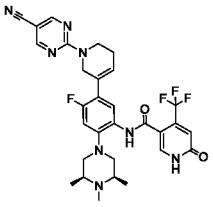
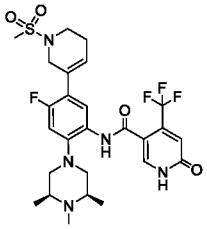
555		2-fluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.00294
556		2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0104
557		N-[5-[2-(4-tert-butylpiperazin-1-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00109
558		N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00378
559		N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00292

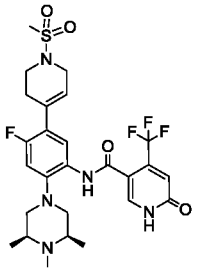
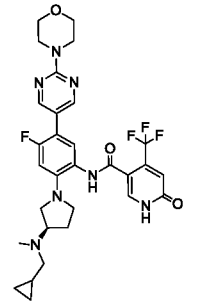
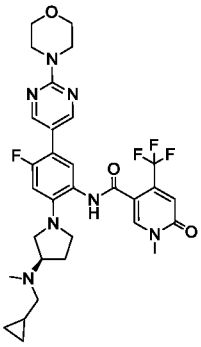
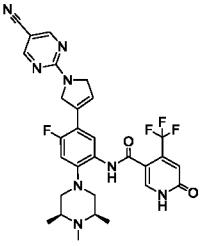
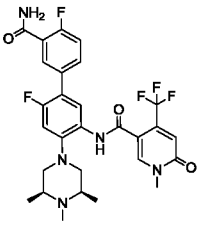
560		N-[5-[2-[4-(cyclopropylmethyl)piperazin-1-yl]pyrimidin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00112
561		N-[2-(4-cyclopropylpiperazin-1-yl)-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0235
562		N-[4-fluoro-5-(5-fluoro-6-oxo-1H-pyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000904
563		benzyl N-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]pyridin-3-yl]carbamate	0.00332
564		N-[4-fluoro-5-(5-fluoro-1-methyl-6-oxopyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00152

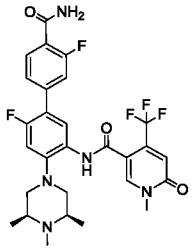
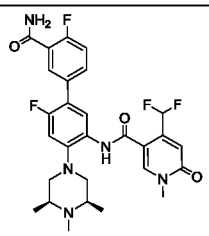
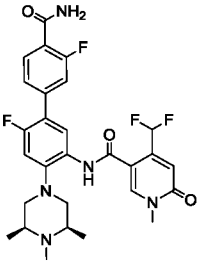
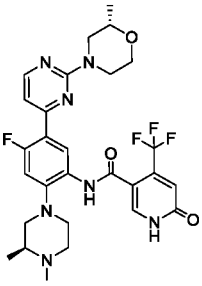
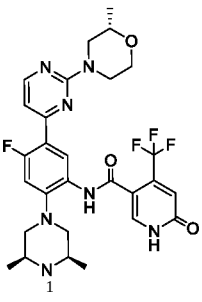
565		N-[4-fluoro-5-[1-(4-methoxybenzoyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000943
566		N-[4-fluoro-5-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000896
567		N-[4-fluoro-5-(1-methyl-2-oxopyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00118
568		N-[4-fluoro-5-(1-methyl-6-oxopyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00458
569		N-[5-[1-(cyclohexanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00199
570		tert-butyl N-[1-[2-[(3,5-dichlorobenzoyl)amino]-5-fluoro-4-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]pyrrolidin-3-yl]-N-methylcarbamate	-

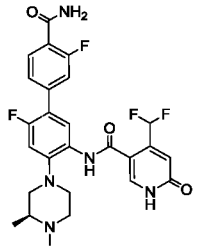
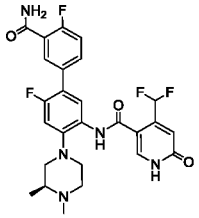
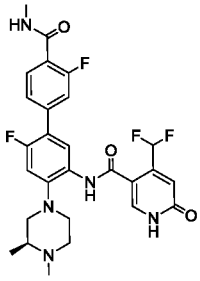
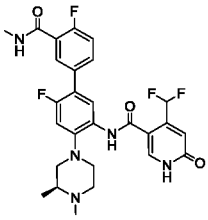
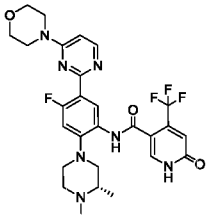
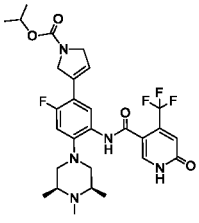
571		3,5-dichloro-N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]benzamide	-
572		N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-1-yl]-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.113
573		N-[4-fluoro-5-[1-(pyrazine-2-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00219
574		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
575		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-

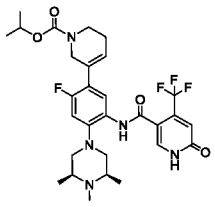
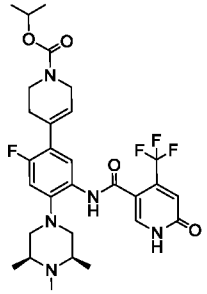
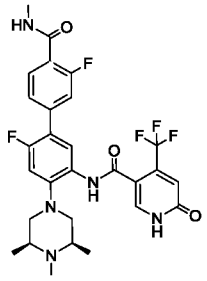
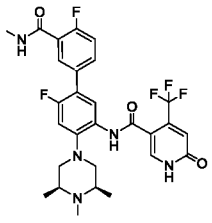
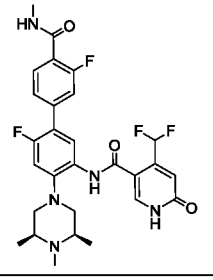
576		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-methoxy-4-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
577		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	-
578		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0169
579		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-

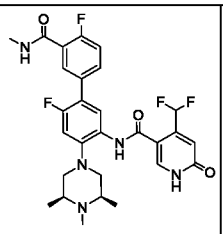
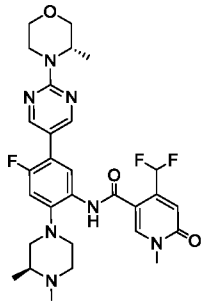
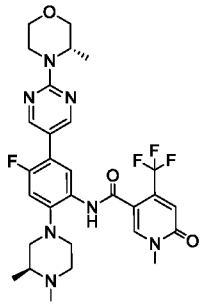
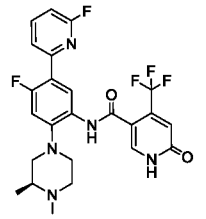
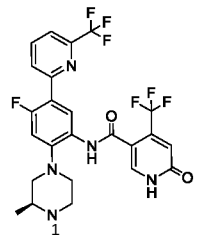
580		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	-
581		N-[4-fluoro-5-(6-methylsulfonylpyridin-3-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000768
582		N-[4-fluoro-5-[2-(methanesulfonamido)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00578
583		N-[5-[1-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000877
584		N-[4-fluoro-5-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00121

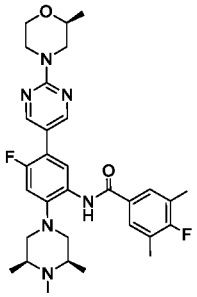
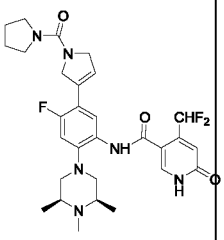
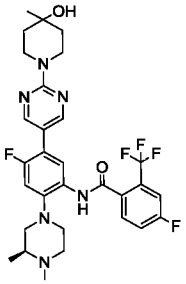
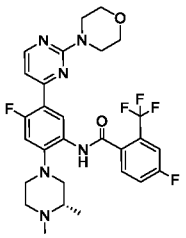
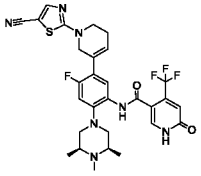
585		N-[4-fluoro-5-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000829
586		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0155
587		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.253
588		N-[5-[1-(5-cyanopyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00172
589		N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00746

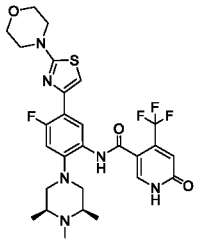
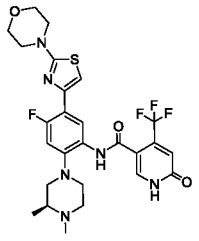
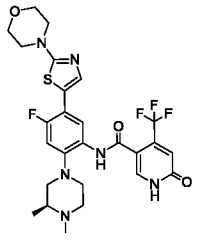
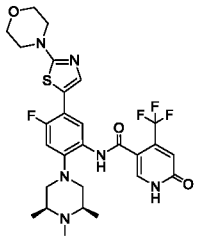
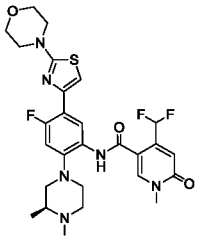
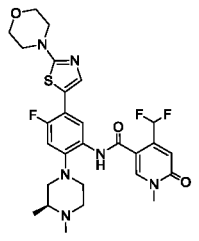
590		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00332
591		N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.0155
592		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.0068
593		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000737
594		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000712

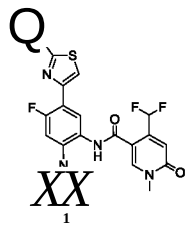
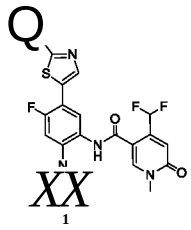
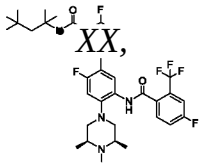
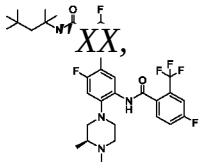
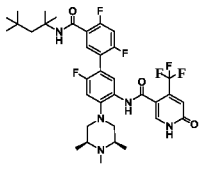
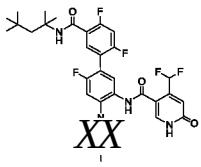
595		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00118
596		N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00403
597		4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.000711
598		4-(difluoromethyl)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00151
599		N-[4-fluoro-5-(4-morpholin-4-ylpyrimidin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00418
600		propan-2-yl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,5-dihydropyrrole-1-	0.000779

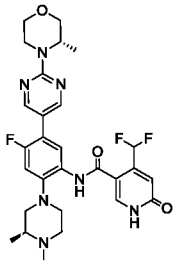
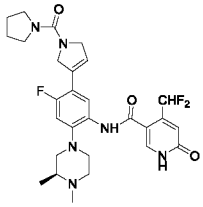
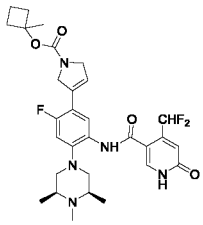
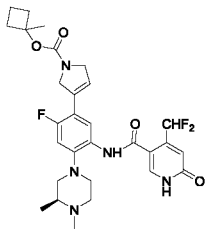
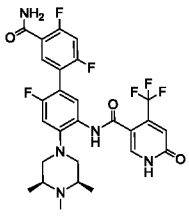
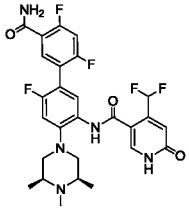
		carboxylate	
601		propan-2-yl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.000271
602		propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.000475
603		N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00109
604		N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00171
605		4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.0006

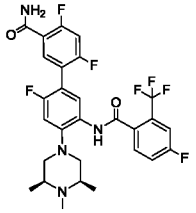
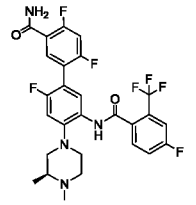
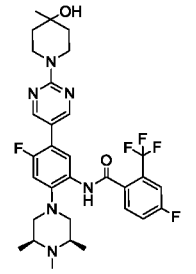
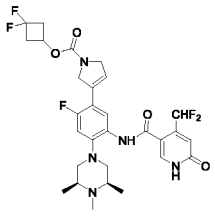
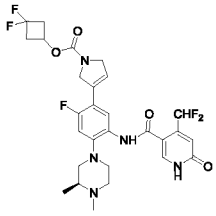
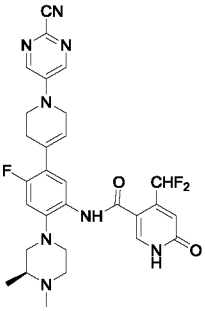
606		4-(difluoromethyl)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00186
607		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00153
608		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.000977
609		N-[4-fluoro-5-(6-fluoropyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000774
610		N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[6-(trifluoromethyl)pyridin-2-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000552

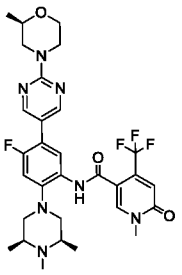
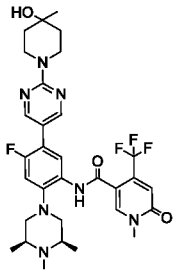
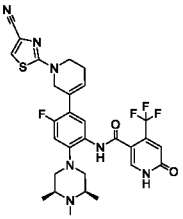
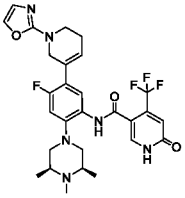
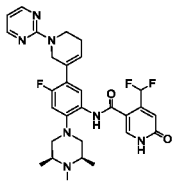
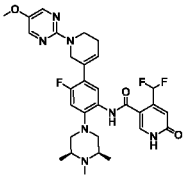
611		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,5-dimethylbenzamide	0.00155
612		4-(Difluoromethyl)-N-(4-fluoro-5-(1-(pyrrolidine-1-carbonyl)-2,5-dihydro-1H-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide	0.00194
613		4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000922
614		4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.000733
615		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000375

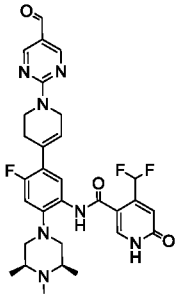
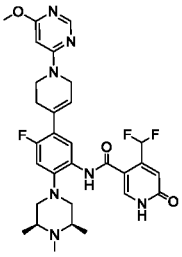
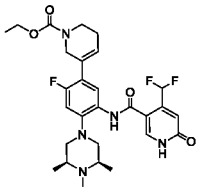
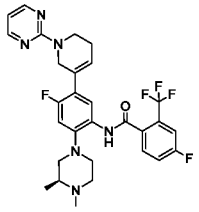
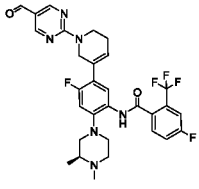
616		N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000748
617		N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	000558
618		N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00113 0.
619		N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.000948
620		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00419
621		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-yl-1,3-thiazol-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00484

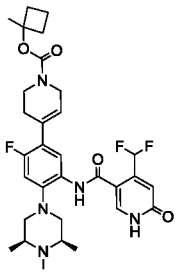
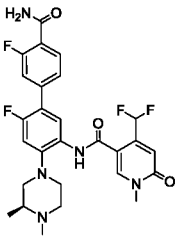
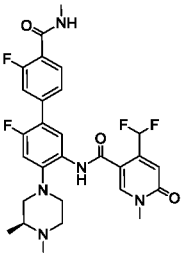
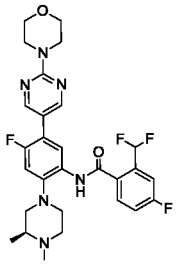
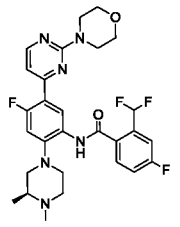
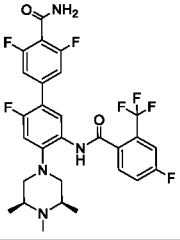
622		4-(difluoromethyl)-N-[4-fluoro-5-(2-methoxypyridin-4-yl-1,3-thiazol-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00515
623		4-(difluoromethyl)-N-[4-fluoro-5-(2-methoxypyridin-4-yl-1,3-thiazol-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00557
624		2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide	-
625		2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide	0.172
626		N-[5-[2,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00524
627		4-(difluoromethyl)-N-[5-[2,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.0233

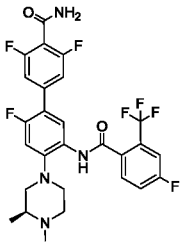
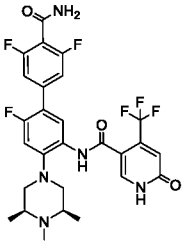
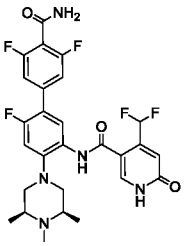
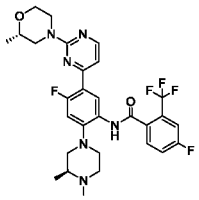
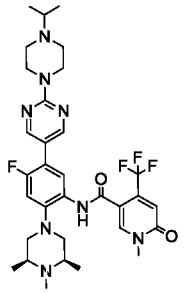
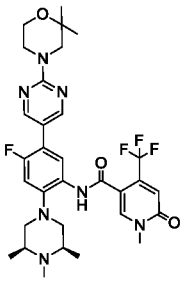
628		4-(difluoromethyl)-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00125
629		(S)-4-(Sifluoromethyl)-N-(2-(3,4-dimethylpiperazin-1-yl)-4-fluoro-5-(1-(pyrrolidine-1-carbonyl)-2,5-dihydro-1H-pyrrol-3-yl)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide	0.00222
630		1-Methylcyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate	0.00198
631		1-Methylcyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-1-yl)-2-fluorophenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate	0.00265
632		N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0114
633		N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.0119

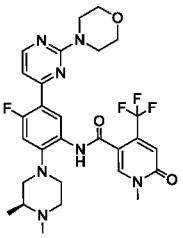
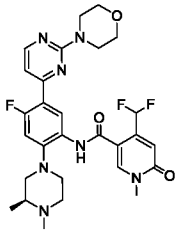
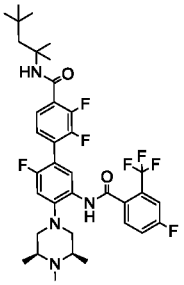
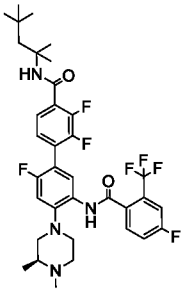
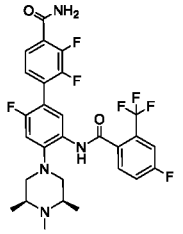
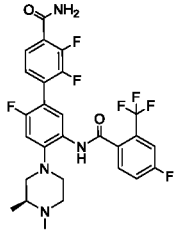
634		2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.0695
635		2,4-difluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.0669
636		4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00142
637		3,3-Difluorocyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate	0.00226
638		3,3-Difluorocyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-1-yl)-2-fluorophenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate	0.00227
639		(S)-N-(5-(1-(2-cyanopyrimidin-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethylpiperazin-1-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide	0.00497

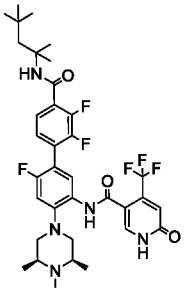
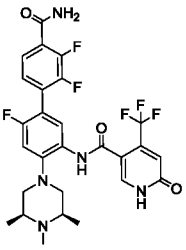
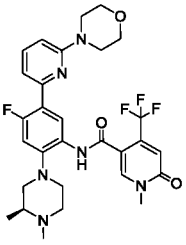
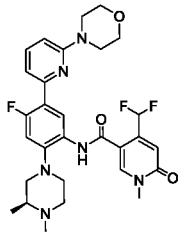
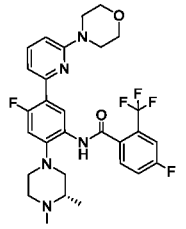
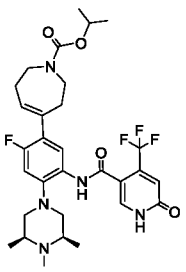
640		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00174
641		N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00192
642		N-[5-[1-(4-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.0013
643		N-[4-fluoro-5-[1-(1,3-oxazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00126
644		4-(difluoromethyl)-N-[4-fluoro-5-(1-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00132
645		4-(difluoromethyl)-N-[4-fluoro-5-[1-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-	0.00141

