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(54) Title: GLUCOSYLCERAMIDE SYNTHASE INHIBITORS FOR THE TREATMENT OF DISEASES

(57) Abstract: Described herein are compounds of Formula I, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds to treat or prevent diseases or conditions associated with the enzyme glucosylceramide synthase (GCS).

GLUCOSYLCERAMIDE SYNTHASE INHIBITORS FOR THE TREATMENT OF DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of priority of U.S. Provisional Application No. 61/880,752, filed September 20, 2013, the content of which is hereby incorporated by reference in its entirety.

FIELD

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds to treat or prevent diseases or conditions associated with the enzyme glucosylceramide synthase (GCS).

BACKGROUND

[0003] Glucosylceramide synthase (GCS) is a key enzyme which catalyzes the initial glycosylation step in the biosynthesis of glucosylceramide-based glycosphingolipids (GSLs) namely via the transfer of glucose from UDP-glucose (UDP-Glc) to ceramide to form glucosylceramide. GCS is a transmembrane, type III integral protein localized in the cis/medial golgi. Glycosphingolipids (GSLs) are believed to be integral in many cell membrane events, including cellular interactions, signaling, and trafficking. Synthesis of GSL structures has been shown (*Proc. Natl. Acad. Sci CISA* **1999**, *96(16)*, 9142-9147) to be essential for embryonic development and for the differentiation of some tissues. Ceramide plays a central role in sphingolipid metabolism, and downregulation of GCS activity has been shown to have marked effects on the sphingolipid pattern with diminished expression of glycosphingolipids. Sphingolipids have a role in physiological as well as pathological cardiovascular conditions. In particular, sphingolipids and their regulating enzymes appear to play a role in adaptive responses to chronic hypoxia in the neonatal rat heart (*Prostaglandins & Other Lipid Mediators* **2005**, *78(1-4)*, 249-263).

[0004] GCS inhibitors have been proposed for the treatment of a variety of diseases (see, for example, WO2005068426). Such diseases include glycolipid storage diseases (e.g., Tay Sachs, Sandhoffs, GM1 gangliosidosis and Fabry diseases), diseases associated with glycolipid accumulation (e.g., Gaucher disease), diseases that cause renal hypertrophy or hyperplasia such as diabetic nephropathy, diseases that cause hyperglycemia or

hyperinsulinemia, cancers in which glycolipid synthesis is abnormal, infectious diseases caused by organisms which use cell surface glycolipids as receptors, infectious diseases in which synthesis of glucosylceramide is essential or important, diseases in which excessive glycolipid synthesis occurs (e.g., atherosclerosis, polycystic kidney disease, and renal hypertrophy), neuronal disorders, neuronal injury, inflammatory diseases or disorders associated with macrophage recruitment and activation (e.g., rheumatoid arthritis, Crohn's disease, asthma and sepsis), pain (see WO200801 1483 - neuropathic pain, inflammatory pain, headache pain, somatic pain, visceral pain, referred pain), cognitive disorders (see WO2008/109286 - agnosia; amnesia; aphasia; an apraxia; delirium; dementia including AIDS dementia complex, Binswanger's disease, dementia with Lewy Bodies, frontotemporal dementia, mild cognitive impairment, multi-infarct dementia, Pick's disease, semantic dementia, senile dementia, and vascular dementia; and learning disorders including Asperger's syndrome, attention deficit disorder, attention deficit hyperactivity disorder, autism, childhood disintegrative disorder, and Rett syndrome), neurodegenerative disorders (such as Alzheimer's disease, corticobasal degeneration, Creutzfeldt-Jacob disease, frontotemporal lobar degeneration, Huntington disease, multiple sclerosis, normal pressure hydrocephalus, organic chronic brain syndrome, Parkinson's disease, Pick disease, progressive supranuclear palsy, and senile dementia (Alzheimer type), glomerular disease, and diabetes mellitus and obesity (see WO 2006053043). Renal hypertrophy induced by diabetes is associated with enhanced synthesis of glycosphingolipids such as glucosylceramide and ganglioside GM₃ which accumulate in the kidney of rats (*J. Clin. Invest.* **1993**, 91(3), 797).

[0005] It has been shown that overexpression of GCS is implicated in multi-drug resistance and disrupts ceramide-induced apoptosis. For example, Turzanski et al. (*Experimental Hematology* **2005**, 33(1), 62-72) have shown that ceramide induces apoptosis in acute myeloid leukemia (AML) cells and that P-glycoprotein (p-gp) confers resistance to ceramide-induced apoptosis, with modulation of the ceramide-glucosylceramide pathway making a marked contribution to this resistance in TF-I cells. Thus, GCS inhibitors can be useful for treatment of proliferative disorders (such as cancer) by inducing apoptosis in diseased cells.

[0006] Sandhoff (or type 2 GM2 gangliosidosis) is caused by a deficiency in β -hexosaminidase A and B activity which leads to an accumulation of the ganglioside GM₂ and other glycolipids causing damage to the central nervous system and eventually is lethal (*PLoS One* **2011**, 6(6), e21758). Tay-Sachs disease (or GM₂ gangliosidosis) is caused by a

deficiency in β -hexosaminidase A which lead to an accumulation of gangliosides in the brain's nerve cells eventually leading to their premature death. Intravenous injection of the missing enzyme(s) is not a viable option as of the enzymes does cross the blood-brain barrier {*Genetics in Medicine* **2009**, 1(6), 425}. Glucosylceramide synthase is a key enzyme in the synthesis of glucosylceramide and other glycosphingolipids. Its inhibition can decrease the amount of the glycosphingolipids which accumulate in Sandhoff disease.

[0007] Fabry disease is caused by loss of activity of the lysosomal hydrolase α -galactosidase which leads to an accumulation of glycosphingolipids (particularly globotriaosylceramide) causing pain, renal disease and failure, cerebral vascular disease, and myocardial infarction {*Kidney International* **2000**, 57, 446}. One treatment strategy is to provide the defective enzyme to the patient; however, enzyme replacement therapy can only slow the progression of the disease and is not a cure. An alternative or complementary strategy is one where glucosylceramide synthase, a key enzyme in the synthesis of glycosphingolipids, is inhibited with a small molecule thus decreasing the amount of globotriaosylceramide and other glucosylceramide-based lipids that need to be broken down by hydrolase α -galactosidase.