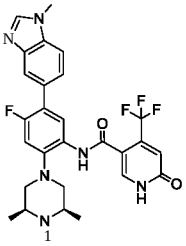
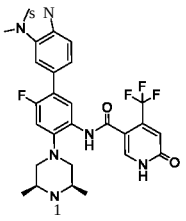
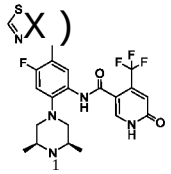
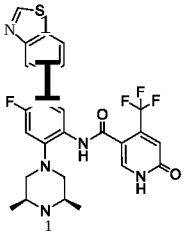
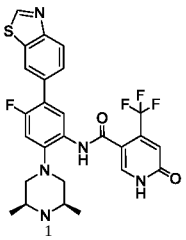
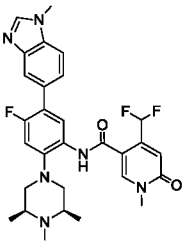
		pyridine-3-carboxamide	
646		4-(difluoromethyl)-N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00141
647		4-(difluoromethyl)-N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00159
648		ethyl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00197
649		4-fluoro-N-[4-fluoro-5-(1-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00187
650		4-fluoro-N-[4-fluoro-5-[1-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00518

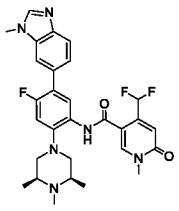
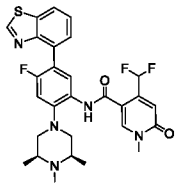
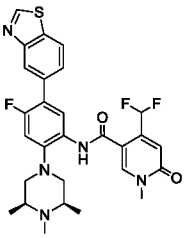
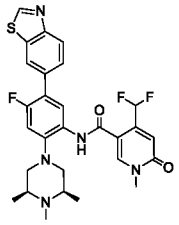
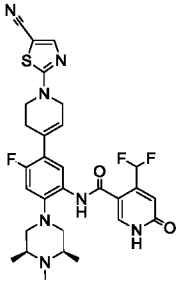
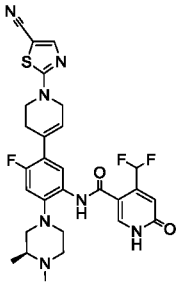
651		(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.000897
652		N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.00529
653		4-(difluoromethyl)-N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00343
654		2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	–
655		2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.00106 –
656		2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00544

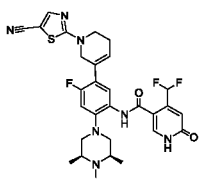
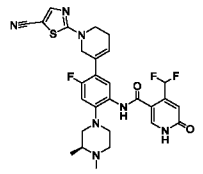
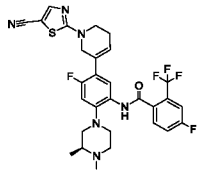
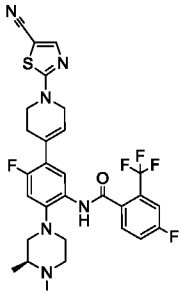
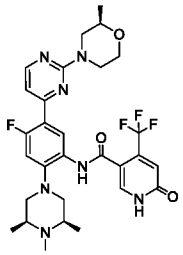
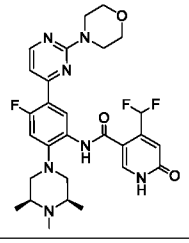
657		2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.00469
658		N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00188
659		N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00193
660		4-fluoro-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00029
661		N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-1-yl)pyrimidin-5-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00323
662		N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00229

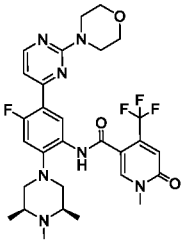
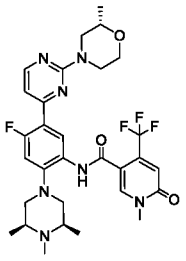
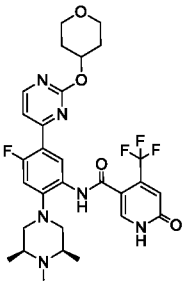
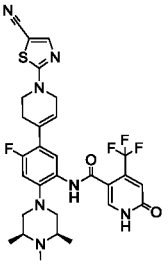
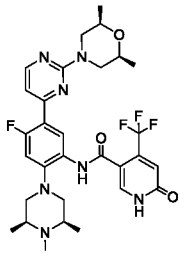
663		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.0025
664		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00268
665		2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide	0.151
666		2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide	0.117
667		2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00965
668		2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide	0.0183

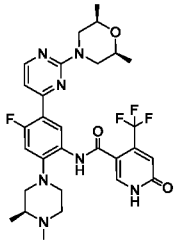
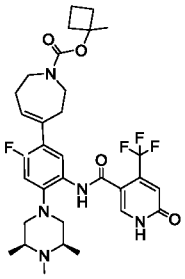
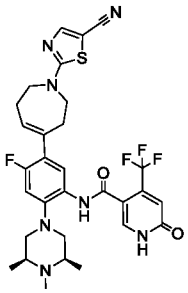
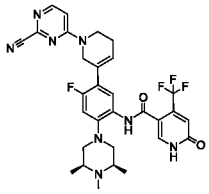
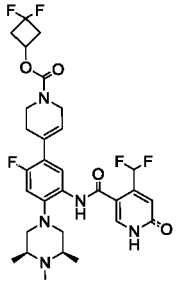
669		N-[5-[2,3-difluoro-4-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00971
670		N-[5-(4-carbamoyl-2,3-difluorophenyl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00385
671		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00442
672		4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00502
673		4-fluoro-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00318
674		propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-**carboxylate**	0.00494

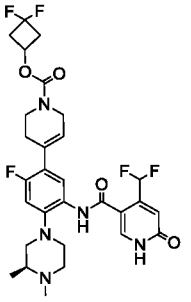
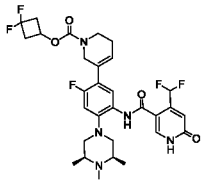
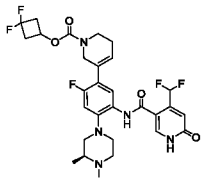
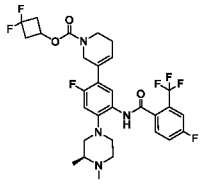
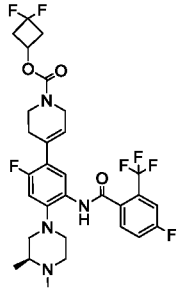
675		N-[4-fluoro-5-(l-methylbenzimidazol-5 -yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-0X0-4-(trifluoromethy 1) -1H-pyridine-3-carboxamide	0.00197
676		N-[4-fluoro-5-(3-methylbenzimidazol-5 -yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-0X0-4-(trifluoromethy 1) -1H-pyridine-3-carboxamide	0.00439
677		N-[5 -(1,3 -benzothiazol-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-0X0-4-(trifluoromethy 1) -1H-pyridine-3-carboxamide	0.00529
678		N-[5 -(1,3 -benzothiazol-5 -yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-0X0-4-(trifluoromethy 1) -1H-pyridine-3-carboxamide	0.00326
679		N-[5 -(1,3 -benzothiazol-6-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-0X0-4-(trifluoromethy 1) -1H-pyridine-3-carboxamide	0.00297
680		4-(difluoromethyl)-N-[4-fluoro-5-(l-methylbenzimidazol-5 -yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide	0.0582

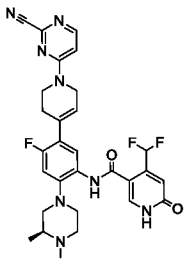
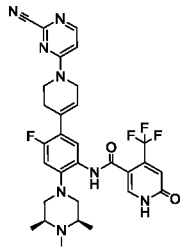
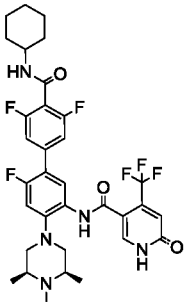
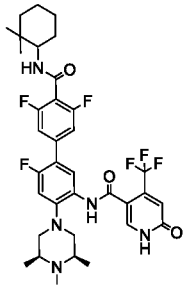
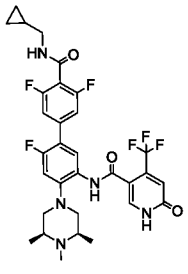
681		4-(difluoromethyl)-N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.0393
682		N-[5-(1,3-benzothiazol-4-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.0204
683		N-[5-(1,3-benzothiazol-5-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.0123
684		N-[5-(1,3-benzothiazol-6-yl)-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide	0.00782
685		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00223
686		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00199

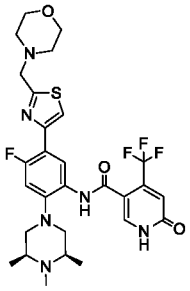
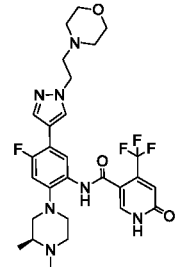
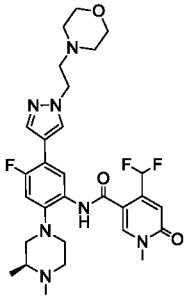
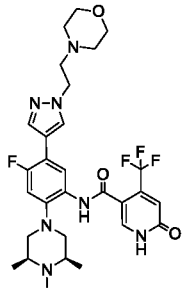
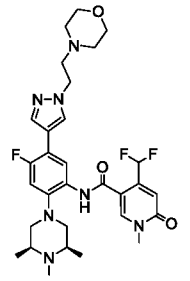
687		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00184
688		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00249
689		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00628
690		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide	0.00417
691		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00131
692		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.0024

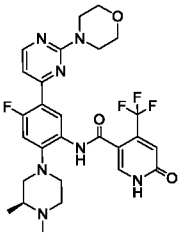
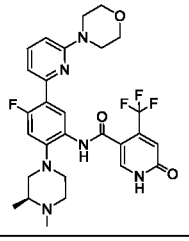
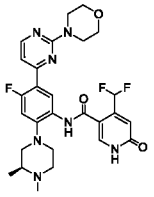
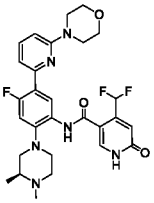
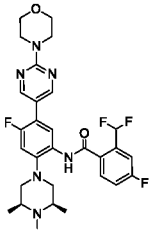
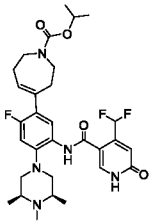
693		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00479
694		N-[4-fluoro-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00492
695		N-[4-fluoro-5-[2-(oxan-4-yloxy)pyrimidin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00253
696		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00131
697		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	–

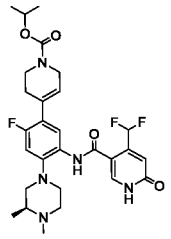
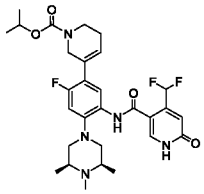
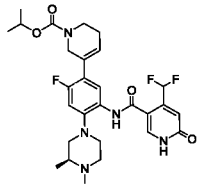
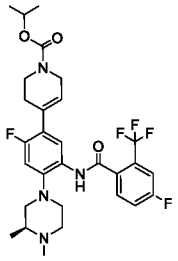
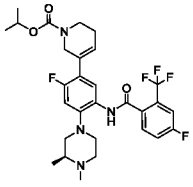
698		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00159
699		(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carbonyl]amino]-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate	0.0037
700		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00731
701		N-[5-[1-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00173
702		(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00347

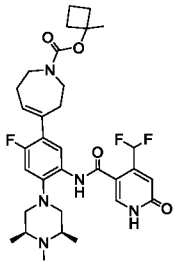
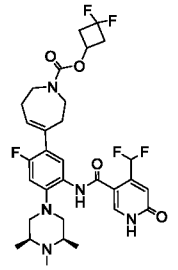
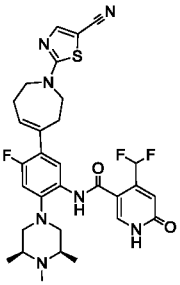
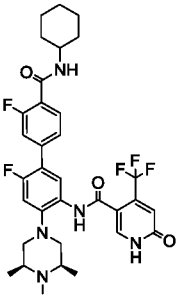
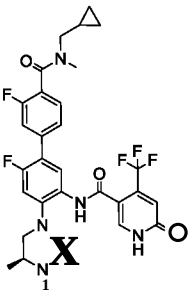
703		(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH -pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate	0.00103
704		(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH -pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate	0.00272
705		(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH -pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate	0.00202
706		(3,3-difluorocyclobutyl) 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate	0.00381
707		(3,3-difluorocyclobutyl) 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate	0.00216

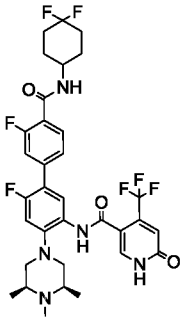
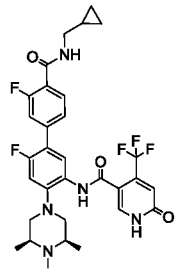
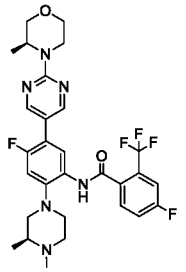
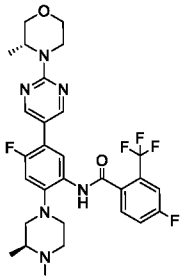
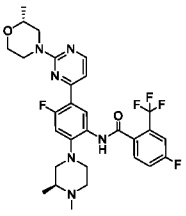
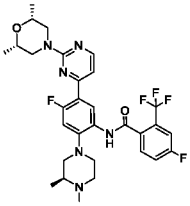
708		N-[5-[1-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00058 –
709		N-[5-[1-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00072 –
710		N-[5-[4-(cyclohexylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00203 –
711		N-[5-[4-[(2,2-dimethylcyclohexyl)carbamoyl]-3,5-difluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00317 –
712		N-[5-[4-(cyclopropylmethylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00223

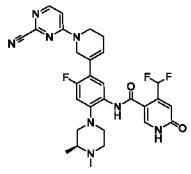
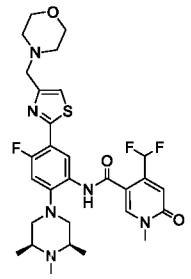
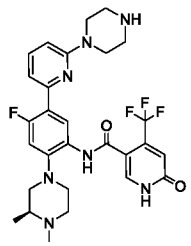
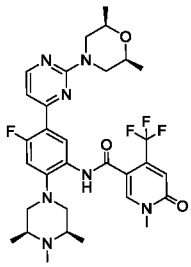
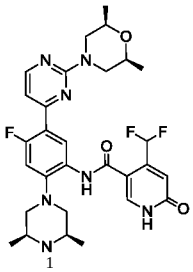
713		N-[4-fluoro-5-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00259
714		N-[4-fluoro-5-[1-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00276
715		4-(difluoromethyl)-N-[4-fluoro-5-[1-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.01092
716		N-[4-fluoro-5-[1-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00242
717		4-(difluoromethyl)-N-[4-fluoro-5-[1-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.02157

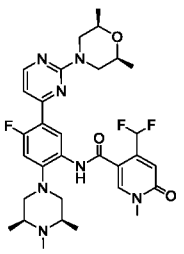
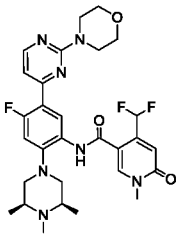
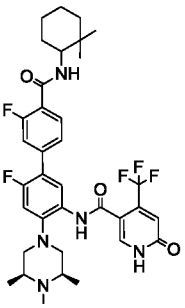
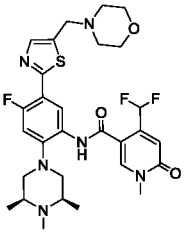
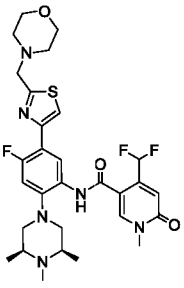
718		N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00109
719		N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00118
720		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00131
721		4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00162
722		2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide	0.00136
723		propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate	0.00312

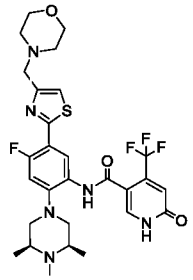
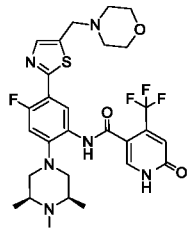
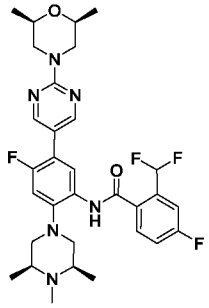
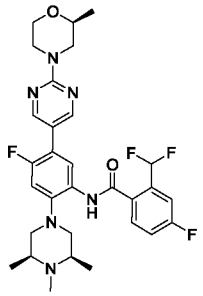
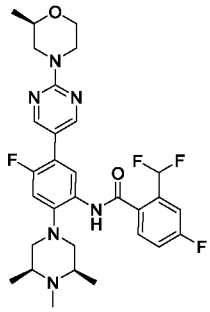
724		propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00282
725		propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00159
726		propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.0021
727		propan-2-yl 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00246
728		propan-2-yl 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate	0.00355

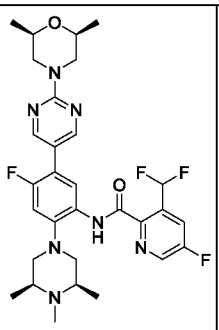
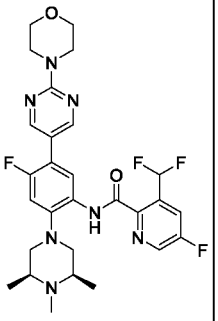
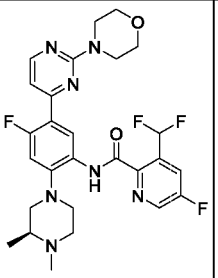
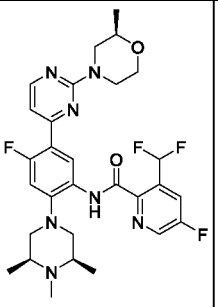
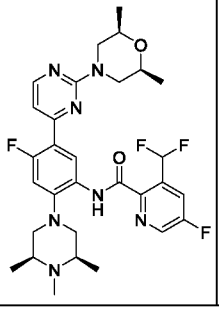
729		(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate	0.00311
730		(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate	0.00799
731		N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00761
732		N-[5-[4-(cyclohexylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00276
733		N-[5-[4-[cyclopropylmethyl(methyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00129

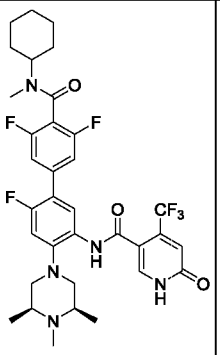
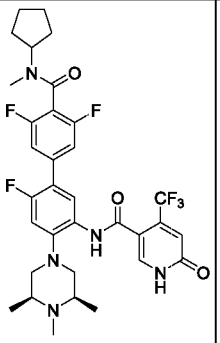
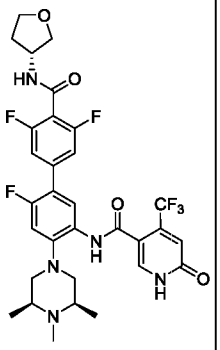
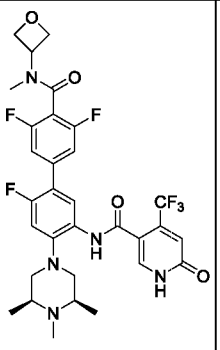
734		N-[5-[4-[(4,4-difluorocyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00413
735		N-[5-[4-(cyclopropylmethylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00423
736		4-fluoro-N-[4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00029
737		4-fluoro-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide	0.00461
738		4-fluoro-N-[4-fluoro-2-[rac-(3S)-3,4-dimethylpiperazin-1-yl]-5-[2-[rac-(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide	0.004
739		4-fluoro-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3R)-3,4-dimethylpiperazin-1-	0.003

		yl]phenyl]-2-(trifluoromethyl)benzamide	
740		N-[5-[1-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide	0.00447
741		4-(difluoromethyl)-N-[4-fluoro-5-[4-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.00675
742		N-[4-fluoro-5-(6-piperazin-1-ylpyridin-2-yl)-2-[rac-(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00287
743		N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide	0.00522
744		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide	0.00276

745		4-(difluoromethyl)-N-[4-fluoro-5-[2-[rac-(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.0056
746		4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	13565
747		N-[5-[4-[(2,2-dimethylcyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00485
748		4-(difluoromethyl)-N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.05181
749		4-(difluoromethyl)-N-[4-fluoro-5-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide	0.01061

750		N-[4-fluoro-5-[4-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00171
751		N-[4-fluoro-5-[5-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]-2-[rac-(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide	0.00827
752		2-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-4-fluorobenzamide	———
753		2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((S)-2-methylmorpholino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)benzamide	———
754		2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)benzamide	-

755		3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-5-fluoropicolinamide	-
756		3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)picolinamide	-
757		(S)-3-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-1-yl)-4-fluoro-5-(2-morpholinopyrimidin-4-yl)phenyl)-5-fluoropicolinamide	-
758		3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyrimidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)picolinamide	-
759		3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)-5-fluoropicolinamide	-

760		N-(4'-(cyclohexyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.002
761		N-(4'-(cyclopentyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.002
762		6-oxo-N-(3',5',6-trifluoro-4'-(((R)-tetrahydrofuran-3-yl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0009
763		6-oxo-N-(3',5',6-trifluoro-4'-(methyl(oxetan-3-yl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	0.0007

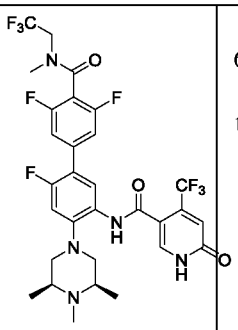
764		6-oxo-N-(3',5',6-trifluoro-4'-(methyl(2,2,2-trifluoroethyl)carbamoyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide	-

Table 2: Inhibitory activity of exemplary compounds of the application in the *in vitro* methyl transferase assay (MLL1-WRAD2 assay).