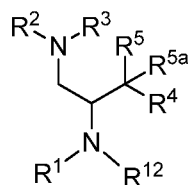
[0008] Gaucher disease is caused by a defect in the enzyme lysosomal glucocerebrosidase which is responsible for catalyzing the breakdown of glucosylceramide which then accumulates in tissues of affected people (*J. Org. Chem.* **2007**, 72(4), 1088) causing liver malfunction, skeletal disorders, painful bone lesions, hypersplenism, pancytopenia, and neurological symptoms (convulsions, hypertonia, mental retardation, apnea, dementia, and ocular muscle apraxia). One treatment strategy is to provide the defective enzyme to the patient; however, enzyme replacement therapy is not suitable for all patients and does not address the neurological manifestations of the disease for those with type 2 and type 3. An alternative or complementary strategy is one where glucosylceramide synthase is inhibited with small molecules thus decreasing the amount of glucosylceramide that needs to be broken down by glucocerebrosidase.

[0009] Nonalcoholic fatty liver disease (NALD) is a disease where fat accumulates in the liver of people who drink little or no alcohol and results in inflammation and scarring of the liver which can progress to liver failure. Inhibition of glucosylceramide synthase in ob/ob mice lowered glucose levels, lowered liver/body weight ratio, decreased the accumulation of triglycerides, and prevented and reversed steatosis {*Hepatology* **2009**, 50(1), 85-93}. Thus GCS inhibitors are useful for the prevention and treatment of NALD.

[00010] Polycystic kidney disease (PKD) is a genetic disease characterized by noncancerous cysts which are filled with fluid and cause the kidneys to enlarge which can result in a decrease in quality of life (e.g., headaches, high blood pressure, back and side pain, colon problems, mitral valve prolapsed, and kidney stones) and can be life-threatening (e.g. kidney failure, aneurysm in the brain, and high blood pressure which can lead to heart disease and stroke). PKD can also damage the liver, spleen, pancreas, vasculature, testes, seminal vesicles, and intestines. Glucosylceramide and ganglioside GM₃ levels in the kidney are higher than in normal tissue {*Nat Med* **2010**, 16(7), 788}. Thus, blocking the synthesis of glucosylceramide with an inhibitor of GCS can be useful in the treatment of PKD to reduce new cyst formation (partial or complete inhibition of cystogenesis), reduce cyst mass, reduce the size and number of cysts, and/or reduce the severity of the symptoms associated. All current treatments for PKD address symptoms and do not treat the underlying cause of the disease (*Nat Med* **2010**, 16(7), 788).

SUMMARY OF THE INVENTION

[00011] In one aspect, provided is a compound of Formula I:



Formula I

where

R¹ is -C(0)C(R⁶)(R^{6a})Pv^{1a} or -C(0)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, 3, or 4 R⁹ groups;

R⁵ is -OH, and R^{5a} is hydrogen;

R⁶ and R^{6a} are halo; R⁶ and R^{6a} are deuterium; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOH) or C(O);

each R⁷, when present, is independently nitro, cyano, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, haloalkoxy, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, heterocycloalkyl,

phenyl, phenylalkyl, phenoxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl; or two R⁸ together with the carbon to which they are attached form C(O);

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a};

each R^{9a}, when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino; and R¹² is hydrogen or C₁₋₅ alkyl;

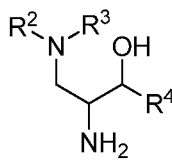
optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00012] In a further aspect, provided is a pharmaceutical composition comprising 1) a compound of Formula I optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

[00013] In a further aspect, provided is a method of treating a disease or disorder comprising administering a compound of Formula I, optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof additionally comprising a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

[00014] In a further aspect, it is provided a method of making a compound of Formula I, comprising

- a) treating an intermediate of formula **100**



100

or a salt thereof, where R^2 , R^3 , R^4 , and all other groups are as defined in the Summary of the Invention or as in any of the embodiments described herein; with an intermediate of formula $R^1C(=O)OH$ using standard amide coupling conditions to yield a Compound of Formula I where R^5 is hydroxy and R^{5a} is hydrogen and R^1 is as defined in the Summary of the Invention or as in any of the embodiments described herein; and

- b) optionally separating individual isomers.

DETAILED DESCRIPTION

Abbreviations

Abbreviation	Meaning
ACN	acetonitrile
aq	aqueous
Boc	tert-butoxycarbonyl
CBz	
conc	concentrated
DAST	diethylaminosulfur trifluoride
DIPEA	diisopropylethylamine
DCM	dichlorormethane
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
h	hours
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOBt	hydroxybenzotriazole
mg	milligram
mHz	megahertz
mL	milliliter
μ L	microliter
Ms	mesyl
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance

Abbreviation	Meaning
PE	petroleum ether
rt or RT	room temperature
sat	saturated
TBAF	tetra-n-butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBS	<i>tert</i> -butyl-silyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Definitions

[00015] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[00016] As used throughout this application and the appended claims, the following terms have the following meanings:

[00017] "About" preceding a numerical value refers to a range of values $\pm 10\%$ of the value specified.

[00018] "Acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00019] "Alkoxy" means an -OR group where R is alkyl, as defined herein. In some embodiments, alkoxy includes, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy.

[00020] "Alkoxy carbonyl" means a -C(=O)R group where R is alkoxy, as defined herein.

[00021] "Alkenyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one double bond. "Lower alkenyl" means an alkenyl group having one to six carbon atoms. In some embodiments, alkenyl includes ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

[00022] "Alkenylene" means a divalent alkenyl group, as defined herein.

[00023] "Alkenyloxy" means an -OR group where R is alkenyl, as defined herein.