Example No.	WDR5 binding affinity (K_D, μM)	*In vitro* MLL1 activity (IC_{50}, μM)	Residence Time (t, min)
1	0.084	15	1.36
2	0.011	2.71	4.62
3	0.002	0.272	26.50
4	0.004	0.82	12.94
5	0.033	1.31	6.76
6	0.003	0.885	14.2
7	0.00006	0.054	299.22
8	0.0003	0.043	132.28
9	0.005	0.984	11.22
10	0.013	8.36	8.23
11	0.005	0.993	17.29
12	0.005	2.07	14.66
13	0.004	9.53	7.51
14	0.005	1.49	13.26
15	0.026	19	1.59
16	0.002	0.467	22.61
17	0.006	2.07	16.20
18	0.009	9.83	4.05
19	0.004	3.67	9.29
20	0.002	0.213	14.93
21	0.0009	0.272	54.29
22	0.0076	6.65	6.49
23	0.017	>30	1.61
24	0.076	>30	1.68
25	0.009	3.34	12.98
26	0.043	>30	1.82
27	0.294	NT	ND
28	0.002	2.74	72.78
29	0.0009	0.182	66.40
30	0.003	1.0	13.65
31	0.001	0.075	31.69

32	0.0004	0.111	56.31
33	0.0005	1.01	39.78
34	0.0001	0.036	114.16
35	0.003	0.620	20.20
36	0.002	0.316	39.78
37	0.0002	0.106	55.93
38	0.004	9.85	2.04
39	0.0003	0.174	69.44
40	0.008	0.774	5.52
41	0.009	4.91	5.39
42	0.009	NT	3.45
43	0.020	15.7	1.35
44	0.005	1.64	7.4
45	0.009	0.78	3.09
46	0.005	2.29	6.96
47	0.019	19.6	4.82
48	0.015	11.2	2.88
49	0.014	17.7	3.38
50	0.012	9.41	1.37
51	0.007	0.478	25.84
52	0.006	1.28	17.25
53	0.006	1.49	7.65
54	0.051	26.7	0.53
55	0.052	NT	0.63
56	0.019	0.864	2.32
57	0.030	9.50	1.26
58	0.004	1.57	11.52

Table 3 : in-cell H3K4 dimethylation of exemplary compounds of the application.

Compound ID	*In vitro* whole cell potency in T24 cells, H3K4Me2 (IC_{50}, µM)
3	0.882
6	1.07
7	0.166
8	0.144
39	0.626

Table 4: Whole cell potency of exemplary compounds of the application in MV-41 1 cells.

Example No.	*In vitro* whole cell potency in MV-411 cells, (IC_{50}, μM)
1	NT
2	2.25
3	0.749
4	0.574
5	0.881
6	0.828
7	0.051
8	0.044
9	0.507
10	>10
11	1.27
12	0.929
13	>10
14	1.524
15	>10
16	0.844
17	NT
18	NT
19	NT
20	0.604
21	0.271
22	5.266
23	>10
24	>10
25	>10
26	>10
27	NT
28	2.76
29	0.045
30	0.21
31	0.571
32	0.067
33	0.072
34	0.038
35	0.669
36	0.85
37	0.054
38	4.07
39	0.213
40	>10

41	0.213
42	0.428
43	NT
44	NT
45	0.491
46	2.90
47	NT
48	>10
49	>10
50	2.895
51	0.389
52	>10
53	>10
54	NT
55	0.389
56	0.435
57	NT
58	1.47
63	0.206
64	0.366
90	0.120
91	0.257
92	0.071
93	0.048
161	0.028
197	0.044
201	0.113
202	0.020
216	0.388
221	0.120
245	0.125
247	0.854
248	0.137
274	0.075
279	0.118
334	0.031
341	0.052
348	0.042
378	0.020
383	0.149
395	0.031
398	0.044
401	0.030
410	0.063
413	0.057
414	0.008

415	0.017
418	0.070
430	0.049
451	0.092
452	0.062
456	0.089
464	0.049
465	0.100
470	0.056
471	0.078
472	0.104
473	0.032
483	0.024
508	0.073
521	0.068
532	0.022
540	0.027
593	0.014
594	0.019
600	0.052
617	0.036

Table 5: Effect of Fluoro-substitution at A on residence time (t) and MLLl inhibition:

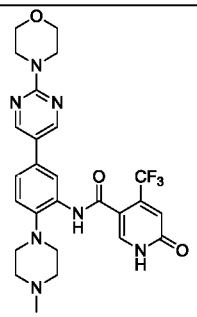
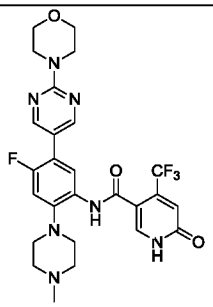
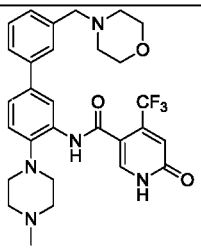
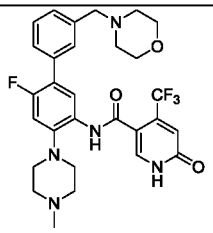
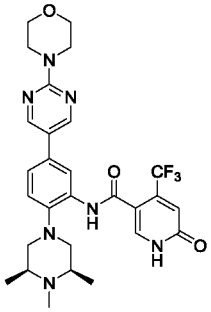
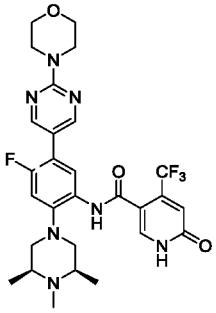
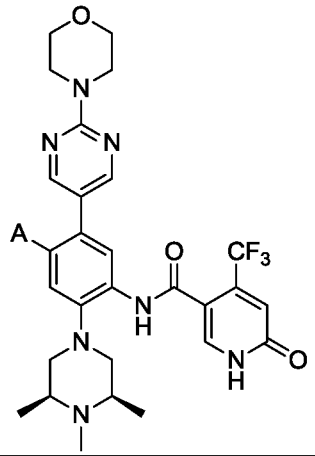
Comp. No.	Structure	Assay Results	Comp. No.	Compound	Assay Results
56		K_D (SPR) = 0.0175 μM τ = 1.8 min IC_{50} (HMT) = 0.86 μM	3		K_D (SPR) = 0.0015 μM τ = 26 min IC_{50} (MLL1) = 0.38 μM
57		K_D (SPR) = 0.036 μM τ = 0.78 min IC_{50} (HMT) = 9.5 μM	2		K_D (SPR) = 0.011 μM τ = 4.6 min IC_{50} (MLL1) = 2.71 μM
58		K_D (SPR) = 0.0035 μM τ = 11.5 min IC_{50} (HMT) = 1.57 μM	8		K_D (SPR) = 0.000323 μM τ = 132 min IC_{50} (MLL1) = 0.043 μM

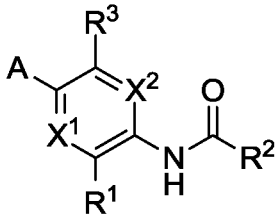
Table 6: **Effect of different substituents at A on residence time (t) and MLLl inhibition:**



Example Number	A	SPR Kd (nM)	T (min)
8	F	<0.5	>100
58	H	3.5	11.5
82	Cl	10	6.7
591	CH_3	26	17.4
592	CF_3	>10000	ND
593	OCH_3	>200	ND

Claims:

1. A compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof:



(I)

wherein:

R^1 is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, $_{C3}$-iocycloalkyl, OR^4, SR^4, NR^5R^6, Ci-galkyleneOR^4, Ci$_{-6}$alkyleneSR^4 and Ci$_{-6}$alkyleneNR^{5}R^6, provided that R^1 comprises at least one basic nitrogen atom;

R^2 is selected from $_{C6}$-ioaryl and heteroaryl, and R^2 is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^7, SR^7 and NR^8R^9;

R^3 is selected from C_6-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci$_-$efluoroalkyl, =0, =S, OR^{10}, SR^{10}, $S0_2R^{10}$, $NR^{11}R^{12}$, R^{13}, Ci$_{-6}$alkyleneR^{13}, **Ci.** salkenyleneR^{13}, OCi$_{-6}$alkyleneR^{13}, SCi$_{-6}$alkyleneR^{13}, C_{1-6}alkyleneNR^{11}R^{12}, **Ci.** salkyleneOR^{10}, Ci$_{-6}$alkyleneSR^{10}, OCi$_{-6}$alkyleneNR^{11}R^{12}, SCi$_{-6}$alkyleneNR^{11}R^{12}, **OCi.** salkyleneOR^{10}, SCi$_{-6}$alkyleneOR^{10}, OCi$_{-6}$alkyleneSR^{10}, SCi$_{-6}$alkyleneSR^{10}, C(0)OR^{10}, C(S)OR^{10}, C(S)NR^{11}R^{12} and C(0)NR^{11}R^{12};

R^4 is selected from H, Ci$_{-6}$alkyl Ci$_{-6}$fluoroalkyl, C(0)Ci$_{-6}$alkyl and C(0)d.$_6$fluoroalkyl;

R^5 and R^6 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl, C(0)Ci$_{-6}$alkyl, **C**(0**)Ci**-$_6$fluoroalkyl, C(0)OCi$_{-6}$alkyl, C(0)NHCi$_-$

$_6$alkyl, S0 $_2$Ci-$_6$alkyl, S0 $_2$HNCi-$_6$alkyl, Ci-$_6$alkyleneOCi- $_6$alkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC $_{3-6}$cycloalkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, OH, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fiuoroalkyl, OCi-efluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci- $_6$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)NHCi $_{-6}$alkyl, S0 $_2$Ci $_{-6}$alkyl, S0 $_2$HNCi $_{-6}$alkyl, Ci.$_6$alkyleneOCi $_{-6}$alkyl, Ci $_{-6}$alkyleneC$_6$-ioaryl, Ci. $_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC $_{3-6}$cycloalkyl;

R^7 is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci- $_6$fluoroalkyl and C(0)Ci_ ealkyl;

R^8 and R^9 are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci_ $_6$fluoroalkyl and C(0)Ci- $_6$alkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, CN, Ci-$_6$alkyl OCi-$_6$alkyl, Ci $_{-6}$fluoroalkyl and OCi $_{-6}$fluoroalkyl;

R^{10} is selected from H, Ci $_{-6}$alkyl, Ci.$_6$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, $_{C\,6}$-ioaryl, heteroaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and is unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, $NR^{15}R^{16}$, Ci $_{-6}$alkyl, C(0)R^{14}, C(0)OR^{14}, C(0)$NR^{15}R^{16}$, S(0)Ci $_{-6}$alkyl, S0 $_2$Ci-$_6$alkyl, $_{C\,6}$-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC $_6$-$_1$oaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci_ $_6$alkyleneheterocycloalkyl, Ci $_{-6}$alkyleneR^{14}, Ci $_{-6}$alkyleneOR^{14}, Ci $_{-6}$alkyleneSR^{14} and Ci $_{-6}$alkyleneN$R^{15}R^{16}$;

R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(O)C$_{6-i0}$aryl, C(O)C$_{3-i0}$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi $_{-6}$alkyl, C(0)OCi $_{-6}$fluoroalkyl, C(O)OC$_{6-i0}$aryl, C(O)OC$_{3-i0}$cycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl,

C(0)NHCi $_{-6}$alkyl, C(0)NHCi $_{-6}$fluoroalkyl, C(0)NHC $_{6}$-ioaryl, C(0)NHC $_{3-1}$ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0 $_{2}$Ci $_{-6}$alkyl, S0 $_{2}$Ci $_{-6}$fluoroalkyl, S0 $_{2}$C $_{6}$-ioaryl, S0 $_{2}$C $_{3}$-iocycloalkyl, S0 $_{2}$heteroaryl, S0 $_{2}$heterocycloalkyl, C $_{3}$-iocycloalkyl, heterocycloalkyl, heteroaryl, C $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{3}$-iocycloalkyl, Ci-$_{6}$alkyleneC $_{6}$-ioaryl, Ci-$_{6}$alkyleneheteroaryl and Ci-$_{6}$alkyleneheterocycloalkyl, and each of R^{11} and R^{12} are independently unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{14}, SR^{14}, NR^{15}R^{16}, Ci $_{-6}$alkyl, C(0)R ^{14}, C(0)OR ^{14}, C(0)NR ^{15}R^{16}, S(0)Ci $_{-6}$alkyl, S0 $_{2}$Ci $_{-6}$alkyl, C$_{6}$-i$_{0}$aryl, heteroaryl, C $_{3-1}$ocycloalkyl, heterocycloalkyl, Ci-$_{6}$alkyleneC $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{3}$-iocycloalkyl, Ci $_{-6}$alkyleneheteroaryl, Ci-$_{6}$alkyleneheterocycloalkyl, Ci-$_{6}$alkyleneR ^{14}, Ci-$_{6}$alkyleneOR ^{14}, Ci-galkyleneSR^{14} and Ci $_{-6}$alkyleneNR ^{15}R^{16}, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, NR^{15}R^{16}, Ci $_{-6}$alkyl, C(0)R ^{14}, C(0)OR ^{14}, C(0)NR ^{15}R^{16}, S(0)Ci $_{-6}$alkyl, S0 $_{2}$Ci $_{-6}$alkyl, C$_{6}$-i$_{0}$aryl, heteroaryl, C$_{3}$-iocycloalkyl, heterocycloalkyl, Ci-$_{6}$alkyleneC $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{3}$-iocycloalkyl, Ci $_{-6}$alkyleneheteroaryl, Ci $_{-6}$alkyleneR ^{14}, Ci $_{-6}$alkyleneOR ^{14}, Ci $_{-6}$alkyleneSR ^{14} and Ci. $_{6}$alkyleneNR ^{15}R^{16};

R^{13} is selected from C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(O)C$_{6}$-i$_{0}$aryl, C(0)C $_{3-1}$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_{3}$-iocycloalkyl, heterocycloalkyl, heteroaryl and C $_{6}$-ioaryl, and R^{13} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{14}, SR^{14}, NR^{15}R^{16}, Ci-galkyl, C(0)R ^{14}, C(0)OR ^{14}, C(0)NR ^{15}R^{16}, S(0)Ci $_{-6}$alkyl, S0 $_{2}$Ci $_{-6}$alkyl, C$_{6}$-i$_{0}$aryl, heteroaryl, C$_{3}$-iocycloalkyl, heterocycloalkyl, Ci-$_{6}$alkyleneC $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{3-1}$ocycloalkyl, Ci $_{-6}$alkyleneheteroaryl, Ci $_{-6}$alkyleneheterocycloalkyl, Ci $_{-6}$alkyleneR ^{14}, Ci-galkyleneOR^{14}, Ci $_{-6}$alkyleneSR ^{14} and Ci $_{-6}$alkyleneNR ^{15}R^{16},

R^{14} is selected from H, Ci $_{-6}$alkyl, Ci $_{-6}$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C$_{3}$-iocycloalkyl, heterocycloalkyl, C $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{6}$-ioaryl, Ci-$_{6}$alkyleneC $_{3-1}$ocycloalkyl and Ci $_{-6}$alkyleneheterocycloalkyl, and R^{14} is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci $_{-6}$alkyl, Ci $_{-6}$fluoroalkyl, OH,

SH, OCi-galkyl, OC^fluoroalkyl, SCi$_{-6}$alkyl, SC^fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci-$_6$alkyl)(Ci-**6alkyl),** C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi.salkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci-$_6$alkyl, **C 6**-ioaryl, heteroaryl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-$_1$oaryl, Ci-$_6$alkyleneC$_{3}$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci_$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci_salkyleneNiCi-galkyOiCi-galkyl);

R^{15} and R^{16} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, $_{C\ 6}$-ioaryl, Ci_$_6$alkyleneC$_6$-ioaryl, Ci.$_6$alkyleneC$_{3}$.iocycloalkyl and Ci$_{-6}$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-i0}aryl, heteroaryl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci-$_6$alkyleneC$_{3}$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci_$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or
R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.$_6$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-i0}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci-$_6$alkyleneC$_{3}$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci_$_6$alkyleneNHCi$_{-6}$alkyl and Ci^alkyleneNiOi-ealkylXCi-ealkyl);

X^1 and X^2 are each independently selected from CR^{17} and N;

R^{17} is selected fromH, F, $Ci\text{-}_6$alkyl and $Ci\text{-}_6$fiuoroalkyl;

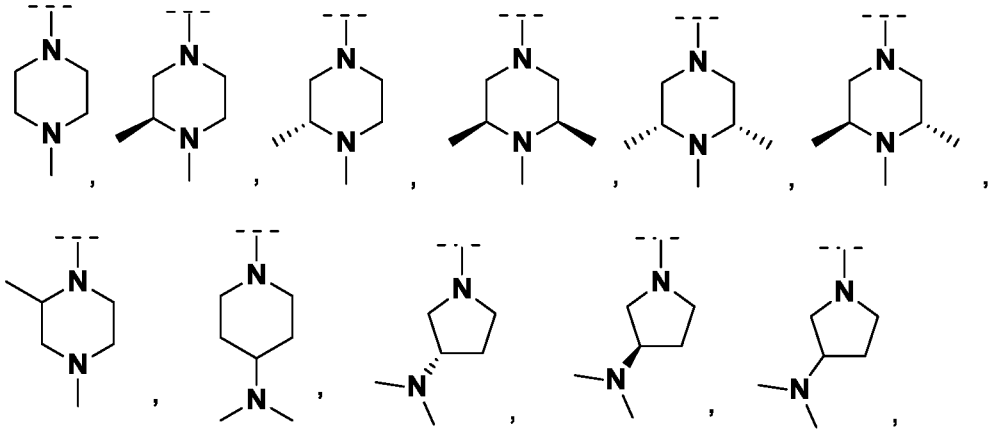
A is F, and
all alkyl and alkylene groups are optionally fluorosubstituted.

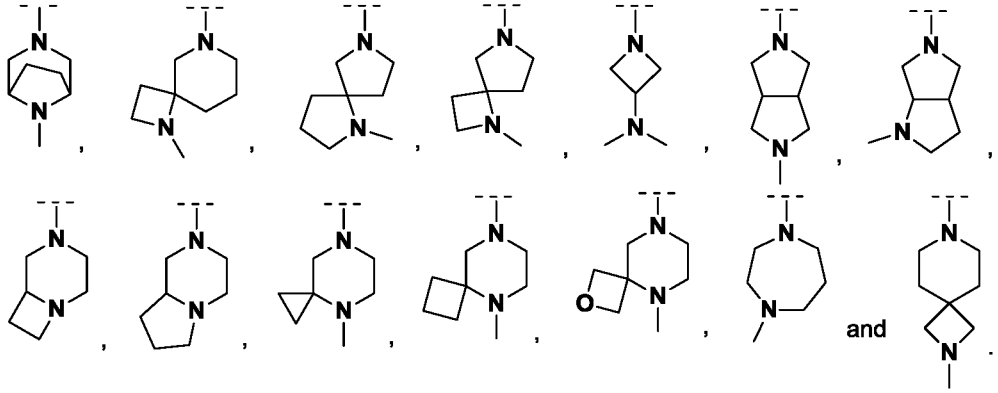
2. The compound of claim 1, wherein R^1 is a heterocycloalkyl that is unsubstituted or substituted with one, two or three substituents selected from halo, Ci_6alkyl, $Ci\text{-}_6$fluoroalkyl, NR^5R^6 and $Ci\text{-}_6$alkyleneNR^5R^6, provided that R^1 comprises at least one basic nitrogen atom.

3. The compound of claim 1 or 2, wherein R^1 is a heterocycloalkyl that is substituted with one or two substituents selected from halo, $Ci\text{-}_6$alkyl and NR^5R^6, provided that R^1 comprises at least one basic nitrogen atom.

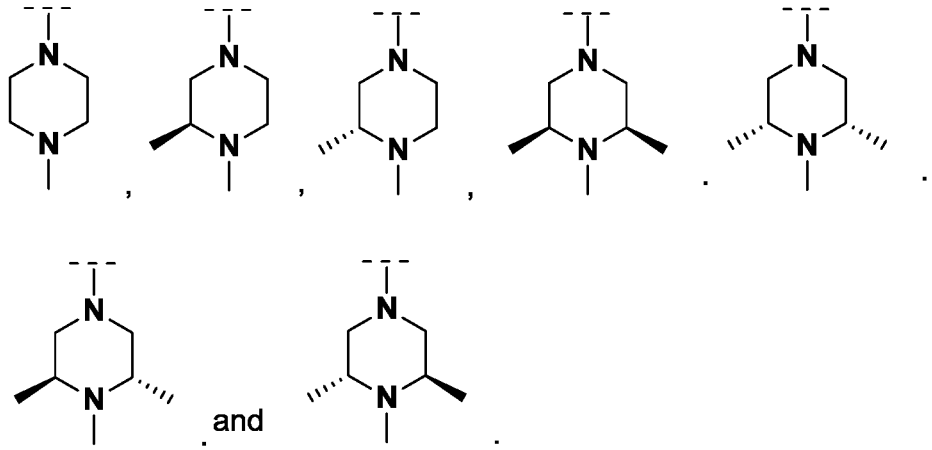
4. The compound of claim 3, wherein R^1 is a heterocycloalkyl that is substituted with one or two substituents selected from Ci_6alkyl and NR^5R^6, provided that R^1 comprises at least one basic nitrogen atom.

5. The compound of claim 4, wherein R^1 is selected from:

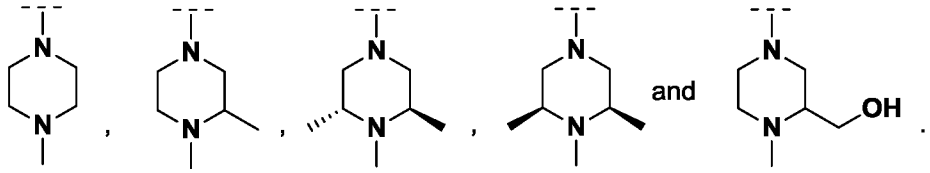




6. The compound of claim 5, wherein R^1 is selected from:



7. The compound of claim 6, wherein R^1 is selected from:

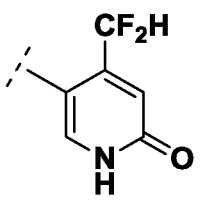
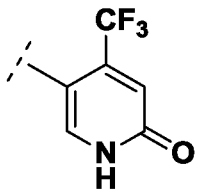
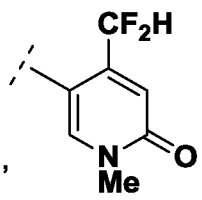
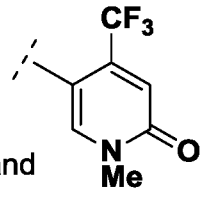


8. The compound of any one of claims 1 to 7, wherein R^2 is selected from C_{6-10}aryl and heteroaryl, and R^2 is unsubstituted or substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl, =0, OR^7, SR^7 and NR^8R^9.

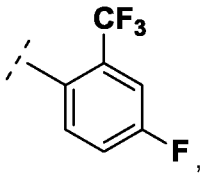
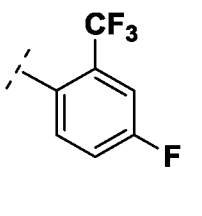
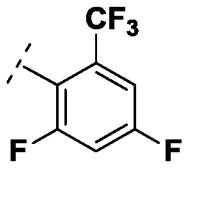
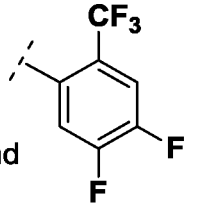
9. The compound of claim 8, wherein R^2 is selected from C_{6-10}aryl and heteroaryl, and R^2 is unsubstituted or substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl, =O and NR^8R^9.

10. The compound of claim 9, wherein R^2 is selected from C_{6-10}aryl and heteroaryl, and R^2 is unsubstituted or substituted with one or two substituents selected from halo, C_{1-6}alkyl, C_{1-6}fluoroalkyl and =O.

11. The compound of claim 10, wherein R^2 is selected from:


,

,

and

, or a **tautomer thereof.**

12. The compound of claim 11, wherein R^2 is selected from:


,

,

and

.

13. The compound of any one of claims 1 to 12, wherein R^3 is selected from C_{6-10}aryl, heteroaryl and heterocycloalkyl, and R^3 is substituted with one, two or three substituents selected from halo, CN, C_{1-6}alkyl, C_{1-6}fluoroalkyl, OR^{10}, $NR^{11}R^{12}$, R^{13}, C_{1-6}alkyleneR^{13}, OC_{1-6}alkyleneR^{13}, C_{1-6}alkyleneNR^{11}R^{12}, C_{1-6}alkyleneOR^{10}, OC_{1-6}alkyleneNR^{11}R^{12}, OC_{1-6}alkyleneOR^{10}, C(0)OR^{10} and C(0)NR^{11}R^{12}.

14. The compound of claim 13, wherein R^3 is selected from C_6-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is substituted with one or two substituents selected from halo, CN, Ci-galkyl, Ci_{-6}fluoroalkyl, OR^{10}, $NR^{11}R^{12}$, R^{13}, Ci_{-6}alkyleneR^{13}, OCi. salkyleneR^{13}, C_{1-6}alkyleneNR^{11}R^{12}, Ci_{-6}alkyleneOR^{10}, OCi.$_6$alkyleneNR^{11}R^{12} and OCi$_{-6}$alkyleneOR^{10}.

15. The compound of claim 14, wherein R^3 is selected from C_6-ioaryl, heteroaryl and heterocycloalkyl, and R^3 is unsubstituted or substituted with one or two substituents selected from halo, CN, Ci_{-6}alkyl, OR^{10}, $NR^{11}R^{12}$, R^{13} and OCi.$_6$alkyleneR^{13}.

16. The compound of claim 15, wherein R^3 is heteroaryl, and R^3 is substituted with one substituent selected from halo, CN, Ci_{-6}alkyl, OR^{10}, $NR^{11}R^{12}$, R^{13} and OCi$_{-6}$alkyleneR^{13}.

17. The compound of claim 16, wherein R^3 is heteroaryl, and R^3 is substituted with one substituent selected from $R^{13.}$

18. The compound of any one of claims 1 to 17, wherein R^5 and R^6 are independently selected from H, Ci-$_6$alkyl and heterocycloalkyl.

19. The compound of claim 18, wherein R^5 and R^6 are independently selected from H and Ci-$_6$alkyl.

20. The compound of any one of claims 1 to 19, wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one, two or three substituents selected from halo and Ci-$_6$alkyl.

21. The compound of claim 20, wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

22. The compound of any one of claims 1 to 21, wherein R^{10} is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, heteroaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl.

23. The compound of claim 22, wherein R^{10} is selected from H, Ci-$_6$alkyl, Ci_$_6$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci_$_6$alkyleneheterocycloalkyl.

24. The compound of claim 23, wherein R^{10} is selected from H, Ci-$_6$alkyl, Ci_$_6$fluoroalkyl, heterocycloalkyl and Ci-$_6$alkyleneC$_3$-iocycloalkyl.

25. The compound of claim 24, wherein R^{10} is selected from Ci-$_6$alkyl and Ci_$_6$fluoroalkyl.

26. The compound of any one or claims 1 to 25, wherein R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci-$_6$alkyl, C3-$_1$ocycloalkyl, heterocycloalkyl, heteroaryl, C_6-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci_$_6$alkyleneC$_6$-ioaryl, Ci$_{-6}$alkyleneheteroaryl and Ci$_{-6}$alkyleneheterocycloalkyl.

27. The compound of claim 26, wherein R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl.

28. The compound of claim 27, wherein R^{11} and R^{12} are each independently selected from H, Ci-ioalkyl and $_{C\ 3}$-iocycloalkyl.

29. The compound of any one of claims 1 to 28, wherein R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted.

30. The compound of any one of claims 1 to 29, wherein R^{13} is selected from C(0)Ci-$_{6}$alkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, heteroaryl and $_{C\ 6}$-ioaryl.

31. The compound of claim 30, wherein R^{13} is selected from $_{C\ 3}$-iocycloalkyl and heterocycloalkyl.

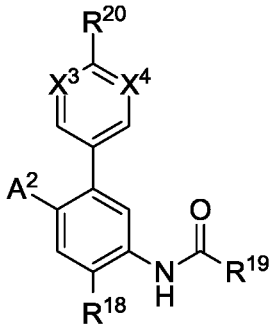
32. The compound of claim 31, wherein R^{13} is heterocycloalkyl.

33. The compound of any one of claims 1 to 32, wherein X^1 and X^2 are each independently selected from CR^{17} and N, in which R^{17} is selected from H and Ci_$_{6}$alkyl.

34. The compound of claim 33, wherein both of X^1 and X^2 are CR^{17}, in which R^{17} is H.

35. The compound of claim 33, wherein one of X^1 and X^2 is CR^{17} and the other of X^1 and X^2 is N, in which R^{17} is H.

36. The compound of claim 1 having the Formula (la), or a pharmaceutically acceptable salt and/or solvate thereof:



(la)

R^{18} is a heterocycloalkyl that is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, $_{C\,3}$-iocycloalkyl, OR^{21}, SR^{21}, $NR^{22}R^{23}$, Ci-galkyleneOR^{21}, Ci$_{-6}$alkyleneSR^{21} and Ci$_{-6}$alkyleneNR^{22}R^{23}, provided that R^{18} comprises at least one basic nitrogen atom;;

R^{19} is selected from C_{6-}ioaryl and heteroaryl, and R^{19} is unsubstituted or substituted with one or more substituents selected from halo, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^{24}, SR^{24} and $NR^{25}R^{26}$;

R^{20} is selected from H, halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, OR^{27}, SR^{27}, S0$_2$R^{27}, $NR^{28}R^{29}$, R^{30}, Ci$_{-6}$alkyleneR^{30}, Ci$_{-6}$alkenyleneR^{30}, OCi$_{-6}$alkyleneR^{30}, SCi$_{-6}$alkyleneR^{30}, Ci$_{-6}$alkyleneNR^{28}R^{29}, Ci$_{-6}$alkyleneOR^{27}, Ci$_{-6}$alkyleneSR^{27}, OCi$_{-6}$alkyleneNR^{28}R^{29}, SCi$_{-6}$alkyleneNR^{28}R^{29}, OCi$_{-6}$alkyleneOR^{27}, SCi$_{-6}$alkyleneOR^{27}, OCi$_{-6}$alkyleneSR^{27}, SCi$_{-6}$alkyleneSR^{27}, C(0)OR ^{27}, C(S)OR^{27}, C(S)NR^{28}R^{29} and C(0)NR ^{28}R^{29};

R^{21} is selected from H, Ci$_{-6}$alkyl Ci$_{-6}$fluoroalkyl, C(0)Ci $_{-6}$alkyl and C(0)Ci$_{-6}$fluoroalkyl;

R^{22} and R^{23} are independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, heterocycloalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(0)OCi $_{-6}$alkyl, C(0)NHCi$_{-6}$alkyl, S0 $_2$Ci-$_6$alkyl, S0 $_2$HNCi-$_6$alkyl, Ci-$_6$alkyleneOCi- $_6$alkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl and Ci-$_6$alkyleneC $_{3-6}$cycloalkyl, or R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, OH, Ci-$_6$alkyl OCi-$_6$alkyl, Ci-$_6$fiuoroalkyl, OCi-sfiuoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)NHCi $_{-6}$alkyl,

S0 2Ci-6alkyl, S0 2HNCi -6alkyl, Ci.6alkyleneOCi -6alkyl, Ci-ealkyleneCe-ioaryl, Ci.6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl and Ci-6alkyleneC 3-6cycloalkyl;

R^{24} is selected froniH, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci- 6alkyl;

R^{25} and R^{26} are independently selected from H, Ci-6alkyl, Ci-6fluoroalkyl and C(0)Ci_6alkyl, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, OH, CN, Ci-6alkyl OCi-6alkyl, Ci-6fiuoroalkyl and OCi-6fluoroalkyl;

R^{27} is selected from H, Ci-6alkyl, Ci-6fluoroalkyl, C(0)Ci- 6alkyl, C 3-iocycloalkyl, heterocycloalkyl, C 6-ioaryl, heteroaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci-ealkyleneCe-ioaryl, Ci-6alkyleneheteroaryl and Ci_6alkyleneheterocycloalkyl, and is unsubstituted or substituted with one or more substituents selected from halo, OR^{31}, SR^{31}, $NR^{32}R^{33}$, Ci-6alkyl, C(0)R 31, C(0)OR 31, C(0)NR 32R33, S(0)Ci -6alkyl, S0 2Ci-6alkyl, C6-i0aryl, heteroaryl, C3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-1ocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 31, Ci-galkyleneOR31, Ci-6alkyleneSR 31 and Ci-6alkyleneNR 32R33;

R^{28} and R^{29} are each independently selected from H, Ci.i0alkyl, Ci.iofluoroalkyl, C(0)Ci -6alkyl, C(O)C6-i0aryl, C(0)C 3-iocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi -6alkyl, C(0)OCi -6fluoroalkyl, C(O)OC6-i0aryl, C(O)OC3-i0cycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi -6alkyl, C(0)NHCi -6fluoroalkyl, C(O)NHC6-i0aryl, C(0)NHC 3-iocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, S0 2Ci-6alkyl, S0 2Ci-6fluoroalkyl, S0 2C 6-ioaryl, S0 2C3-iocycloalkyl, S0 2heteroaryl, S0 2heterocycloalkyl, C3-1ocycloalkyl, heterocycloalkyl, heteroaryl, C 6-ioaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci_6alkyleneC 6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and each of R^{28} and R^{29} are independently unsubstituted or substituted with one or more substituents selected from halo, CN, OR^{31}, SR^{31}, $NR^{32}R^{33}$, Ci-6alkyl, C(0)R 31, C(0)OR 31, C(0)NR 32R33, S(0)Ci -6alkyl, S0 2Ci-6alkyl, C6-i0aryl, heteroaryl, C3-1ocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-iocycloalkyl, Ci_6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR 31, Ci-6alkyleneOR 31, Ci-galkyleneSR31 and Ci-6alkyleneNR 32R33, or

R^{28} and R^{29} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{31}, SR^{31}, $NR^{32}R^{33}$, C_{1-6}alkyl, C(0)R^{31}, C(0)OR^{31}, C(0)$NR^{32}R^{33}$, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci-$_6$alkyleneC$_{3}$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneR^{31}, Ci-$_6$alkyleneOR^{31}, Ci-$_6$alkyleneSR^{31} and Ci$_{-6}$alkyleneNR^{32}R^{33};

R^{30} is selected from C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(O)C_6-i$_0$aryl, C(0)C$_{3-10}$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, heteroaryl and C$_6$-ioaryl, and R^{30} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, OR^{31}, SR^{31}, $NR^{32}R^{33}$, Ci-galkyl, C(0)R^{31}, C(0)OR^{31}, C(0)$NR^{32}R^{33}$, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci-$_6$alkyleneC$_{3}$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{31}, Ci-galkyleneOR^{31}, Ci$_{-6}$alkyleneSR^{31} and Ci$_{-6}$alkyleneNR^{32}R^{33},

R^{31} is selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, C_6-ioaryl, Ci$_{-6}$alkyleneC$_{6}$-ioaryl, Ci$_{-6}$alkyleneC$_{3}$.iocycloalkyl and Ci.$_6$alkyleneheterocycloalkyl, and R^{31} is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH_2, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_6-i$_0$aryl, heteroaryl, C$_{3-10}$ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci-$_6$alkyleneC$_{3}$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-ealkyleneNiOi-ealkylXCi-ealkyl);

R^{32} and R^{33} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C_3-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_{6}$-ioaryl, Ci$_{-6}$alkyleneC$_{3}$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{15} and R^{16} is unsubstituted or substituted with one or more substituents independently selected from halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi$_{-6}$fluoroalkyl, SCi.

salkyl, SC^fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci-$_6$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heteroCycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci$_{-6}$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{32} and R^{33} together with the nitrogen atom to which they are attached form a 3-10 membered heterocycle that is unsubstituted or substituted with one or more substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fiuoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH_2, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C_{6-10}aryl, heteroaryl, C_{3-1}ocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci$_{-6}$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci$_{-6}$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl);

X^3 and X^4 are each independently selected from CR^{34} and N;

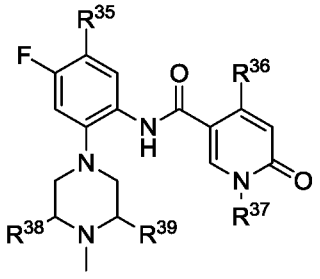
R^{34} is selected from H, Ci-$_6$alkyl and Ci-$_6$fluoroalkyl;

A^2 is F; and

alkyl and alkylene groups are optionally fluorosubstituted.