[00024] "Alkyl" means a straight or branched saturated hydrocarbon radical containing from 1-10 carbon atoms, in another example 1-6 carbon atoms. In some embodiments, alkyl includes, but is not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylhexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[00025] "Alkylamino" means a -NHR radical where R is alkyl as defined herein, or an N-oxide derivative thereof. In some embodiments, alkylamino includes methylamino, ethylamino, *n*-, *iso*-propylamino, *n*-, *iso*-, *tert*-butylamino, or methylamino-N-oxide, and the like.

[00026] "Alkylaminoalkyl" means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[00027] "Alkylaminocarbonyl" means a -C(0)NHR group where R is alkyl, as defined herein.

[00028] "Alkylene" means a divalent alkyl group, as defined herein.

[00029] "Alkynyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one triple bond.

[00030] "Amino" means -NH₂.

[00031] "Aminoalkyl" means an alkyl group substituted with at least one, for example one, two, or three, amino groups.

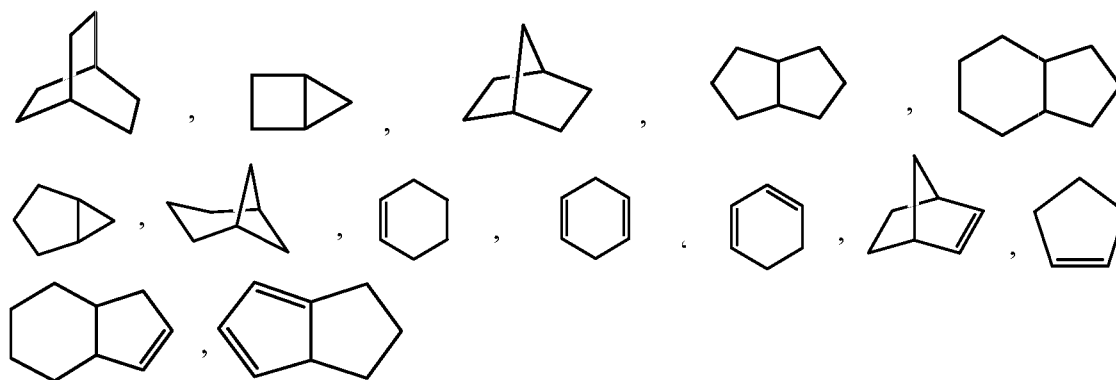
[00032] "Aminocarbonyl" means a -C(0)NH₂ group.

[00033] "Aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. In some embodiments, the examples of aryl include phenyl, naphthyl, and indanyl, and the like.

[00034] "Carboxy" means a -C(0)OH group.

[00035] "Cycloalkyl" means a monocyclic or fused bicyclic, saturated or partially unsaturated (but not aromatic), hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged rings. Cycloalkyl includes spirocycloalkyl rings. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group.

[00036] In some embodiments, cycloalkyl includes but is not limited to:



[00037] "Cycloalkylene" means a divalent cycloalkyl group, as defined herein.

[00038] "Cycloalkylalkyl" means an alkyl group, as defined herein, substituted with at least one, in another example 1 or 2, cycloalkyl groups as defined herein.

[00039] "Cycloalkylalkyloxy" means an -OR group where R is a cycloalkylalkyl group as defined herein.

[00040] "Cycloalkyloxy" means an -OR group where R is cycloalkyl, as defined herein.

[00041] "Cycloalkylthio" means an -SR group where R is cycloalkyl, as defined herein.

[00042] "Dialkylamino" means an -NRR' radical where R and R' are independently alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof. In some embodiments, dialkylamino includes dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.

[00043] "Dialkylaminoalkyl" means an alkyl group substituted with at least one, for example one or two, dialkylamino group(s), as defined herein.

[00044] "Dialkylaminocarbonyl" means a -C(=O)NRR' group where R and R' are alkyl, as defined herein.

[00045] "Haloalkoxy" means an alkoxy group, as defined herein, substituted with one or more halo atoms, in another example by 1, 2, or 3 halo atoms.

[00046] "Haloalkyl" means an alkyl group substituted with one or more halo atoms, in another example by 1, 2, 3, 4, 5, or 6 halo atoms, in another example by 1, 2, or 3 halo atoms. In some embodiments, haloalkyl includes, but is not limited to, trifluoromethyl, chloromethyl, and the like.

[00047] "Heteroaryl" means monocyclic, fused bicyclic, or fused tricyclic, radical of 5 to 14 ring atoms containing one or more, in another example one, two, three, or four ring

heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(H)-, and N-oxide, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic (but does not have to be a ring which contains a heteroatom, e.g. 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl). One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting.

[00048] In some embodiments, heteroaryl includes, but is not limited to, triazolyl, tetrazolyl, pyrrolyl, imidazolyl, thienyl, furanyl, pyrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiadiazolyl, indolyl, 2,3-dihydro-1 *H*-indolyl (including, for example, 2,3-dihydro-1 *H*-indol-2-yl or 2,3-dihydro-1 *H*-indol-5-yl, and the like), indazolyl, phthalimidyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothienyl, benzopyranyl, benzothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoliny, isoquinoliny, tetrahydroisoquinoliny (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-*c*]pyridinyl (including, for example, pyrrolo[3,2-*c*]pyridin-2-yl or pyrrolo[3,2-*c*]pyridin-7-yl, and the like), pyrrolo[1,2-*£*]pyridazinyl, imidazo[1,2-*a*]pyridinyl, thiazolyl, benzo[*i*][1,3]dioxolyl, 2,3-dihydrobenzo[*£*][1,4]dioxinyl, furo[2,3-*i*]thiazolyl, thieno[2,3-*i*]oxazolyl, thieno[3,2-*£*]furanyl, furo[2,3-*J*]pyrimidinyl, furo[3,2-*¾*]pyridinyl, furo[3,2-*c*]pyridinyl, 6,7-dihydro-5*H*-cyclopenta[*£*]pyridinyl, and 7,8-dihydro-6*H*-cyclopenta[*g*]quinoxaliny; and derivatives, N-oxide and protected derivatives thereof.

[00049] "Heteroarylalkyl" means an alkyl group, as defined herein, substituted with one or two heteroaryl groups, as defined herein.

[00050] "Heteroaryloxy" means an -OR group where R is heteroaryl as defined herein.