37. The compound of claim 1 having the Formula (lb), or a pharmaceutically acceptable salt and/or solvate thereof:

:



(Ib)

wherein:

R^{35} is selected from phenyl, C_{5-6}heteroaryl and C_{5-6}heterocycloalkyl, and R^{35} is substituted with one substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, =0, =S, OR^{40}, SR^{40}, $S0_2R^{40}$, $NR^{41}R^{42}$, R^{43}, Ci$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkenyleneR^{43}, OCi. salkyleneR^{43}, SCi$_{-6}$alkyleneR^{43}, Ci$_{-6}$alkyleneNR^{41}R^{42}, Ci$_{-6}$alkyleneOR^{40}, Ci. salkyleneSR^{40}, OCi$_{-6}$alkyleneNR^{41}R^{42}, SCi$_{-6}$alkyleneNR^{41}R^{42}, OCi$_{-6}$alkyleneOR^{40}, SCi. salkyleneOR^{40}, OCi$_{-6}$alkyleneSR^{40}, SCi$_{-6}$alkyleneSR^{40}, C(0)OR ^{40}, C(S)OR^{40}, C(S)NR^{41}R^{42} and C(0)NR ^{41}R^{42};

R^{36} is selected from CF_2H and CF_3;

R^{37} is selected from H and CH_3;

R^{38} and R^{39} are independently selected from H and CH_3

R^{40} is selected from H, Ci$_{-6}$alkyl, Ci.$_6$fluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, $_{C\ 6}$-ioaryl, heteroaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and is unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{44}, SR^{44}, $NR^{45}R^{46}$, Ci$_{-6}$alkyl, C(0)R ^{44}, C(0)OR ^{44}, C(0)NR ^{45}R^{46}, S(0)Ci $_{-6}$alkyl, $S0_2$Ci$_{-6}$alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci$_{-6}$alkyleneC $_{6-1}$oaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR ^{44}, Ci-$_6$alkyleneOR ^{44}, Ci-$_6$alkyleneSR ^{44} and Ci$_{-6}$alkyleneNR^{45}R^{46};

R^{41} and R^{42} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci $_{-6}$alkyl, C(0)Ci $_{-6}$fluoroalkyl, C(O)C$_{6-i0}$aryl, C(O)C$_{3-i0}$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi $_{-6}$alkyl, C(0)OCi $_{-6}$fluoroalkyl, C(0)OC $_6$-ioaryl, C(0)OC $_3$-iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi $_{-6}$alkyl, C(0)NHCi $_{-6}$fluoroalkyl, C(O)NHC$_{6-i0}$aryl, C(0)NHC $_{3-1}$ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, $S0_2$Ci$_{-6}$alkyl, $S0_2$Ci$_{-6}$fluoroalkyl, $S0_2$C $_6$-ioaryl, $S0_2$C$_3$-iocycloalkyl, $S0_2$heteroaryl, $S0_2$heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl, $_{C\ 6}$-ioaryl, Ci-$_6$alkyleneC $_3$-iocycloalkyl, Ci-$_6$alkyleneC $_6$-ioaryl, Ci-$_6$alkyleneheteroaryl and Ci-$_6$alkyleneheterocycloalkyl, and

each of R^{41} and R^{42} are independently unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{44}, SR^{44}, $NR^{45}R^{46}$, C_{1-6}alkyl, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NR^{45}R^{46}$, $S(O)C_{1-6}$alkyl, SO_2C_{1-6}alkyl, C_{6-10}aryl, heteroaryl, C_{3-11}ocycloalkyl, heterocycloalkyl, C_{1-6}alkyleneC$_{6-10}$aryl, C_{1-6}alkyleneC$_{3-11}$ocycloalkyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneheterocycloalkyl, C_{1-6}alkyleneR^{44}, C_{1-6}alkyleneOR^{44}, C1-galkyleneSR^{44} and C_{1-6}alkyleneNR^{45}R^{46}, or

R^{41} and R^{42} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{44}, SR^{44}, $NR^{45}R^{46}$, C_{1-6}alkyl, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NR^{45}R^{46}$, $S(O)C_{1-6}$alkyl, SO_2C_{1-6}alkyl, C_{6-10}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, C_{1-6}alkyleneC$_{6-10}$aryl, C_{1-6}alkyleneC$_{3-11}$ocycloalkyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneR^{44}, C_{1-6}alkyleneOR^{44}, C_{1-6}alkyleneSR^{44} and C_{1-6}alkyleneNR^{45}R^{46};

R^{43} is selected from $C(O)C_{1-6}$alkyl, $C(O)C_{1-6}$fluoroalkyl, $C(O)C_{6-10}$aryl, $C(O)C_{3-11}$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl and C_{6-10}aryl, and R^{43} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{44}, SR^{44}, $NR^{45}R^{46}$, C1-galkyl, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NR^{45}R^{46}$, $S(O)C_{1-6}$alkyl, SO_2C_{1-6}alkyl, C_{6-10}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, C_{1-6}alkyleneC$_{6-10}$aryl, C_{1-6}alkyleneC$_{3-11}$ocycloalkyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneheterocycloalkyl, C_{1-6}alkyleneR^{44}, C1-galkyleneOR^{44}, C_{1-6}alkyleneSR^{44} and C_{1-6}alkyleneNR^{45}R^{46};

R^{44} is selected from H, C_{1-6}alkyl, C_{1-6}fluoroalkyl, $C(O)C_{1-6}$alkyl, $C(O)C_{1-6}$fluoroalkyl, C_3-iocycloalkyl, heterocycloalkyl, C_{6-10}aryl, C_{1-6}alkyleneC$_{6-10}$aryl, C_{1-6}alkyleneC$_{3-11}$ocycloalkyl and C_{1-6}alkyleneheterocycloalkyl, and R^{44} is unsubstituted or substituted with one to three substituents selected from halo, CN, C_{1-6}alkyl, C_{1-6}fiuoroalkyl, OH, SH, OC1-galkyl, OC_{1-6}fluoroalkyl, SC_{1-6}alkyl, SC_{1-6}fluoroalkyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $C(O)C_{1-6}$alkyl, $C(O)C_{1-6}$fluoroalkyl, C(0)OH, C(0)OC1-salkyl, $C(O)NH_2$, $C(O)NHC_{1-6}$alkyl, $C(O)N(C_{1-6}alkyl)(C_{1-6}alkyl)$, SO_2C_{1-6}alkyl, $S(O)C_{1-6}$alkyl, C_{6-10}aryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, C_{1-6}alkyleneC$_{6-10}$aryl, C_{1-6}alkyleneC$_{3-11}$.iocycloalkyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneheterocycloalkyl, C_{1-6}alkyleneOH, C_{1-6}alkyleneOC$_{1-6}$alkyl, C_{1-6}alkyleneSH,

Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci_$_6$alkyleneN(Ci-$_6$alkyl)(Ci^alkyl);

R^{45} and R^{46} are each independently selected from H, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, $_{C\ 6}$-ioaryl, Ci_$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{45} and R^{46} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_6$-i$_0$aryl, heteroaryl, $_{C\ 3}$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci$_{-6}$alkyleneheteroaryl, Ci$_{-6}$alkyleneheterocycloalkyl, Ci$_{-6}$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci_$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl), or

R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fiuoroalkyl, OH, SH, OCi$_{-6}$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_6$-i$_0$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci_$_6$alkyleneNHCi-$_6$alkyl and Ci-$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl).

In some embodiments, R^{35} is selected from phenyl, pyrimidinyl, pyridinyl, dihydropyridine, pyrrolyl and dihydropyrrolyl, each of which is substituted with one substituent selected from halo, CN, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, =0, =S, OR^{40}, SR^{40}, S0$_2$R^{40}, NR^{41}R^{42}, R^{43}, Ci-galkyleneR^{43}, Ci$_{-6}$alkenyleneR^{43}, OCi$_{-6}$alkyleneR^{43}, SCi.salkyleneR^{43}, Ci$_{-6}$alkyleneNR^{41}R^{42}, Ci$_{-6}$alkyleneOR^{40}, Ci$_{-6}$alkyleneSR^{40}, OCi.$_6$alkyleneNR^{41}R^{42}, SCi$_{-6}$alkyleneNR^{41}R^{42}, OCi$_{-6}$alkyleneOR^{40}, SCi$_{-6}$alkyleneOR^{40}, OCi.$_6$alkyleneSR^{40}, SCi$_{-6}$alkyleneSR^{40}, C(0)OR^{40}, C(S)OR^{40}, C(S)NR^{41}R^{42} and C(0)NR^{41}R^{42}.

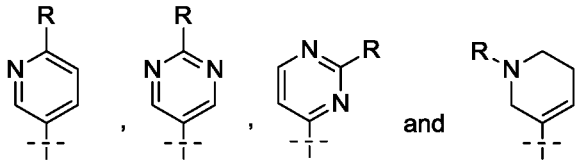
38. The compound of claim 37, wherein R^{35} is substituted with one substitutent selected from Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, OR^{40}, $NR^{41}R^{42}$, R^{43}, Ci_{-6}alkyleneR^{43}, OCi. salkyleneR^{43}, Ci_{-6}alkylene$NR^{41}R^{42}$, Ci_{-6}alkyleneOR^{40}, OCi_{-6}alkylene$NR^{41}R^{42}$, OCi. salkyleneOR^{40}, C(0)OR^{40} and C(0)$NR^{41}R^{42}$.

39. The compound of claim 38, wherein R^{35} is substituted with R^{43} or Ci_{-6}alkyleneR^{43} wherein R^{43} is selected from C_{5-6}cycloalkyl, Cs-eheterocycloalkyl, C_{5-6}heteroaryl and phenyl, and R^{43} is unsubstituted or substituted with one to three substituents independently selected from halo and Ci_{-6}alkyl.

40. The compound of claim 39, wherein R^{43} is C_6-heterocycloalkyl. In some embodiments, R^{43} is selected from piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l *H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl.

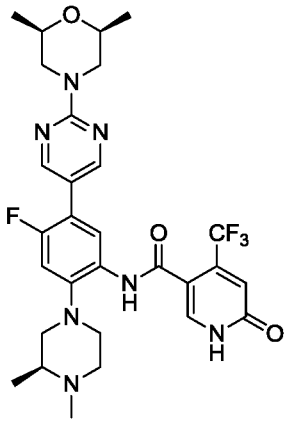
41. The compound of claim 40, wherein R^{43} is morpholinyl, optionally substituted with one or two Me.

42. The compound of claim 37, wherein R^{35} is selected from:



, wherein R is the subsituent.

43. The compound of claim 37, wherein the compound of Formula lb is selected from: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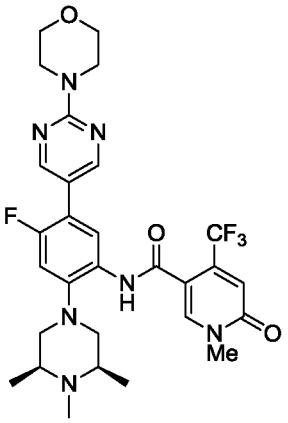
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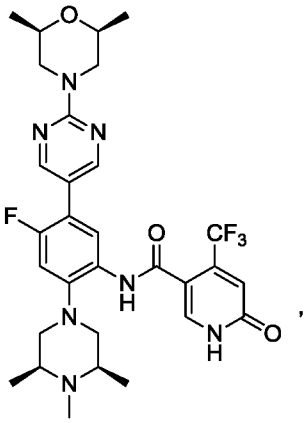
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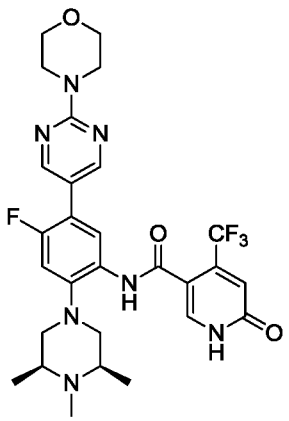
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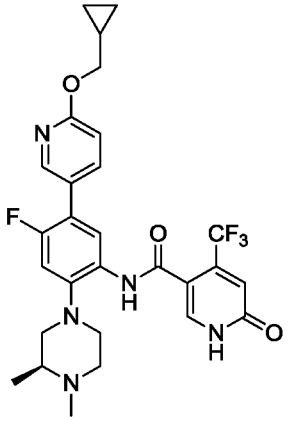
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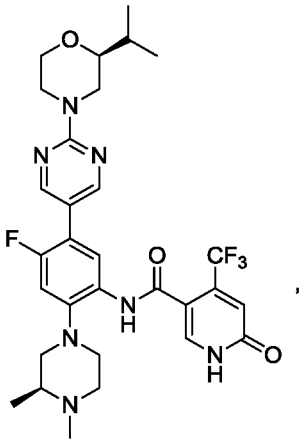
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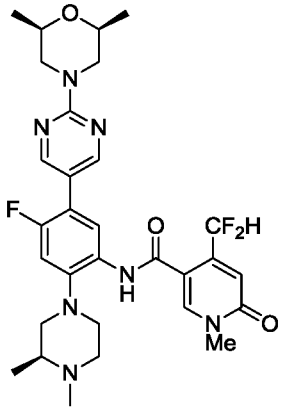
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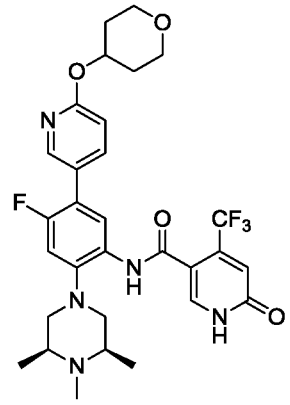
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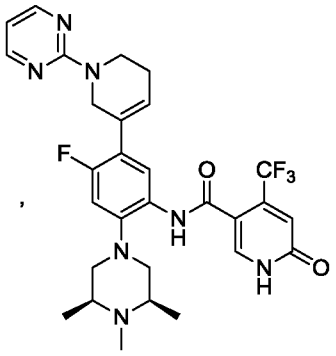

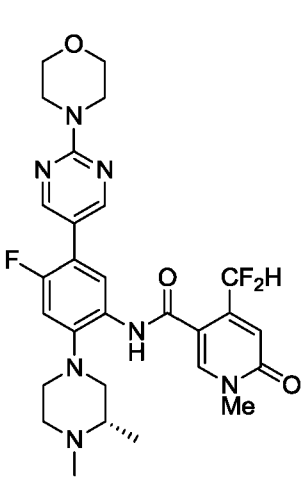
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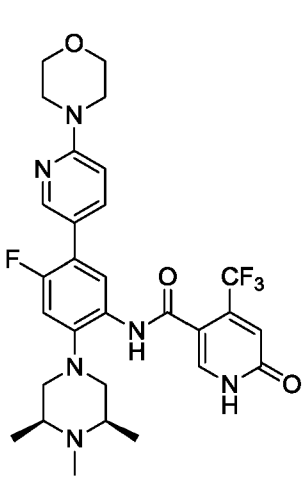
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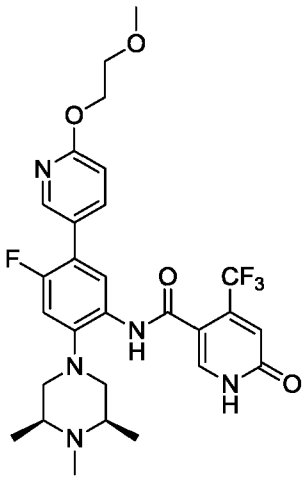
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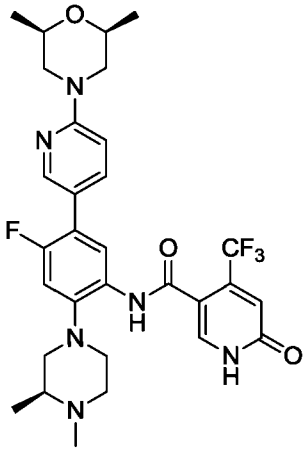
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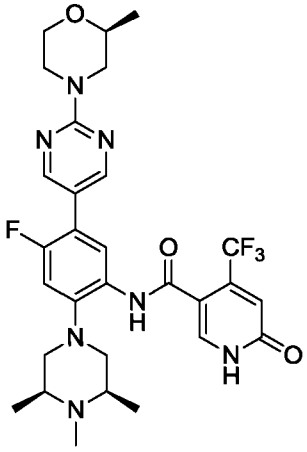
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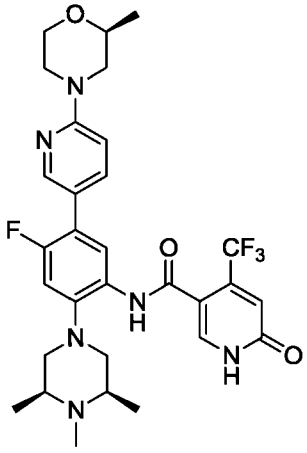
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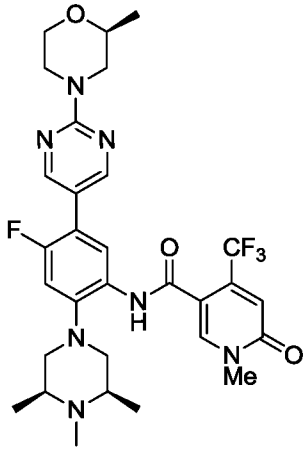
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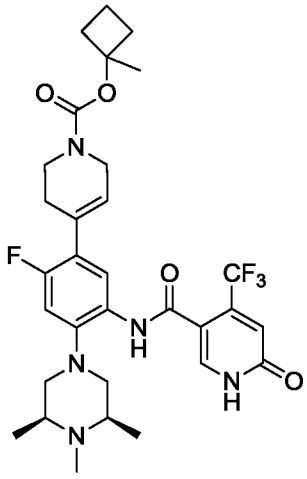
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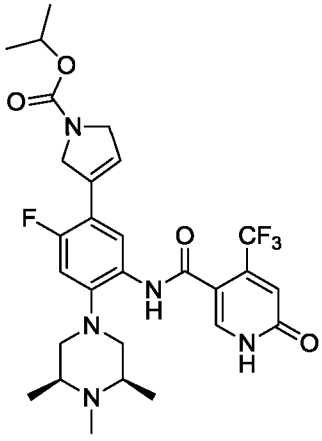
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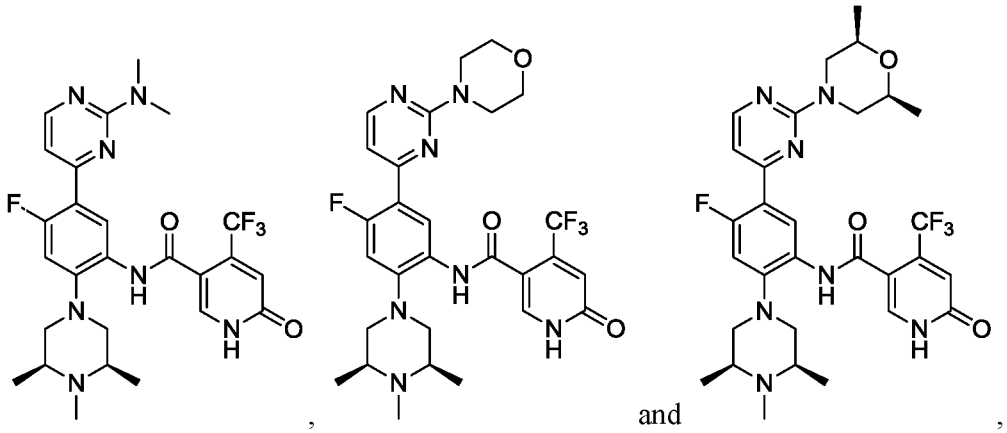
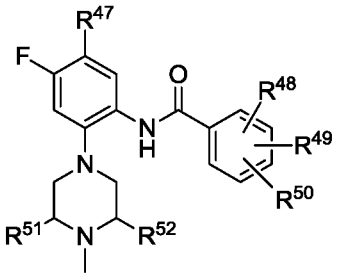


or a pharmaceutically acceptable salt and/or solvate thereof.