[00051] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 9 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more heteroatoms, for example one, two, three, or four ring heteroatoms, independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N=, -NH-, and N-oxide, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems.

Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Heterocycloalkyl includes spiroheterocycloalkyl rings.

[00052] In some embodiments, heterocycloalkyl includes, but is not limited to, azetidiny, pyrrolidiny, 2-oxopyrrolidiny, 2,5-dihydro-1 *H*-pyrroliny, 2,5-dioxo-1 *H*-pyrroly, 2,5-dioxo-pyrrolidiny, 2,5-dihydro-1 *H*-pyrroly, piperidiny, 2-oxopiperidiny, 4-piperidony, morpholiny, piperaziny, 2-oxopiperaziny, dioxopiperaziny, pyranly, tetrahydropyranly, tetrahydrothiopyranly, 1,3-dioxiny, 1,3-dioxany, 1,4-dioxiny, 1,4-dioxany, thiomorpholiny, thiamorpholiny, perhydroazepiny, pyrazolidiny, imidazoliny, imidazolidiny, 2,4-dioxo-imidazolidiny, dihydropyridiny, tetrahydropyridiny, oxazoliny, oxazolidiny, isoxazolidiny, thiazoliny, thiazolidiny, quinuclidiny, isothiazolidiny, octahydroindoly, octahydroisoindoly, decahydroisoquinoly, tetrahydrofury, 2-azaspiro[3.3]heptany, 7-azabicyclo[2.2.1]heptany, and 8-azabicyclo[3.2.1]octany, and the derivatives thereof and N-oxide (for example 1-oxido-pyrrolidin-1-yl) or a protected derivative thereof.

[00053] "Heterocycloalkylalkyl" means an alkyl group substituted with at least one, in another example 1 or 2, heterocycloalkyl groups, as defined herein.

[00054] "Heterocycloalkylalkyloxy" means an -OR group where R is an heterocycloalkylalkyl group, as defined herein.

[00055] "Heterocycloalkyloxy" means an -OR group where R is heterocycloalkyl, as defined herein.

[00056] "Hydroxyalkyl" means an alkyl group, as defined herein, substituted with 1, 2, or 3 hydroxy groups.

[00057] "Hydroxyalkyloxy" means an -OR group where R is hydroxyalkyl, as defined herein.

[00058] "Phenylalkyl" means an alkyl group, as defined herein, substituted with one or two phenyl groups.

[00059] "Phenyloxy" means an -OR group where R is phenyl.

[00060] The term "protecting group" refers to a removable group which modifies the reactivity of a functional group, for example, a hydroxyl, ketone or amine, against undesirable reaction during synthetic procedures and to be later removed. Examples of hydroxy-protecting groups include, but not limited to, methylthiomethyl, tert-dimethylsilyl, tert-butyldiphenylsilyl, ethers such as methoxymethyl, and esters including acetyl, benzoyl, and the like. Examples of ketone protecting groups include, but not limited to, ketals, oximes,

O-substituted oximes for example O-benzyl oxime, O-phenylthiomethyl oxime, 1-isopropoxycyclohexyl oxime, and the like. Examples of amine protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc) and carbobenzyloxy (Cbz).

[00061] "Stereoisomers" include (but are not limited to) geometric isomers, enantiomers, diastereomers, and mixtures of geometric isomers, enantiomers or diastereomers. In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[00062] As used herein, "amelioration" of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[00063] The term "carrier" includes pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical compositions. Lactose, corn starch, or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatin capsules, other than the soft gelatin itself. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oils and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

[00064] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents include chemicals used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in some or any embodiments, including, but not limited to a phosphate buffered saline solution.

[00065] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will

relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

[00066] "Excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.* \ Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.* \ Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.* \ Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[00067] "Pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt s not specifically limited as far as it can be used in medicaments. Examples of a salt that the compound of the present invention forms with a base include the following:

salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

[00068] The term "pharmaceutical composition" refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00069] "Subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

[00070] "Treat," "treating," and "treatment," in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof. Often, the beneficial effects that a subject derives from a therapeutic agent do not result in a complete cure of the disease, disorder or condition.

Embodiments

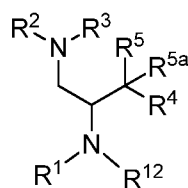
[00071] The following paragraphs present a number of embodiments of the compounds disclosed herein. In each instance the embodiment includes both the recited compound(s) as well as a single stereoisomer or mixture of stereoisomers thereof, as well as a pharmaceutically acceptable salt thereof. The compounds include the *N*-oxides or pharmaceutically acceptable salts thereof. In some situations, the compounds exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

[00072] The compounds described herein, as well as their corresponding pharmaceutically acceptable salts thereof, can exist in isotopically-labeled form, in which one or more atoms of the compounds are replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Isotopically labeled compounds of the present invention, as well as pharmaceutically acceptable salts thereof, generally can be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations herein, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00073] In the compounds of the invention, unless otherwise stated, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom at its natural abundance. When a position is designated as "H" or "hydrogen," the position is to be understood to have hydrogen at its naturally abundant isotopic composition, with the understanding that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. When a particular position is designated as "D" or "deuterium," it is to be understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%, and typically has at least 50% deuterium incorporation at that position.

[00074] The methods disclosed herein also include methods of treating diseases by administering deuterated compounds of the invention or other isotopically-labeled compounds of the invention alone or as pharmaceutical compositions. In some of these situations, substitution of hydrogen atoms with heavier isotopes such as deuterium can afford certain therapeutic advantages resulting from greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). Moreover, certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays such as positron emission tomography (PET). Tritiated (^3H) and carbon-14 (^{14}C) isotopes are useful for these embodiments.