44. The compound of claim having the Formula (Ic) or a pharmaceutically acceptable salt and/or solvate thereof:



(Ic)

wherein:

R^{47} is selected from phenyl, Cs-eheteroaryl and Cs-eheterocycloalkyl, and R^{47} is substituted with one substituents selected from halo, CN, Ci_{-6}alkyl, Ci_{-6}fluoroalkyl, =0, =S, OR^{53}, SR^{53}, $S0_2R^{53}$, $NR^{54}R^{55}$, R^{56}, Ci_{-6}alkyleneR^{56}, Ci_{-6}alkenyleneR^{56}, OCi. salkyleneR^{56}, SCi_{-6}alkyleneR^{56}, Ci_{-6}alkyleneNR^{54}R^{55}, Ci_{-6}alkyleneOR^{53}, Ci. salkyleneSR^{53}, OCi_{-6}alkyleneNR^{54}R^{55}, SCi_{-6}alkyleneNR^{54}R^{55}, OCi_{-6}alkyleneOR^{53}, SCi. salkyleneOR^{53}, OCi_{-6}alkyleneSR^{53}, SCi_{-6}alkyleneSR^{53}, C(0)OR ^{53}, C(S)OR^{53}, C(S)NR^{54}R^{55} and C(0)NR ^{54}R^{55};

R^{48}, R^{49} and R^{50} are independently selected from H, F, CF_3 and CF_2H, provided that at least one of R^{48}, R^{49} and R^{50} is not H;

R^{51} and R^{52} are independently selected from H and CH_3

R^{53} is selected from H, Ci_6alkyl, Ci.6fluoroalkyl, C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C_{3-}iocycloalkyl, heterocycloalkyl, C_{6-}ioaryl, heteroaryl, Ci_6alkyleneC_3.iocycloalkyl, Ci-6alkyleneC_6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and is unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci-galkyl, $C(0)R^{57}$, $C(0)OR^{57}$, $C(0)NR^{58}R^{59}$, S(0)Ci_6alkyl, $S0_2$Ci-6alkyl, C_6-ioaryl, heteroaryl, C_3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC_6-_1oaryl, Ci-6alkyleneC_3-iocycloalkyl, Ci-6alkyleneheteroaryl, Ci_6alkyleneheterocycloalkyl, Ci-6alkyleneR^57, Ci-6alkyleneOR^57, Ci-6alkyleneSR^57 and Ci_6alkyleneNR^58R^59;

R^{54} and R^{55} are each independently selected from H, Ci-ioalkyl, Ci-iofluoroalkyl, C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, $C(O)C_{6-i0}$aryl, $C(O)C_{3-i0}$cycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C(0)OCi_6alkyl, C(0)OCi_6fluoroalkyl, C(0)OC_6-ioaryl, C(0)OC_3-iocycloalkyl, C(0)Oheteroaryl, C(0)Oheterocycloalkyl, C(0)NHCi_6alkyl, C(0)NHCi_6fluoroalkyl, $C(O)NHC_{6-i0}$aryl, C(0)NHC_3-_1ocycloalkyl, C(0)NHheteroaryl, C(0)NHheterocycloalkyl, $S0_2$Ci_6alkyl, $S0_2$Ci.6fluoroalkyl, $S0_2C_6$-ioaryl, $S0_2C_3$-iocycloalkyl, $S0_2$heteroaryl, $S0_2$heterocycloalkyl, C_3-iocycloalkyl, heterocycloalkyl, heteroaryl, C_6-ioaryl, Ci-6alkyleneC_3-iocycloalkyl, Ci-6alkyleneC_6-ioaryl, Ci-6alkyleneheteroaryl and Ci-6alkyleneheterocycloalkyl, and each of R^{54} and R^{55} are independently unsubstituted or substituted with one to three substituents selected from halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci_6alkyl, $C(0)R^{57}$, $C(0)OR^{57}$, $C(0)NR^{58}R^{59}$, S(0)Ci_6alkyl, $S0_2$Ci_6alkyl, C_{6-i0}aryl, heteroaryl, C_{3-}_1ocycloalkyl, heterocycloalkyl, Ci-6alkyleneC_6-ioaryl, Ci-6alkyleneC_3-iocycloalkyl, Ci_6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneR^57, Ci-6alkyleneOR^57, Ci-galkyleneSR^57 and Ci_6alkyleneNR^58R^59, or

R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents independently selected from halo, CN, OR^{57}, SR^{57}, $NR^{58}R^{58}$, Ci_6alkyl, $C(0)R^{57}$, $C(0)OR^{57}$, $C(0)NR^{58}R^{59}$, S(0)Ci_6alkyl, $S0_2$Ci_6alkyl, C_{6-i0}aryl, heteroaryl, C_{3-}iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC_6-ioaryl, Ci-6alkyleneC_3-iocycloalkyl,

Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{57}, Ci$_-$salkyleneOR^{57}, Ci$_{-6}$alkyleneSR^{57} and Ci$_{-6}$alkyleneNR^{58}R^{59};

R^{56} is selected from C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(O)C$_{6-}$i$_0$aryl, C(0)C$_{3-}$$_1$ocycloalkyl, C(0)heteroaryl, C(0)heterocycloalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, heteroaryl and C$_6$-ioaryl, and R^{56} is unsubstituted or substituted with one to three substituents independently selected halo, CN, OR^{57}, SR^{57}, NR^{58}R^{58}, Ci$_-$salkyl, C(0)R^{57}, C(0)OR^{57}, C(0)NR^{58}R^{59}, S(0)Ci$_{-6}$alkyl, S0$_2$Ci$_{-6}$alkyl, C$_{6-i0}$aryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci-$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneR^{57}, Ci-galkyleneOR^{57}, Ci$_{-6}$alkyleneSR^{57} and Ci$_{-6}$alkyleneNR^{58}R^{59};

R^{57} is selected from H, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci-$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-$_1$ocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl, and R^{57} is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-galkyl, OCi$_{-6}$fluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_-$$_6$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci$_{-6}$alkyl)(Ci$_{-6}$alkyl), S0$_2Ci_{-6}$alkyl, S(0)Ci-$_6$alkyl, C$_6$-ioaryl, heteroaryl, C$_3$-iocycloalkyl, heterocycloalkyl, Ci-$_6$alkyleneC$_6$-$_1$oaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl, Ci-$_6$alkyleneheteroaryl, Ci$_-$$_6$alkyleneheterocycloalkyl, Ci-$_6$alkyleneOH, Ci-$_6$alkyleneOCi-$_6$alkyl, Ci-$_6$alkyleneSH, Ci-$_6$alkyleneSCi-$_6$alkyl, Ci-$_6$alkyleneNH$_2$, Ci-$_6$alkyleneNHCi-$_6$alkyl and Ci$_-$$_6$alkyleneN(Ci-$_6$alkyl)(Ci-$_6$alkyl); and

R^{58} and R^{59} are each independently selected from H, Ci$_{-6}$alkyl, Ci$_{-6}$fluoroalkyl, C(0)Ci-$_6$alkyl, C(0)Ci-$_6$fluoroalkyl, C$_3$-iocycloalkyl, heterocycloalkyl, C$_6$-ioaryl, Ci$_-$$_6$alkyleneC$_6$-ioaryl, Ci-$_6$alkyleneC$_3$-iocycloalkyl and Ci-$_6$alkyleneheterocycloalkyl and each of R^{58} and R^{59} is unsubstituted or substituted with one to three substituents independently selected from halo, CN, Ci-$_6$alkyl, Ci-$_6$fluoroalkyl, OH, SH, OCi-$_6$alkyl, OCi-gfluoroalkyl, SCi$_{-6}$alkyl, SCi$_{-6}$fluoroalkyl, NH$_2$, NHCi$_{-6}$alkyl, N(Ci.$_6$alkyl)(Ci.salkyl), C(0)Ci$_{-6}$alkyl, C(0)Ci$_{-6}$fluoroalkyl, C(0)OH, C(0)OCi$_{-6}$alkyl, C(0)NH$_2$, C(0)NHCi$_{-6}$alkyl, C(0)N(Ci.$_6$alkyl)(Ci$_{-6}$alkyl), S0$_2$Ci$_{-6}$alkyl, S(0)Ci$_{-6}$alkyl, C$_{6-i0}$aryl,

heteroaryl, C 3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-1ocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneOH, Ci-6alkyleneOCi- 6alkyl, Ci-6alkyleneSH, Ci-6alkyleneSCi- 6alkyl, Ci-6alkyleneNH 2, Ci_6alkyleneNHCi- 6alkyl and Ci-6alkyleneN(Ci- 6alkyl)(Ci- 6alkyl), or

R^{58} and R^{59} together with the nitrogen atom to which they are attached form a 3-6 membered heterocycle that is unsubstituted or substituted with one to three substituents selected from halo, CN, Ci-6alkyl, Ci-6fiuoroalkyl, OH, SH, OCi-6alkyl, OCi-gfluoroalkyl, SCi_6alkyl, SCi_6fluoroalkyl, NH_2, NHCi_6alkyl, N(Ci._6alkyl)(Ci.salkyl), C(0)Ci_6alkyl, C(0)Ci_6fluoroalkyl, C(0)OH, C(0)OCi_6alkyl, C(0)NH 2, C(0)NHCi_6alkyl, C(0)N(Ci. 6alkyl)(Ci_6alkyl), S0 2Ci_6alkyl, S(0)Ci_6alkyl, C_{6-10}aryl, heteroaryl, C 3-iocycloalkyl, heterocycloalkyl, Ci-6alkyleneC 6-ioaryl, Ci-6alkyleneC 3-1ocycloalkyl, Ci-6alkyleneheteroaryl, Ci-6alkyleneheterocycloalkyl, Ci-6alkyleneOH, Ci-6alkyleneOCi- 6alkyl, Ci-6alkyleneSH, Ci-6alkyleneSCi- 6alkyl, Ci-6alkyleneNH 2, Ci_6alkyleneNHCi- 6alkyl and Ci_6alkyleneN(Ci-6alkyl)(Ci- 6alkyl).

45. The compound of claim 44, wherein R^{47} is selected from phenyl, pyrimidinyl, pyridinyl, dihydropyridine, pyrrolyl and dihydropyrrolyl, each of which is substituted with one substituent selected from halo, CN, Ci_6alkyl, Ci_6fiuoroalkyl, =0, =S, OR^{53}, SR^{53}, S0 $_2R^{53}$, $NR^{54}R^{55}$, R^{56}, Ci_6alkyleneR^{56}, Ci_6alkenyleneR^{56}, OCi_6alkyleneR^{56}, SCi._salkyleneR^{56}, Ci_6alkyleneNR^{54}R^{55}, Ci_6alkyleneOR^{53}, Ci_6alkyleneSR^{53}, OCi._6alkyleneNR^{54}R^{55}, SCi_6alkyleneNR^{54}R^{55}, OCi_6alkyleneOR^{53}, SCi_6alkyleneOR^{53}, OCi._salkyleneSR^{53}, SCi_6alkyleneSR^{53}, C(0)OR ^{53}, C(S)OR^{53}, C(S)NR^{54}R^{55} and C(0)NR ^{54}R^{55}.

46. The compound of claim 45, wherein R^{47} is substituted with one substitutent selected from Ci_6alkyl, Ci_6fluoroalkyl, OR^{53}, $NR^{54}R^{55}$, R^{56}, Ci_6alkyleneR^{56}, OCi._salkyleneR^{56}, Ci_6alkyleneNR^{54}R^{55}, Ci_6alkyleneOR^{53}, OCi_6alkyleneNR^{54}R^{55}, OCi._salkyleneOR^{53}, C(0)OR ^{53} and C(0)NR ^{54}R^{55}.

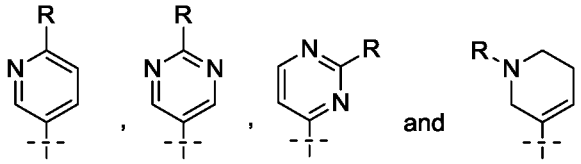
47. The compound of claim 46, wherein R^{47} is substituted with R^{56} or Ci_6alkyleneR ^{56} wherein R^{56} is selected from C 5-6cycloalkyl, Cs-eheterocycloalkyl, C 5-6heteroaryl and phenyl, and R^{56} is unsubstituted or substituted with one to three substituents independently selected from halo and Ci-6alkyl.

48. The compound of claim 47, wherein R^{56} is $_{C\,6}$-heterocycloalkyl.

49. The compound of claim 48, wherein R^{56} is selected from piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-l*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-l,3-dioxepinyl, and hexamethylene oxidyl.

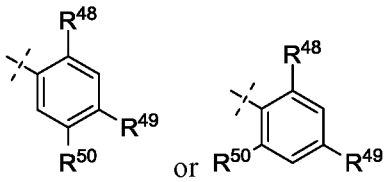
50. The compound of claim 48, wherein R^{56} is morpholinyl, optionally substituted with one or two Me.

51. The compound of any one of claims 44 to 50, wherein R^{47} is selected from:



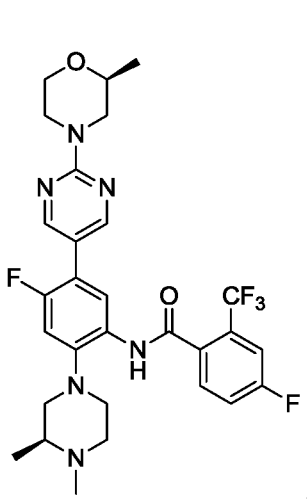
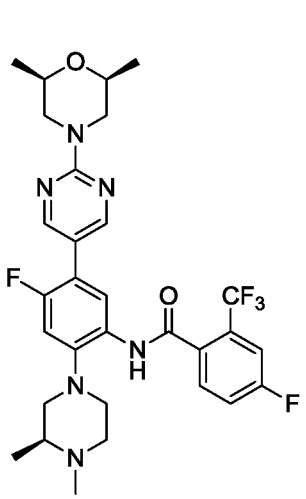
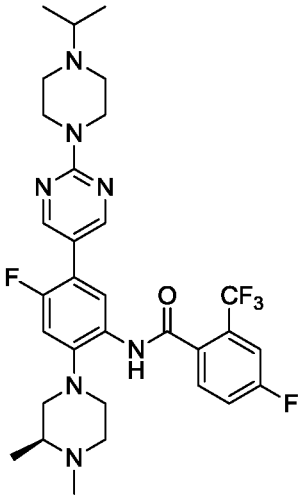
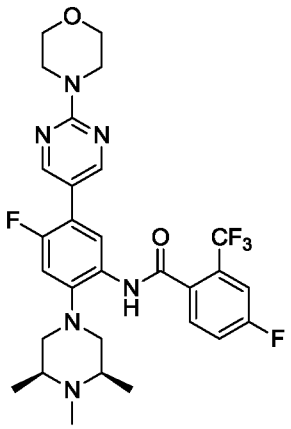
, wherein R is the subsituent.

52. The compound of any one of claims 44 to 51, wherein R^{48}, R^{49} and R^{50} are located on the phenyl ring as follows:



or , wherein R^{48} is selected from CF_3 and CF_2H and R^{49} and R^{50} are independently selected from H and F..

53. The compound of claim 44, selected from:


,

,

and

, or a pharmaceutically acceptable salt and/or solvate thereof.

54. The compound of Formula I of claim 1, selected from:

4-fluoro-N-[4-fluoro-2-(4-methylpiperazin-1-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-3,5-dimethylbenzamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[3-(morpholin-4-ylmethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholin-4-ylpyrirnidin-5-yl)phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(6-morpholin-4-ylpyridin-3-yl)phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxarnide;

N-[5-(l ,3-benzodioxol-5-yl)-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3R)-3,4-dimethylpiperazin-l-yl]-4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3S)-3,4-dimethylpiperazin-l-yl]-4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3 -carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2^yn olidin-l-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(cyclopropylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(cyclohexylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-ethoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-methylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclohexylamino)pyridin-3-yl]-4-fluoro-2-(4-me1hylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-hydroxypyrimidin-5-yl)-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[2-(2,2,2-trifluoroe1hoxy)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-pyrimidin-5-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,4-dime1hoxypyrimidin-5-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-

oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N- [4-fluoro-2-(4-methylpiperazin- 1-yl)-5 -(2-ηιοφ1ιο1ίη-4-ylpyrimidin-5 -yl)phenyl] -6-oxo- 1H-pyridine-3 -carboxamide;

N-[2-[3-(dimethylamino)pyrrolidin-l^ -4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-(4-methylpiperazin-l-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl] phenyl] -3-methylbenzamide;

6-acetamido-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl] phenyl] -4-(tafluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

N-[4-fluoro-5-(4-mo ϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(oxan-4-yloxy)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-me%lpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl] phenyl] -6-oxo- 1H-pyridine-3-carboxarnide;

N-[4-fluoro-5-pyridin-3-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-pyridin-4-yl-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[(3S)-3-(dimethylamino)pyn·olidin-1-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-(4-methylpiperazin-1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-[6-(morpholin-4-ylmethyl)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)- lH-pyrazole-4-carboxamide;

N-(2',6-difluoro-4-(4-methylpiperazin-1-yl)-5'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(3'-((cyclopentylamino)methyl)-6-fluoro-4-(4-methylpiperazin- 1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-moϕ holinopyridin-4-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(moϕ holinomethyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

N-(4-fluoro-2-(4-methylpiperazin-l-yl)-5-(5-(((tetrahydro-2H-pyran-4-yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

(R)-N-(4-fluoro-2-(4-methylpiperazin-1-yl)-5-(5-(((tetrahydrofuran-3 -

yl)amino)methyl)pyridin-3-yl)phenyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

(R)-N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

(S)-N-(4-(3,4-dimethylpiperazin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxamide;

N-(6-fluoro-3'-(morpholinomethyl)-4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-6-fluoro-3'-(morpholinomethyl)-[1,1'-biphenyl]-3-yl)-6-oxo-4-(trifluoromethyl)-l,6-dihydropyridine-3-carboxamide;

N-[4-fluoro-2-(4-methylpiperazin-l-yl)-5-(2-morpholin-4-ylpyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluorophenyl)-4-fluorobenzamide;

N-[5-(l,3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxarnide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrirnidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-methoxy-6-oxo-1H-pyridine-3-carboxamide;

N-[5-[2-(cyclopropylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-[(cyclohexylamino)methyl]phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-cWoro-4-morpholin-4-ylphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3,4-dihydro-2H-l,5-benzodioxepin-7-yl)-4-fluoro-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-l,4-benzodioxin-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-methyl-2,3-dihydro-l,4-benzoxazin-7-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-acetamidopyrimidin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-phenyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]benzamide;

4-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-methoxybenzamide;

3,5-dichloro-N-[4-fluoro-5<2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridazine-3 -carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]furan-2-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]pyridine-3-carboxamide;

N-[4-fluoro-5<2-moϕ holin-4-ylpyridin-4-yl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl] -2-methoxybenzamide;

2-chloro-4-cyano-N-[4-cyano-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,58)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

5-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -3-methoxybenzamide;

N-[4-fluoro-5-[4-(2-methoxyethoxy)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-chloro-6-(2-methylpropoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[3-chloro-4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[5-(3,6-dihydro-2H-pyran-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-(l,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl] -3-(trifluoromethyl)- 1H-pyrazole-4-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-

dimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

N-[5-(3-chloro-5-cyano-4-hydroxyphenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-cyano-6-phenylmethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-(4-cyanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-cyanophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(dimethylamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5,6-dime1hoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-1,3-benzodioxole-4-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-4-methoxybenzamide;

4-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(3-fluoro-5-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

2-chloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

2-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-3-methoxybenzamide;

3,4-difluoro-N-[4-fluoro-5<2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5<4-methoxyphenyl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<4^yrrolidin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-acetamido-N-[4-fluoro-5<2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methylindazole-3-carboxamide;

N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-1-methylindazole-3-carboxamide;

N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[3-[(4-fluoropiperidin-l-yl)methyl]phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-(3,4,6,7,9,9a-hexahydro-lH-pyrazino[2, 1-c][1,4]oxazin-8-yl)-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methylpyrazole-4-carboxamide;

N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-1-methylpyrazole-4-carboxamide;

N-[5-(5-cyano-6-hydroxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-hydroxyphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[3-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3<dimethylamino)-N-[4-fluoro-5<2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl]-1,3-oxazole-4-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(6-cyanopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(6-cyano-5-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-methoxy-6-(trifluoromethyl)pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-methoxy-6-methylpyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-cyano-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxypyridine-3-carboxamide;

3-chloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

2,6-dichloro-N-[4-fluoro-5<2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

3-chloro-2-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

tert-butyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl] -3,6-dihydro-2H-pyridine-1-carboxylate;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(trifluoromethyl)phenyl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[4-(trifluoromethoxy)phenyl] phenyl] -6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-phenyl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-chlorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(4-methoxyphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-methylpyridazin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-methylpropyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(cyclopropylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3R,5S)-3,4,5-trime%lpiperazin-l-yl]-5-[l-(3,3,3-trifluoropropyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[(4-fluorophenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541-^yridin-3-ylme1hyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-541<thiophen-3-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazm -1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-5-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

3,5-difluoro-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-

trimethylpiperazin- 1-yl] phenyl] benzamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin^-yl]-541<l,3-thiazol-2-ylmethyl)-3,6-dihydro-2H^yridin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(2-methyl- 1,3-oxazol-5-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-mmethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(1-methylpyrazol-4-yl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-mmethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[(4-moϕ holin-4-ylphenyl)methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-mmethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[[4-(4-methylpiperazin-l-yl)phenyl]methyl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(oxan-4-ylmethyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3,5-dichloro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin- 1-yl] phenyl] benzamide;

3,5-dichloro-N-[4-fluoro-5-(4-moϕ holin-4-ylphenyl)-2-[(3R)-3-(dimethylamino)pyrrolidin- 1-yl] phenyl] benzamide;