[00075] In one aspect, provided is a compound of Formula I:



Formula I

where

R¹ is -C(O)C(R⁶)(R^{6a})R^{1a} or -C(O)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, 3, or 4 R⁹ groups;

R⁵ is halo, -OH, -OTBS, -N₃, -NH₂, -NH(OCH₃), -NHC(O)CH₃, or -NHC(O)H; and R^{5a} is hydrogen, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are attached form C(O) or C(NOH);

R⁶ is halo or deuterium; and R^{6a} is hydrogen, halo, or deuterium; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOR¹⁰) or C(O);

each R⁷, when present, is independently nitro, cyano, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxy-carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenoxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl; or two R⁸ together with the carbon to which they are attached form C(O);

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, -NRⁿC(O)NR^{11a}R^{11b}, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy,

haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a};

each R^{9a}, when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino;

R¹⁰ is hydrogen, alkyl, or phenyl;

R^u, R^{lla}, and R^{llb} are independently hydrogen, alkyl, or cycloalkyl; and

R¹² is hydrogen or C₁₋₅ alkyl;

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00076] In some or any embodiments, the compound of Formula I is that where

R¹ is -C(O)C(R⁶)(R^{6a})R^{1a} or -C(O)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, 3, or 4 R⁹ groups;

R⁵ is -OH, and R^{5a} is hydrogen;

R⁶ and R^{6a} are halo; R⁶ and R^{6a} are deuterium; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOH) or C(O);

each R⁷, when present, is independently nitro, cyano, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, haloalkoxy, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenyloxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl; or two R⁸ together with the carbon to which they are attached form C(O);

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a}; each R^{9a}, when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino; and R¹² is hydrogen or C₁₋₅ alkyl; optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00077] In some or any embodiments, the compound of Formula I is that where

R¹ is -C(O)C(R⁶)(R^{6a})R^{1a} or -C(O)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is -OH, and R^{5a} is hydrogen;

R⁶ and R^{6a} are halo; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOH) or C(O);

each R⁷, when present, is independently nitro, cyano, halo, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenyloxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently amino, alkylamino, dialkylamino, alkyl, halo, or cycloalkyl; or two R⁸ together with the carbon to which they are attached form C(O);

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy,

heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a}; each R^{9a}, when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino; and R¹² is hydrogen or CH₃; optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00078] In some or any embodiments, the compound of Formula I is that where

R¹ is -C(O)C(R⁶)(R^{6a})R^{1a} or -C(O)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene or alkenylene;

R^{1a} is heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1 or 2 R⁷ groups;

R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is -OH, and R^{5a} is hydrogen;

R⁶ and R^{6a} are halo; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOH) or C(O);

each R⁷, when present, is independently cyano, halo, haloalkyl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenoxy, heteroaryl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently amino, alkyl, or halo; or two R⁸ together with the carbon to which they are attached form C(O);

each R⁹, when present, is independently amino, halo, haloalkyl, alkyl, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a}; each R^{9a}, when present, is independently selected from alkyl or halo;

R¹⁰ is hydrogen or CH₃;

R¹² is hydrogen; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00079] In some or any embodiments, the compound of Formula I is that where

R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$ or $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$;

X^1 is alkylene;

R^{1a} is heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^7 groups;

R^2 and R^3 together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R^8 ;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^9 groups;

R^5 is $-OH$, and R^{5a} is hydrogen;

R^6 and R^{6a} are halo; or R^6 and R^{6a} together with the carbon to which they are attached form or $C(O)$;

each R^7 , when present, is independently nitro, cyano, halo, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenyloxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a} ;

each R^{7a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R^8 , when present, is independently amino, alkylamino, dialkylamino, alkyl, or halo;

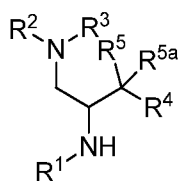
each R^9 , when present, is independently amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a} ;

each R^{9a} , when present, is independently selected from alkyl and halo; and

R^{12} is hydrogen or CH_3 ;

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00080] In another aspect, provided is a compound of Formula II:



Formula II

where

R¹ is -C(O)C(R⁶)(R^{6a})R^{1a} or -C(O)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is halo, -OH, -OTBS, -N₃, -NH₂, -NH(OCH₃), -NHC(O)CH₃, or -NHC(O)H and R^{5a} is hydrogen, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are attached form C(O) or C(NOH);

R⁶ is halo or deuterium; and R^{6a} is hydrogen, halo, or deuterium; or R⁶ and R^{6a} together with the carbon to which they are attached form C(=NOR¹⁰) or C(O);

each R⁷, when present, is independently nitro, cyano, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxy-carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or heteroaryl;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, -NRⁿC(O)NR^{11a}R^{11b}, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyloxy, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy;

R¹⁰ is hydrogen, alkyl, or phenyl;

R^u, R^{11a}, and R^{11b} are independently hydrogen, alkyl, or cycloalkyl; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00081] In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; R^6 and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)CF_2R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; R^6 is halo and R^{6a} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(H)(F)R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)CD_2R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; R^6 and R^{6a} together with the carbon to which they are attached form $C(=NOR^{10})$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; R^6 and R^{6a} together with the carbon to which they are attached form $C(O)$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00082] In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; R^6 and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)CF_2-X^1-R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00083] In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; X^1 is alkylene; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-CH_2-R^{1a}$;

and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-CH_2CH_2-R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; X^1 is alkenylene; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; X^2 is $-CH=CH-$ or $-C(=CH_2)CH_2-$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00084] In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$ which is $-C(O)C(halo)_2CH_2R^{1a}$, $-C(O)C(halo)_2CH_2CH_2R^{1a}$, $-C(O)C(O)CH_2CH_2R^{1a}$, $-C(O)C(=NOH)CH_2CH_2R^{1a}$, $-C(O)C(=NOCH_3)CH_2CH_2R^{1a}$, $-C(O)C(halo)_2-CH=CHR^{1a}$, or $-C(O)C(halo)_2-C(=CH_2)CH_2R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$ which is $-C(O)CF_2CH_2R^{1a}$, $-C(O)CF_2CH_2CH_2R^{1a}$, $-C(O)CF_2-CH=CHR^{1a}$, or $-C(O)CF_2-C(=CH_2)CH_2R^{1a}$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00085] In some or any embodiments, the compound of Formula I or II is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; R^6 and R^{6a} together with the carbon to which they are attached form $C(O)$; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00086] In some or any embodiments, the compound of Formula I or II is that where R^{1a} is alkyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is methyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00087] In some or any embodiments, the compound of Formula I or II is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is naphthyl optionally