N-[5-(5-cyano-6-moϕ holin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(5-methyl-6-mo rpholin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-lH-pyrrolo[2,3-b]pyridin-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-545<trifluoromethyl)pyridin-3-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-(tert-butylcarbamoyl)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

3-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(4-mo ϕ holin-4-ylphenyl)-2-[(3R)-3-(dimethylan^ino)pyn·olidin-l-yljphenyl] -1H-pyrazole-4-carboxamide;

N-[4-fluoro-5-(5-methylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-carbamoylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-545<trifluoromethyl)pyridin-3-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-methyl-l,3-thiazole-2-carboxamide;

2-[(dim ethylarnin o)m ethyl]-N -[4-f uoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -1,3 -thiazole-4-carboxamide;

4-chloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -lH-pyrazole-3 -carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-3-(trifluoromethyl)-lH-pyrazole-4-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide;

2-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)benzamide;

3-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-methoxybenzamide;

3,5-dichloro-N-[4-fluoro-5-(4-morpholin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methylpyrazole-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-lH-pyrazole-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-4-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-l,3-thiazole-5-carboxamide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-methyl-4-(trifluoromethyl)-l,3-thiazole-5-carboxamide;

3,5-dichloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R)-3,4-dime1hylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmorpholin-4-yl]pyrirnidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2<4-me1hyl-l,4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5<4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(5-cyanopyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-chloropyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyclohexyloxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[2-(4-methoxyphenyl)acetyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(2-methoxyethoxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2^yrrolidin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl] -3-(trifluoromethyl)thiophene-2-carboxamide;

3,5-ώchlθrθ-4-AυoΓθ-N-[4-AυoΓθ-5-(2^ oφHo 1ιη-4^1 pyrimiώη-5^1)-2-[(3R,58)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,3-dichloro-N-[4-fluoro-5<2-moφholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

N-[4-fluoro-5-[3-[[methyl(oxetan-3-yl)amino]methyl]phenyl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-(5-ethoxypyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(Muo rомethyl)-N-[4-fluorO-5-(2-moφholin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(6-acetamidopyridin-3-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-5-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-1-methyl-6-oxopyridine-3-carboxamide;

N-[5-[6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[5-cyano-6-(dimethylamino)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(dimethylamino)-5-fluoropyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-chloro-6-moφholin-4-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-[l,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-(difluoromethyl)-N-(2-((S)-3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-((S)-2-methylmo ϕ holino)pyrimidin-5-yl)phenyl)-4-fluorobenzan^ide;

N-[4-fluoro-5 -(2-mo ϕ holin-4-ylpyrimidin-5 -yl)-2-(3 ,3,4-trimethylpiperazin- 1-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyridin-4-yl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5<4^yrrolidin-l-ylphenyl)-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethoxy)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

2,3-difluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] benzamide;

2-chloro-4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-(l-cyclopentyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[1-(4-methoxyphenyl)ethyl] -3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(l-butan-2-yl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-L· yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5^iperidin-4-yl-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-

4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3-(dimethylamino)pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyrii^ e-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-propan-2-yloxypyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2,3-dihydro-[l,4]dioxino[2,3-b]pyridin-7-yl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-541<l-methylpiperidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2,2-dimethylpropanoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<l^yrirnidin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-

1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(l-methylsulfonyl-2,5-dihydropyrrol-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3,5-dichloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

2-chloro-N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-4-fluorobenzamide;

N-[5-(l-acetyl-3,6-dihydro-2H-pyridin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

ethyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5 S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

2-methylpropyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[5-[1-(3,3-dimethylbutanoyl)-3,6-dihydro-2H-pyridin-4-yl] -4-fluoro-2-[(3R,5 S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-fluoropyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[4-(dimethylamino)piperidin-l-yl]-4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[4-[2-(dime1hylan^ino)ethyl]piperazin-l-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[2-[2-[(dimethylan^ino)methyl]morpholin-4-yl]-4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(6^yrrolidin-l-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(5-cyano-6-pyrrolidin-l-ylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-(2,2-difluoro-l,3-benzodioxol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

3-chloro-4-Auoro-N-[4-Auoro-5-(2^ oφHo 1ίη-4-ylpyrimίdίη-5^1)-2-[(3R,58)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

3-chloro-N-[4-fluoro-5-(2-moφholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-methoxybenzamide;

3-chloro-2,4-ώAuoro-N-[4-Auoro-5-(2^ oφHo 1ίη-4^1pyrimidiη-5^1)-2-[(3R,58)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

N-[4-fluoro-5-(l-methyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-(2-moφholin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-(6-cyano-4-methylpyridin-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-pyridin-2-yl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-me%lpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541<5-chloropyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

ethyl 2-[4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridin-l-yl]pyrimidine-4-carboxylate;

N-[4-fluoro-2-[3-(methylamino)pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[2-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-1Hϕ yridine-3-carboxamide;

N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3-hydroxy-5-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-3-hydroxybenzamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-

1-yl]phenyl]-3-hydroxy quinoline-4-carboxamide;

N-[4-fluoro-5-(2^ ophno 1in-4-ylpyrimidin-5-yl)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[4-fluoro-5-(2-moph holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[541<dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541-^yn-olidine-l-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(4-methylpiperazine- 1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

phenyl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-5-[l-[(2R,6S)-2,6-dimethyloxan-4-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moph holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-4-hydroxy-2-(trifluoromethyl)benzamide;

2,3-difluoro-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-5-hydroxybenzamide;

N-[5-[2-(cyclobutylmethoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylpropoxy)pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[5-[2-(diethylarrino)pyrimidin-5-yl]-4-fl^ oro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3 -carboxamide;

3-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

3,4,5-trifluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]benzamide;

2-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

3,5-dichloro-N-[4-fluoro-2-[3-(methylamino)pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl]benzamide;

N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[4-(4-methylpiperazin-l-yl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-2-[3-[methyl(propyl)amino]pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5 -yl)phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

3,5-dichloro-N-[4-fluoro-2-[3-[methyl(propyl)anlino]pyrrolidin-l-yl]-5-(2-mo rpholin-4-ylpyrimidin-5-yl)phenyl]benzamide;

N-[5-[l-[2-(dime%lamino)acetyl]-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-[4-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]pyrimidin-2-yl]piperazin-l-yl]-4-

oxobutanoic acid;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-24(3R,4R)-3<dime%lan^ino)-4-fluoropyrrolidin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 - carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,4R)-3-(dime1hylamino)-4-fluoropyrrolidin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 - carboxamide;

N-[4-fluoro-2-mo rpholin-4-yl-5-(2-piperazin-l-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-(dime1hylan^ino)-4-fluoropyrrolidin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,4R)-3-(dime1hylamino)-4-fluoropyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-hydroxypyridin-3-yl)-2-[(3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

tert-butyl 4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -4-(difluoromethyl)-6-oxo- 1H-pyridine-3-carboxamide;

l-ethyl-N-[4-fluoro-5-(2-mo rpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-methylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(tafluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[6-(4-methylpiperazin-l-yl)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

2,3-dichloro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-

dimethylpiperazin-l-yl]phenyl]benzarnide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-(2,2,6,6-tetramefliylm^ rpholin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarrd de;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[2-(2,2,6,6-tetramethylmo rpholin-4-yl)pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromet^^ l)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-5-(trifluoromethyl)-lH-pyrazole-3-carboxamide;

tert-butyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH^yriine-3-carbonyl]amino]-4-[(3R,5 S)-3,4,5-trimethylpiperazin-l -yljphenyl] -3,6-dihydro-2H-pyridine- 1-carboxylate;

tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH^yriine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

tert-butyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH^yriine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate;

tert-butyl 5-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]armno]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H - pyridine- 1-carboxylate;

tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

tert-butyl 3-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate;

N-[4-fluoro-24(3R,5S)-3,4,5-trime%lpiperazin4-yl]-5<l,2,3,64etrahydropyridin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH^yriine-3-carboxamide;

N-[5<2,5-dihydro-lH^yrrol-3-yl)-4-fluoro-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH^yriine-3-carboxarnide;

N-[5-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[5<2-butan-2-yloxypyridin-4-yl)-4-fluoro-24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-morpholin-4-ylpyrimidin-5-yl)-24(3R,4R)-3<dime%lan^ino)-4-methoxypyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-pyrirnidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-pyrimidin-2-yl-2,5-dihydropyrrol-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(8-pyrirnidin-2-yl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-yl-l,4,5,6-tetrahydropyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-

dimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-1-methyl-6-oxopyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(lR,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl] phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-[ethyl(methyl)amino]-4-fluoropyn olidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[e1hyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-[ethyl(methyl)amino]-4-fluoropyrrolidin- 1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-propan-2-ylmo ϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R)-2-propan-2-ylmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

N-[5-[2-(2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-7-(trifluoromethyl)-[l,2,4]triazolo[4,3-a]pyridine-6-carboxamide;

N-[5-[2-(7-azabicyclo[2.2.1]heptan-7-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-fluoro-4-moϕ holin-4-ylphenyl)-2-[(3R,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-[e%l(me%l)amino]-4-methoxypyrrolidin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)-1H-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[me%l-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5424me%l-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fluoropyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[1-(4,6-dimethylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424me%l(oxan-4-yl)amino]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5424me%l(oxan-4-yl)amino]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541<dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

ethyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l -yljphenyl] -3,6-dihydro-2H-pyridine- 1-carboxylate;

N-[4-fluoro-541-^yn-olidine-l-carbonyl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-me%lpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-541<5-fluoropyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[2<4-me%lpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[542<dime%lamino)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -4-fluoro-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-[2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]pyrimidin-5 -yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-me1hylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl] -2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridazin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-

1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[4-fluoro-5424(2R)-2-me%lmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro -24(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-[(2R)-2-methylmoϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH^yridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<l^yrirnidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-[4-[(4-fluorophenyl)methyl]piperazin-l-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-pyrimidin-2-ylpiperazin-l-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-5-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl] pyrimidin-5 -yl]phenyl] -6-oxo- lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylnK^holin-4-yl] pyrimidin-5 -yl]phenyl] -6-oxo- lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-methylsulfonylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-methyl-l,4-diazepan-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-(difluoromethyl)-N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxamide;

N-[5-[l-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(moϕ holin-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trime%lpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-methylpropyl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(Muo Ɽomethyl)-N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(hydroxymethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-[5-[(dimethylamino)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-(mo ϕ holin-4-ylmethyl)pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3S)-3-(dime%lamino)pyrrolidin-l-yl]-5-[2-[(2R,6S)-2,6-dimethylmoϕ holin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrirnidin-5-yl]-2-[(3S)-3-[e1hyl(methyl)amino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl] -6-oxo-4-(mfluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-5-yl)-2-[(3R)-3-[methyl(propan-2-y^aminolpyn-olidin-l-ylJphenylJ -e-oxo^-^rifluoromethy^-lH-pyridine-S-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo rpholin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R)-3,4-dime1hylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3S)-3-(dime%lamino)pyrrolidin-l-yl]-5-[2-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyrin^idin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrirnidin-5-yl]-2-[(3S)-3-[ethyl(methyl)amino] pyrrolidin- 1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-(diethylamino)pyrrolidin-1-yl]phenyl] -1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrirnidin-5-yl)-2-[(3R)-3-[methyl(propan-2-yl)armno]pyrrolidin-l-yl]phenyl]-l-methyl-6-oxo-4-(mfluoromethyl)pyridine-3-

carboxamide;

4-fluoro-N-[4-fluoro-5 -[24(2R,6S)-2,6-dime%lmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5 -[24(2R,6S)-2,6-dime%lmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluorome1hyl)benzamide;

4-fluoro-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluorome1hyl)benzamide;

N-[4-fluoro -24(3R)-3,4-dime%lpiperazin-l-yl]-5-[6-[(2R)-2-methylmorpholin-4-yl]pyridin-3 -yl]phenyl] -6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -4-fluoro-2-(trifluoromethyl)benzamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxarnide;

N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-me%lpyrirnidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(5-fluoropyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(pyrrolidine-l-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-

trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(pyrazine-2-carbonyl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2-methylpropyl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-541<5-fonnylpyrirnidin-2-yl)-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylpyrazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<4-cyano-l,3-thiazol-2-yl)-4-fluoro -24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<5-cyano-l,3-thiazol-2-yl)-4-fluoro -24(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- 1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxopyridine-3 -carboxamide;

N-[4-fluoro -24(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin- 1-yl]phenyl] - 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 -carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmo ϕ holin-4-yl] pyrimidin-5 -yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-[(2R)-2-me1hylmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-

3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(4-cyclopropylpiperazin-l-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[l-[5-[(dimethylarrino)methyl]pyrirm din-2-yl]-2,5-dihydropyrrol-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-[5-(moϕholin-4-ylmethyl)pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-[5-[(4-methylpiperazin-l-yl)methyl]pyrimidin-2-yl]-2,5-dihydropyrrol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmoϕholin-4-yl]pyrimidin-5-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R)-2-me%lmo ϕholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(2R,6S)-2,6-dime%lmo ϕholin-4-yl]pyrin^idin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrol-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-piperazin-1-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyriume-3-carboxamide;

N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(1-methylcyclobutyl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(1-methylcyclobutyl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-5-(6-moϕholin-4-ylpyriώn-2-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕholin-4-ylpyrazin-2-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(3R)-3-methylmoϕholin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-

carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-l-propyl-2,3,3a,4,6,6a-hexahydropyn ·oloP^-clpyrrol-S-yllphenyll -e-oxo^-^fluoromethy^-lH-pyridine-S-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-24(3aR,6aR)-l-methyl-2,3,3a,4,6,6a-hexahydropyn ·oloP^-clpyrrol-S-yllphenyll -e-oxo^-^fluoromethy^-lH^yridine-S-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(3-fluoro-4-mo ϕ holin-4-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,4,5-tetramethylpiperazin-4-ium- 1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmc^holin-4-yl] pyrimidin-5 -yl] phenyl] - 1-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R)-2-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-4-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-4-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-4-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-

thiazole-4-carboxamide;

N-[4-fluoro-5-[4-(moϕ holine-4-carbonyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-544<4-me%lpiperazine-l-carbonyl)4,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(3-methyloxetan-3-yl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(3-methyloxetan-3-yl) 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(3-methyloxetan-3-yl) 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]arnino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

N-[4-fluoro-5-[5-(moϕholin-4^1methyl)thiophen-2^1]-2-[(3R,58)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-2-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]-5-thiophen-3-ylphenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[5-(moϕ holin-4-ylmethyl)thiophen-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-5-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-5-carboxamide;

N-(cyclopropylmethyl)-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-5-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thia^^ le-5-carboxamide;

N-cyclohexyl-2-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-5-carboxamide;

N-[4-fluoro-5-[5-(moϕ holine-4-carbonyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-545<4-me%lpiperazine-l-carbonyl)4,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

5-amino-4-fluoro-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[5-[l-(6-cyclopropylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541-(6-ethylpyridazin-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[6-(oxan-4-yloxy)pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-6-methoxy-4-(trifluoromethyl)pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-6-oxo-lH-pyridine-3-carboxan^ide;

4<difluorome%l)-N-[4-fluoro-546-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-6-oxo-lH ϕ yridine-3-carboxan^ide;

4<difluorome%l)-N-[4-fluoro-546-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH^yridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

5-an^ino-4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-5-yl)-2-[(3aR,6aR)-l-ethyl-2,3,3a,4,6,6a-hexahydropyn-oloP^-clpyrrol-S-ylJphenylJ -e-oxo^-^fluoromethy^-lH-pyridine-S-carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl] -2-[(3 S)-3,4-dimethylpiperazin- 1-yl]phenyl] -6-oxo- lH-pyridine-3 -carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]phenyl]-l-me1hyl-6-oxopyridine-3-carboxan^ide;

4-(difluoromethyl)-N-[4-fluoro-5-[6-[(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[6-[(2R,6S)-2,6-dimethylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-[(2R)-2-methylmoϕ holin-4-yl]pyridin-3-yl]phenyl]-l-me1hyl-6-oxopyridine-3-carboxan^ide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(2,2,2-trifluoroethyl)amino]pyrrolidin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-1H-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[2-[(3R)-3-me%lmo ϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxarnide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[l-me1hyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[l-me1hyl-6-oxo-4-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-[4-fluoro-5-[2-(moϕ holine-4-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(4-me%lpiperazine-l-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzarnide;

4-fluoro-N-[4-fluoro-5-(6-piperazin-l-ylpyridin-3-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-(cyclopropylmethyl)-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-l,3-thiazole-2-carboxamide;

N-cyclohexyl-4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-N-methyl-l,3-thiazole-2-carboxamide;

N-[4-fluoro-5-[2-(moϕ holine-4-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-542<4-me%lpiperazine-l-carbonyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[2-(cyclohexylamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(methylamino)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiper^ n-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(2-cyanopyrimidin-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[542<dime%lamino)pyrimidin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[4-fluoro-2-[4-(methylan^ino)piperidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5464(2R)-2-methylmo ϕ holin-4-yl]pyridin-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-[6-(cyclopropylmethoxy)pyridin-3-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmo rpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxami de;

4-fluoro-N-[4-fluoro-5 -[24(2R)-2-me%lmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(2-piperazin-l-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-(6-mo ϕ holin-4-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-(6^iperazin-l-ylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(4-piperazin-l-ylphenyl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

2-fluoro-5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-

dimethylpiperazin-l-yl]phenyl]benzamide;

2-fluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

2-fluoro-5-[2-fluoro-54[4-fluoro-2<trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]benzamide;

N-[5-[2-(4-tert-butylpiperazin-l-yl)pyrinidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-(2,2-dimethylmorpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[2-[4-(cyclopropylmethyl)piperazin-l-yl]pyrimidin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[2-(4-cyclopropylpiperazin-l-yl)-4-fluoro-5-(2-mo ϕ holin-4-ylpyrin^idin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(5-fluoro-6-oxo-lH-pyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

benzyl N-[5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]pyridin-3-yl]carbamate;

N-[4-fluoro-5-(5-fluoro-l-methyl-6-oxopyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(4-methoxybenzoyl)-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5 S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-oxo-l,3-dihydropyrrolo[2,3-b]pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methyl-2-oxopyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-

yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methyl-6-oxopyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[541<cyclohexanecarbonyl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

tert-butylN-[l-[2-[(3,5-dicWorobenzoyl)amino]-5-fluoro-4-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]pyrrolidin-3-yl]-N-methylcarbamate;

3,5-dichloro-N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l-yl]-5-(2-moϕ holin-4-ylpyrimidin-5-yl)phenyl]benzan^ide;

N-[4-fluoro-2-[3-[3-methoxypropyl(methyl)amino]pyrrolidin-l-yl]-5-(2-mo ϕ holin-4-ylpyrimidin-5-yl)phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-[1-(pyrazine-2-carbonyl)-3,6-dihydro-2H-pyridin-4-yl] -2-[(3R,5 S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[methyl(methylsulfonyl)amino]pyrrolidin- 1-yl]phenyl]-6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-methoxy-4-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[2-methoxyethyl(methyl)amino] pyrrolidin- 1-yl] phenyl] -6-oxo-4-(trifluoromethyl)- 1H-

pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R,4R)-3-fluoro-4-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[2-methoxyethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(6-methylsulfonylpyridin-3-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(mfluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(methanesulfonamido)pyrirnidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyanopyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylsulfonyl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(l-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)aniino]pyrrolidin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-5-yl)-2-[(3R)-3-[cyclopropylmethyl(methyl)amino]pyrrolidin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-[l-(5-cyanopyrimidin-2-yl)-2,5-dihydropyrrol-3-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-24(3R)-3,4-dime%lpiperazin-l-yl]-5-[2-[(2R)-2-methylmo rpholin-4-yl]pyrimidin-4-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-methylmo rpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-(3-carbamoyl-4-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-543-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxarnide;

N-[4-fluoro-5-(4-moϕ holin-4-ylpyrimidin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

propan-2-yl 3-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,5-dihydropyrrole-l-carboxylate;

propan-2-yl 5-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

N-[4-fluoro-5-[3-fluoro-4-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[4-fluoro-3-(methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-543-fluoro-4<methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-544-fluoro-3<methylcarbamoyl)phenyl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylnK^holin-4-yl] pyrimidin-5 -yl]phenyl] - 1-methyl-6-oxopyridine-3-carboxamide;