substituted with 1 or 2 R⁷ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is naphthyl optionally substituted with 1 or 2 R⁷ groups and each R⁷, when present, is halo; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is indanyl optionally substituted with 1 or 2 R⁷ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is indanyl optionally substituted with 1 or 2 R⁷ groups and each R⁷, when present, is independently heteroaryl (in another example pyridinyl) or halo; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is phenyl optionally substituted with 1 or 2 R⁷ groups and each R⁷, when present, is independently halo, haloalkoxy, or heteroaryl (in another example pyridinyl); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is phenyl optionally substituted with 1 or 2 R⁷ groups and each R⁷, when present, is independently aryl or heteroaryl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is phenyl optionally substituted with 1 or 2 R⁷ groups and each R⁷, when present, is independently phenyl or heteroaryl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00088] In some or any embodiments, the compound of Formula I or II is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is fused bicyclic heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is benzofuranyl, benzothienyl, indolyl, benzimidazolyl, 6,7-dihydro-5*H*-cyclopenta[ϵ]pyridinyl, benzothiazolyl, furo[3,2-*c*]pyridinyl, pyrrolo[1,2- $\frac{3}{4}$]pyridazinyl, imidazo[1,2-*a*]pyridinyl,

furo[3,2- ϵ]pyridinyl, furo[2,3-d]pyrimidinyl, thieno[3,2- ϵ]furanlyl, thieno[2,3- $\langle i \rangle$]oxazolyl, or furo[2,3- $\langle J \rangle$]thiazolyl, each of which is optionally substituted with 1 or 2 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is benzofuranyl, benzothienyl, indolyl, benzimidazolyl, 6,7-dihydro-5*H*-cyclopenta[$\frac{3}{4}$]pyridinyl, or benzothiazolyl, each of which is optionally substituted with 1 or 2 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is benzofuranyl optionally substituted with 1 or 2 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00089] In some or any embodiments, the compound of Formula I or II is that where R^{1a} is fused bicyclic heteroaryl optionally substituted with 1, 2, or 3 R^7 groups where each R^7 , when present, is independently halo, alkyl, or haloalkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is fused bicyclic heteroaryl optionally substituted with 1, 2, or 3 R^7 groups where each R^7 , when present, is independently chloro, bromo, fluoro, methyl, or trifluoromethyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00090] In some or any embodiments, the compound of Formula I or II is that where R^{1a} is fused tricyclic heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{1a} is 7,8-dihydro-6*H*-cyclopenta[$\langle g \rangle$]quinoxalinylyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00091] In some or any embodiments, the compound of Formula I or II is that where each R^7 , when present, is independently optionally substituted with 1, 2 or 3 R^{7a} groups, where each R^{7a} , when present, is independently cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where each R^7 , when present, is aryl or heteroaryl, either alone or as part of another group, such aryl or heteroaryl is independently optionally substituted with 1, 2 or 3 R^{7a} groups, as described herein. In some or any embodiments, the compound of Formula I or II is that where each R^7 , when present, is phenyl or heteroaryl,

either alone or as part of another group, such phenyl or heteroaryl is independently optionally substituted with 1, 2 or 3 R^{7a} groups, as described herein.

[00092] In some or any embodiments, the compound of Formula I or II is that where R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² is hydroxy and R³ is alkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00093] In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form a 4-8 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form azetidiny, pyrrolidinyl, 2-azabicyclo[2.2.1]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 2-azaspiro[3.3]heptanyl, 1-oxidopyrrolidinyl, piperidinyl, piperazinyl, or 8-azabicyclo[3.2.1]octanyl, each of which is optionally substituted with 1 or 2 R⁸; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form pyrrolidinyl optionally substituted with 1, 2, 3, or 4 R⁸; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form pyrrolidinyl optionally substituted with 1 or 2 R⁸; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together with the nitrogen to which they are attached form pyrrolidinyl optionally substituted with 1, 2, 3, or 4 R⁸ where each R⁸, when present, is independently deuterium, amino, alkyl, halo, or cycloalkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R² and R³ together

with the nitrogen to which they are attached form unsubstituted pyrrolidinyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^2 and R^3 together with the nitrogen to which they are attached form azetidinyll optionally substituted with 1 or 2 R^8 ; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^2 and R^3 together with the nitrogen to which they are attached form azetidinyll optionally substituted with 1 or 2 R^8 where each R^8 , when present, is independently alkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00094] In some or any embodiments, the compound of Formula I or II is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 where each R^8 , when present, is independently deuterium, amino, alkyl, halo, or cycloalkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 where each R^8 , when present, is independently deuterium, amino, methyl, fluoro, or cyclopropyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1 or 2 R^8 where each R^8 , when present, is independently amino, methyl, fluoro, or cyclopropyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00095] In some or any embodiments, the compound of Formula I or II is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^4 is phenyl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^4 is phenyl optionally substituted with 1, 2, or 3 R^9 groups where each R^9 , when present, is independently halo, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, heterocycloalkyloxy, or heterocycloalkylalkyloxy which is optionally

substituted with one hydroxy; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is phenyl optionally substituted with 1 or 2 R⁹ groups where each R⁹, when present, is independently bromo, chloro, fluoro, methoxy, difluoromethyl, trifluoromethyl, trifluoromethoxy, cyclopropyloxy, tetrahydrofuranlyloxy, or tetrahydropyranylmethyl which is optionally substituted with one hydroxy; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is phenyl optionally substituted with 2 R⁹ groups one of which is halo, and one of which is alkoxy; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

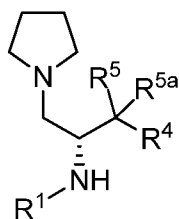
[00096] In some or any embodiments, the compound of Formula I or II is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is pyridinyl, 1*H*-indazolyl, benzofuranyl, 2,3-dihydrobenzo[ϵ][1,4]dioxin-6-yl, or quinolinyl each of which is optionally substituted with 1 or 2 R⁹ groups; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is pyridinyl, 1*H*-indazolyl, benzofuranyl, 2,3-dihydrobenzo[ϵ][1,4]dioxin-6-yl, or quinolinyl; R⁹, when present, is halo, alkyl, alkoxy, haloalkoxy, cycloalkyloxy, or heterocycloalkylalkyloxy which is optionally substituted with one hydroxy; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is pyridinyl, 1*H*-indazolyl, benzofuranyl, 2,3-dihydrobenzo[ϵ][1,4]dioxin-6-yl, or quinolinyl; R⁹, when present, is chloro, fluoro, methyl, methoxy, isopropoxy, 2,2,2-trifluoroethoxy, cyclopropyloxy, or tetrahydropyranylmethyl which is optionally substituted with one hydroxy; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁴ is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxin-6-yl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00097] In some or any embodiments, the compound of Formula I or II is that where R⁵ is halo, -OH, -OTBS, -N₃, -NH₂, -NH(OCH₃), -NHC(O)CH₃, or -NHC(O)H and R^{5a} is hydrogen, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are

attached form C(O) or C(NOH); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is -OH, -NH₂, -NH(OCH₃), -NHC(O)CH₃, or -NHC(O)H and R^{5a} is hydrogen, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are attached form C(O) or C(NOH); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is OH and R^{5a} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is -NH₂ and R^{5a} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is OH and R^{5a} is deuterium; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is -NH(OCH₃) and R^{5a} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is OH and R^{5a} is alkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is -NHC(O)H and R^{5a} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ and R^{5a} together with the carbon to which they are attached form C(O); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ and R^{5a} together with the carbon to which they are attached form C(NOH); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R⁵ is OH and R^{5a} is hydrogen, R⁵ is -NH₂ and R^{5a} is hydrogen, R⁵ is OH and R^{5a} is deuterium, R⁵ is -NH(OCH₃) and R^{5a} is hydrogen, R⁵ is OH and R^{5a} is alkyl, R⁵ is -NHC(O)H and R^{5a} is hydrogen, R⁵ and R^{5a} together with the carbon to which they are attached form C(O), or R⁵ and R^{5a} together with the carbon to which they are attached form C(NOH); and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00098] In some or any embodiments, the compound of Formula I or II is that where R^{10} is hydrogen; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{10} is alkyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{10} is methyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein. In some or any embodiments, the compound of Formula I or II is that where R^{10} is phenyl; and all other groups are as defined in the Summary of the Invention or any of the embodiments described herein.

[00099] In some or any embodiments, the compound of Formula I is according to Formula 1(a):

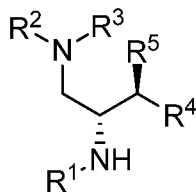


Formula 1(a)

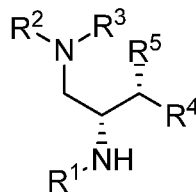
where all groups are as defined in the Summary of the Invention or as defined in any of the above embodiments. In another embodiment, the compound of Formula 1(a) is that where R^{5a} is hydrogen; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(a) is that where R^5 is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(a) is that where R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(a) is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(a) is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(a) is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is

optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000100] In some or any embodiments, the compound of Formula I is according to Formula 1(b) or 1(c):



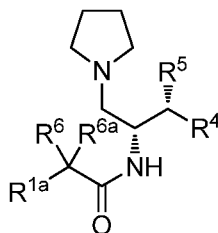
Formula 1(b)



Formula 1(c)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R¹ is -C(=O)C(R⁶)(R^{6a})R^{1a}; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R¹ is -C(=O)C(R⁶)(R^{6a})R^{1a}; R^{1a} is unsubstituted indanyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(b) or 1(c) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

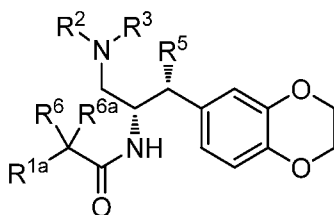
[000101] In some or any embodiments, the compound of Formula I is according to Formula 1(d):



Formula 1(d)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R⁶ and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(d) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

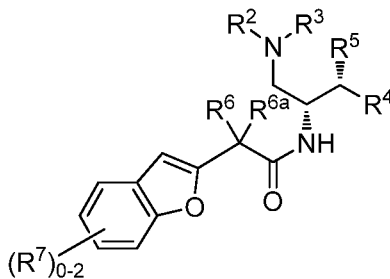
[000102] In some or any embodiments, the compound of Formula I is according to Formula 1(e):



Formula 1(e)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(e) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(e) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(e) is that where R⁶ and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(e) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or δ R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(e) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000103] In some or any embodiments, the compound of Formula I is according to Formula 1(f):

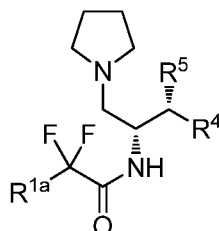


Formula 1(f)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as

defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where R⁶ and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(f) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000104] In some or any embodiments, the compound of Formula I is according to Formula 1(g):

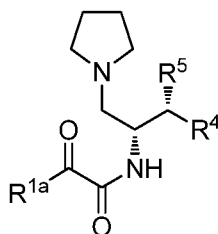


Formula 1(g)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R⁴ is unsubstituted 2,3-dihydrobenzo[*f*][1,4]dioxinyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the

Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula 1(g) is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000105] In some or any embodiments, the compound of Formula I is according to Formula I(s):



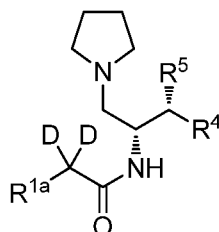
Formula I(s)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^5 is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^4 is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxinyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where at least one R^7 is halo; and all other

groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000106] In another embodiment, the compound of Formula I(s) is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where R^7 is phenyl or heteroaryl optionally substituted with at least one R^{7a} ; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(s) is that where at least one R^{7a} is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000107] In some or any embodiments, the compound of Formula I is according to Formula I(t):

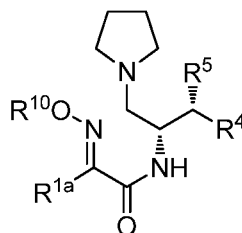


Formula I(t)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where R^5 is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound

of Formula I(t) is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where R^4 is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxinyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(t) is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000108] In some or any embodiments, the compound of Formula I is according to Formula I(u):