N -[4-fluoro-2 -[(3R)-3,4-dimethylpiperazin -1-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl]pyrimidin-5-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxami de;

N-[4-fluoro-5-(6-fluoropyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[6-(trifluoromethyl)pyridin-2-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5 -[24(2R)-2-me%lmoϕ holin-4-yl]pyrimidin-5-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,5-dimethylbenzamide;

4-(Difluoromethyl)-N-(4-fluoro-5 -(1 -(pyrrolidine- 1-carbonyl)-2,5 -dihydro- 1H-pyrrol-3-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-me1hylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R)-3,4-dime1hylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)berizarnide;

4-fluoro-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -2-(trifluoromethyl)benzamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4^1-1,3-thiazol-4^1)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-yl4,3-thiazol-4-yl)-24(3R)-3,4-dime%lpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5<2-mo ϕ holin-4-yl4,3-thiazol-5-yl)-24(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-yl-l,3-thiazol-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-yl-l,3-thiazol-5-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluoromethyl)-N-[4-fluoro-5-(2-mo ϕ holin-4-yl-l,3-thiazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin- 1-yl]phenyl] -N-(2,4,4-trimethylpentan-2-yl)benzamide;

N-[542,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-

pyridine-3-carboxamide;

4-(difluoromethyl)-N-[5-[2,4-difluoro-5-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo- 1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmorpholin-4-yl] pyrimidin-5 -yl]phenyl] -6-oxo- lH-pyridine-3-carboxamide

(S)-4-(Sifluoromethyl)-N-(2-(3,4-&methylpip^ razin-1-yl)-4-fluoro-5-(1-(pyrrolidine-1-carbonyl)-2,5-dihydro- lH-pyrrol-3-yl)phenyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

1-Methylcyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-2,5-dihydro-lH-pyrrole-1 -carboxylate;

1-Methylcyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-4-(3,4-dimethylpiperazin-l-yl)-2-fluorophenyl)-2,5-dihydro-lH-pyrrole- 1-carboxylate;

N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -6-oxo-4-(trifluoromethyl)- lH-pyridine-3 -carboxamide;

N-[5-(5-carbamoyl-2,4-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl] -4-(difluoromethyl)-6-oxo- 1H-pyridine-3-carboxamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,4-difluoro-542-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

4-fluoro-N-[4-fluoro-5-[2-(4-hydroxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2-(trifluoromethyl)benzamide;

3,3-Difluorocyclobutyl 3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-carboxamido)-2-fluoro-4-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-2,5-dihydro-lH-pyrrole-1 -carboxylate;

3,3-Difluorocyclobutyl (S)-3-(5-(4-(difluoromethyl)-6-oxo-l,6-dihydropyridine-3-

carboxamido)-4-(3,4-dimethylpiperazin-l-yl)-2-fluorophenyl)-2,5-dihydro-lH-pyrrole- 1-carboxylate;

(S)-N-(5-(l-(2-cyanopyrimidin-5-yl)-l,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethylpiperazin- 1-yl)-4-fluorophenyl)-4-(difluoromethyl)-6-oxo- 1,6-dihydropyridine-3-carboxamide;

N-[4-fluoro-5424(2R)-2-me%lmo rpholin-4-yl]pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]- 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 - carboxamide;

N-[4-fluoro-542<4½droxy-4-methylpiperidin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin- 1-yl]phenyl]- 1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3 - carboxamide;

N-[5-[l-(4-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(l,3-oxazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamid e

4-(difluoromethyl)-N-[4-fluoro-5-(l-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2 - [(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(5-methoxypyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-541<5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(6-methoxypyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

ethyl 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5 S)-3,4,5-trimethylpiperazin-l -yl]phenyl]-3,6-dihydro-2H-pyridine- 1-

carboxylate;

4-fluoro-N-[4-fluoro-5<l-pyrimidin-2-yl-3,6-dihydro-2H-pyridin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[l-(5-formylpyrimidin-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yljphenyl]-2-(trifluoromethyl)benzamide;

(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

N-[5-(4-carbamoyl-3-fluorophenyl)-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-543-fluoro-4<methylcarbamoyl)phenyl]-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2<difluorome%l)-4-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrin^idin-5-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide;

2<difluorome%l)-4-fluoro-N-[4-fluoro-5<2-mo rpholin-4-ylpyrin^idin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]benzamide;

2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,6-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- lH-pyridine-3 -carboxamide;

N-[5-(4-carbamoyl-3,5-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-1H-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmoϕ holin-4-yl]pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-(4-propan-2-ylpiperazin-l-yl)pyrimidin-5-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[542<2,2-dimethylmo rpholin-4-yl)pyrimidin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-(Muo Гomethyl)-N-[4-fluoIO-5-(2-moϕ holin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

2,3-difluoro-4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,3-difluoro-442-fluoro-54[4-fluoro-2<trifluorome%l)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-N-(2,4,4-trimethylpentan-2-yl)benzamide;

2,3-difluoro-442-fluoro-54[4-fluoro-2<trifluoromethyl)benzoyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

2,3-difluoro-442-fluoro-54[4-fluoro-2<trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]benzamide;

N-[5-[2,3-Muoro-4-(2,4,4-trimethylpentan-2-ylcarbamoyl)phenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-(4-carbamoyl-2,3-difluorophenyl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-5-(6-moϕ holin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

propan-2-yl 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate;

N-[4-fluoro-5-(l-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5<l,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<l-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-(3-methylbenzimidazol-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[5-(l,3-benzothiazol-4-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(l,3-benzothiazol-5-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-(l,3-benzothiazol-6-yl)-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-l-methyl-6-oxopyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[1-(5-cyano-1,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[5-[1-(5-cyano-1,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide;

N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-(2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

N-[4-fluoro-5-(2-moϕholin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R)-2-methylmorpholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(oxan-4-yloxy)pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(5-cyano-l,3-1hiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmoϕholin-4-yl]pyrimidin-4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-[(2R,6S)-2,6-dimethylmoϕholin-4-yl]pyrimidin-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(tafluoromethyl)- 1H-pyridine-3-carboxamide;

(1-methylcyclobutyl) 4-[2-fluoro-5-[[6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carbonyl]amino]-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-1-yljphenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(3,3-difluorocyclobutyl) 5-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(3,3-difluorocyclobutyl) 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)berizoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

(3,3-difluorocyclobutyl) 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)berizoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-

carboxamide;

N-[5-[4-(cyclohexylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluorome1hyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[(2,2-dime1hylcyclohexyl)carbamoyl]-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethylcarbamoyl)-3,5-difluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluorome%l)-N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-[l-(2-morpholin-4-ylethyl)pyrazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-[l-(2-morpholin-4-yle1hyl)pyrazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxarnide;

4-(difluoromethyl)-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-4-yl)-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

4-(difluoromethyl)-N-[4-fluoro-5-(6-morpholin-4-ylpyridin-2-yl)-2-[(3R)-3,4-

dimethylpiperazin-1-yl]phenyl]-6-oxo-1H-pyridine-3-carboxamide;

2-(difluoromethyl)-4-fluoro-N-[4-fluoro-5-(2-morpholin-4-ylpyrimidin-5-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]benzamide;

propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,54rimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-l-carboxylate;

propan-2-yl 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[5-[[4-(difluoromethyl)-6-oxo-1H-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 4-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

propan-2-yl 5-[2-fluoro-5-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-4-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-3,6-dihydro-2H-pyridine-l-carboxylate;

(1-methylcyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

(3,3-difluorocyclobutyl) 4-[5-[[4-(difluoromethyl)-6-oxo-lH-pyridine-3-carbonyl]amino]-2-fluoro-4-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-2,3,6,7-tetrahydroazepine-1-carboxylate;

N-[5-[1-(5-cyano-1,3-thiazol-2-yl)-2,3,6,7-tetrahydroazepin-4-yl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclohexylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[cyclopropylmethyl(methyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-[(4,4-difluorocyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[5-[4-(cyclopropylmethylcarbamoyl)-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4-fluoro-N-[4-fluoro-2-[(3R)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmc^holin-4-yl] pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(3R)-3-methylmc^holin-4-yl] pyrimidin-5-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-2-[(3S)-3,4-dimethylpiperazin-l-yl]-5-[2-[(2R)-2-methylmoϕ holin-4-yl]pyrimidin-4-yl]phenyl]-2-(trifluoromethyl)benzamide;

4-fluoro-N-[4-fluoro-5-[24(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-4-yl]-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-2-(trifluoromethyl)benzamide;

N-[5-[l-(2-cyanopyrimidin-4-yl)-3,6-dihydro-2H-pyridin-5-yl]-4-fluoro-2-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl]-4-(difluoromethyl)-6-oxo-lH-pyridine-3-carboxamide;

4-((1iAυoΓoηethyl)-N-[4-fluoΓθ-5-[4-(ηιoϕ ho1iη-4^1η6%1)-1,3-thiaζo1-2^1]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-(6^iperazin-l-ylpyridin-2-yl)-2-[(3R)-3,4-dimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo rpholin-4-yl]pyrirnidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxo-4-(trifluoromethyl)pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrin^idin-

4-yl]-2-[(3S,5R)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5424(2R,6S)-2,6-dime%lmo ϕ holin-4-yl]pyrimidin-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5<2-mo ϕ holin-4-ylpyrimidin-4-yl)-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]phenyl]-1-methyl-6-oxopyridine-3-carboxamide;

N-[5-[44(2,2-dimethylcyclohexyl)carbamoyl]-3-fluorophenyl]-4-fluoro-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[5-(mo ϕ holin-4-ylmethyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

4<difluorome%l)-N-[4-fluoro-5-[2-(mo ϕ holin-4-ylmethyl)-l,3-thiazol-4-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-l-methyl-6-oxopyridine-3-carboxamide;

N-[4-fluoro-5-[4-(moϕ holin-4-ylmethyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

N-[4-fluoro-5-[5-(moϕ holin-4-ylmethyl)-l,3-thiazol-2-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-l-yl]phenyl]-6-oxo-4-(trifluoromethyl)-lH-pyridine-3-carboxamide;

2<difluorome%l)-N-(5<2<(2S,6R)-2,6-dime%lmo rpholino)pyrin^idin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-4-fluorobenzamide;

2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((S)-2-methylmorpholino)pyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)benzamide;

2-(difluoromethyl)-4-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyr midin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)benzamide,

3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmo rpholino)pyrimidin-5-yl)-4-

fluoro-2-((3S,5R)-3,4,54rimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide;

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;

(S)-3-(difluoromethyl)-N-(2-(3,4-dimethylpiperazin-l-yl)-4-fluoro-5-(2-morpholinopyrinlidin-4-yl)phenyl)-5-fluoropicolinamide;

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-((R)-2-methylmorpholino)pyrimidin-4-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;

3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-4-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide;

N-(4'-(cyclohexyl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)- [1,1'-biphenyl] -3-yl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

N-(4'-(cyclopen†yl(methyl)carbamoyl)-3',5',6-trifluoro-4-((3S,5R)-3,4,5-trimethylpiperazin- 1-yl)- [1,1'-biphenyl] -3-yl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

6-oxo-N-(3',5',6-trifluoro-4'-(((R)-tetrahydrofuran-3-yl)carbamoyl)-4-((3S,5R)-3,4,5 -trimethylpiperazin- 1-yl)-[1,1'-biphenyl] -3-yl)-4-(trifluoromethyl)- 1,6-dihydropyridine-3-carboxamide;

3-(difluoromethyl)-N-(5-(2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)-4-fluoro-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)-5-fluoropicolinamide; and

3-(difluoromethyl)-5-fluoro-N-(4-fluoro-5-(2-morpholinopyrimidin-5-yl)-2-((3S,5R)-3,4,5-trimethylpiperazin-l-yl)phenyl)picolinamide;

or a pharmaceutically acceptable salt and/or solvate thereof.

55. A pharmaceutical composition comprising one or more compounds of Formula (I) of any one of claims 1 to 54, or a pharmaceutically acceptable salt, and/or solvate thereof, and a pharmaceutically acceptable carrier and/or diluent.

56. The pharmaceutical composition of claim 55 further comprising an additional therapeutic agent.

57. A method of treating one or more diseases, disorders or conditions mediated or treatable by inhibition of binding between WDR5 protein and its binding partners comprising administering an effective amount of one or more compounds of any one of claims 1 to 54, or a pharmaceutically acceptable salt, and/or solvate thereof, to a subject in need thereof.

58. The method of claim 57, wherein the disease, disorder or condition is a neoplastic disorder.

59. The method of claim 58, wherein the neoplastic disorder is cancer.

60. The method of claim 59, wherein the cancer is selected from solid cancer and leukemias.

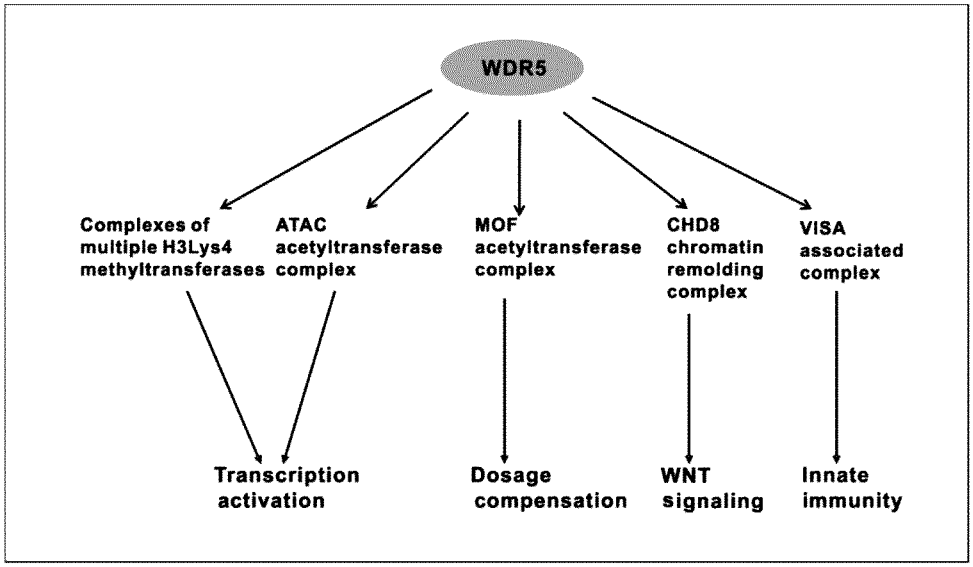
61. The method of claim 59, wherein the cancer is selected from leukaemia, lymphoma, non-Hodgkin's lymphoma, Burkitt lymphoma, MLL-fusion lymphoma, primary effusion leukemia and multiple myeloma.

62. The method of claim 59, wherein the cancer is selected from leukemia, melanoma, lung cancer, bladder cancer, colon cancer, brain cancer, ovarian cancer, breast cancer, prostate cancer, neuroblastoma and kidney cancer.

63. The method of claim 59, wherein the cancer is selected from leukemia, bladder cancer, prostate cancer, brain cancer and neuroblastoma.

64. The method of claim 59, wherein the cancer is selected from bladder cancer, acute myeloid leukemia (AML), gliomas, glioblastomas and MYCN-amplified neuroblastoma.

Figure 1


WDR5
Complexes of multiple H3Lys4 methyltransferases
ATAC acetyltransferase complex
MOF acetyltransferase complex
CHD8 chromatin remolding complex
VISA associated complex
Transcription activation
Dosage compensation
WNT signaling
Innate immunity

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2017/050269

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 413/14*** (2006.01) , ***A61K 31/496*** (2006.01) , ***A61K 31/506*** (2006.01) , ***A61K 31/5377*** (2006.01) , ***A61P 35/00*** (2006.01) , ***A61P 35/02*** (2006.01) (more IPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 413/14 (2006.01) , A61K 31/496 (2006.01) , A61K 31/506 (2006.01) , A61K 31/5377 (2006.01) , A61P 35/00 (2006.01) , A61P 35/02 C07D 401/14 (2006.01) , C07D 403/10 (2006.01) , C07D 405/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
n/a

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases used: STN, Orbit, Intellect, American Chemical Society publication search, Espacenet, Scopus, PubMed, ScienceDirect, and Google Patents. Keywords used: WDR5 protein, WDR5-MLL binding inhibitors, Wdr5 inhibitors, Wdr5 protein binding inhibitors, Wdr5-MLL interaction inhibitors, pyridinecarboxamide, fluoro + benzamide + heteroaryl, lH-pyridine-5-carboxamide, pyrazine+ benzamide compounds+inhibit+binding+between WDR5, fluorobenzamide+piperazine, fluorobenzamide+heteroaryl.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Pharmacological targeting of the Wdr5-MLL interaction in C/EBPa N-terminal leukemia". Florian Grebien et al. *Nat Chem Biol.* August 2015, 11(8), p.571-578 Whole document	1-64
A	"Small-molecule inhibition of MLL activity by disruption of its interaction with WDR5". Gullermo Senisterra et al. *Biochem J*. 2013, 449, 151-159 Whole document	1-64
A	"Synthesis, Optimization, and Evaluation of Novel Small Molecules as Antagonists of WDR5-MLL Interaction". Yuri Bolshan et al. *ACS Medicinal Chemistry Letters* 2013, 4, 353-357 Whole document	1-64
A	CN105175284 (YOU QIDONG et al.) 23 December 2015 (23-12-2015) Whole document	1-64

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2017 (14-06-2017)	28 June 2017 (28-06-2017)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, CI 14 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer **Wendy Young (819) 639-9418**

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Structure-based design of conformationally constrained cyclic peptidomimetics to target the MLL1-WDR5 protein-protein interaction as inhibitors of the MLLl methyltransferase activity". Hacer Karatas et al. *Chinese Chemical Letters* 2015, 26, 455-458 Whole document	1-64
A	"Analysis of the Binding Mixed Lineage Leukemia 1 (MLLl) and Histone 3 Peptides to WD repeat Domain 5 (WDR5) for the design of Inhibitors of the MLL1-WDR5 Interaction". Hacer Karatas et al. *J. Med. Chem.* 2010, 53, 5179-5185 Whole document	1-64
A	WO201 1159685 (WANG, S et al.) 22 December 2011 (22-12-201 1) Whole document	1-64
A	"WDR5 Interacts with Mixed Lineage Leukemia (MLL) Protein via the Histone H3-binding Pocket". Ji-Joon Song et al. *Journal of Biological Chemistry* 2008, 283(50), 35258-35264 Whole document	1-64
A	WO2014003124 (YOKOTANI, J et al.) 03 January 2014 (03-01-2014) Whole document	1-64
A	CA2944959 (DONG, X) 1st October 2015 (01-10-2015) Whole document	1-64

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2017/050269

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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WO201 1159685A2	22 December 201 1 (22-1 2-201 1)	WO201 1159685A2	22 December 201 1 (22-1 2-201 1)
		WO201 1159685A3	12 April 2012 (12-04-201 2)
		CN103189067A	03 July 2013 (03-07-201 3)
		US201 1312997A1	22 December 201 1 (22-1 2-201 1)
		US9233086B2	12 January 201 6 (12-01-201 6)
WO201 40031 24A1	03 January 2014 (03-01-2014)	WO201 40031 24A1	03 January 2014 (03-01-2014)
		AR091 586A1	11 February 201 5 (11-02-2015)
		TW201406736A	16 February 2014 (16-02-2014)
CA2944959A1	01 October 201 5 (01-1 0-201 5)	CA2944959A1	01 October 201 5 (01-1 0-201 5)
		CN1 04926788A	23 September 201 5 (23-09-201 5)
		CN104926801 A	23 September 201 5 (23-09-201 5)
		EP3124486A1	01 February 201 7 (01-02-2017)
		JP201 751 2796A	25 May 201 7 (25-05-201 7)
		US201 710721 3A1	20 April 2017 (20-04-201 7)
		WO201 5144021A1	01 October 201 5 (01-1 0-2015)

C07D 401/14 **(2006.01)** **,** ***C07D 403/10*** **(2006.01)** **,** ***C07D 405/14*** **(2006.01)**