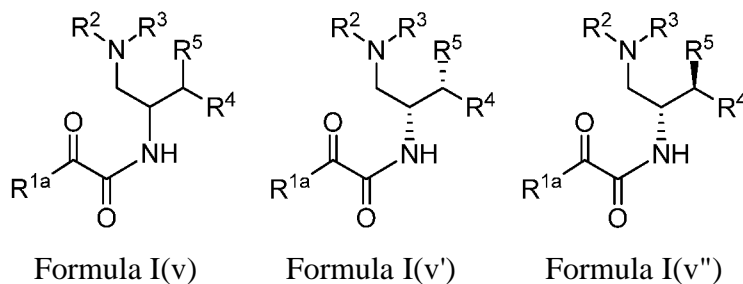


Formula I(u)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where R^5 is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where R^4 is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxinyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described

herein. In another embodiment, the compound of Formula I(u) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(u) is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000109] In some or any embodiments, the compound of Formula I is according to Formula I(v), Formula I(v'), or Formula I(v''):

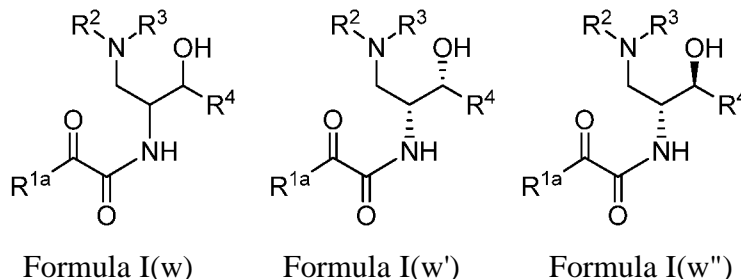


where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R⁴ is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxinyl; and all other groups are as defined in the Summary of the

Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where at least one R⁹ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where at least one R⁹ is alkoxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where R⁷ is phenyl or heteroaryl optionally substituted with at least one R^{7a}; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where at least one R^{7a} is

halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

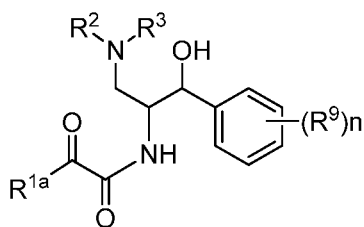
[000110] In some or any embodiments, the compound of Formula I is according to Formula I(w), Formula I(w'), or Formula I(w''):



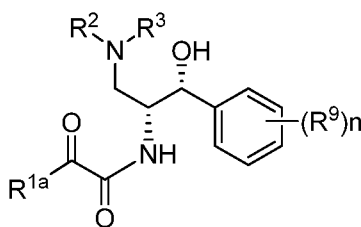
where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R⁴ is unsubstituted 2,3-dihydrobenzo[ϵ][1,4]dioxinyl; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where at least one R⁹ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where at least one R⁹ is alkoxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In

another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where R⁷ is phenyl or heteroaryl optionally substituted with at least one R^{7a}; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(w), Formula I(w'), or Formula I(w'') is that where at least one R^{7a} is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

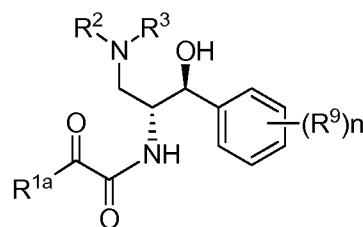
[000111] In some or any embodiments, the compound of Formula I is according to Formula I(x), Formula I(x'), or Formula I(x''):



Formula I(x)



Formula I(x')



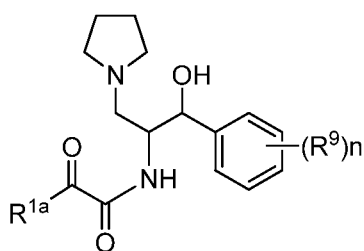
Formula I(x'')

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R² and R³ together with the nitrogen to which

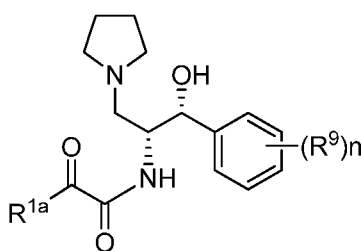
they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where at least one R⁹ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where at least one R⁹ is alkoxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where there are 2 R⁹ groups, where one R⁹ is halo and one R⁹ is alkoxy, preferably cyclopropyloxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where R⁷ is phenyl or heteroaryl optionally substituted with at least one R^{7a}; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In

another embodiment, the compound of Formula I(x), Formula I(x'), or Formula I(x'') is that where at least one R^{7a} is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

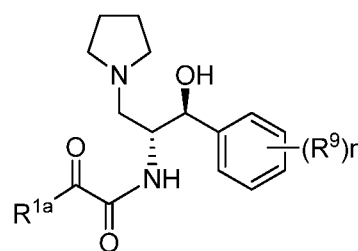
[000112] In some or any embodiments, the compound of Formula I is according to Formula I(y), Formula I(y'), or Formula I(y''):



Formula I(y)



Formula I(y')

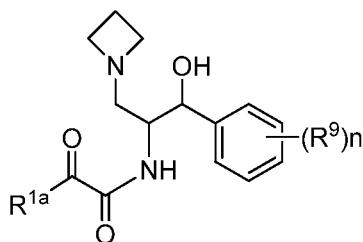


Formula I(y'')

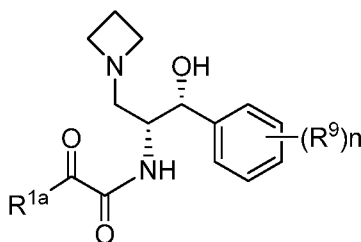
where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where at least one R^9 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where at least one R^9 is alkoxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where there are 2 R^9 groups, where one R^9 is halo and one R^9 is alkoxy, preferably cyclopropyloxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^{1a} is aryl optionally substituted with 1, 2, or 3

R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where R^7 is phenyl or heteroaryl optionally substituted with at least one R^{7a} ; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(y), Formula I(y'), or Formula I(y'') is that where at least one R^{7a} is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

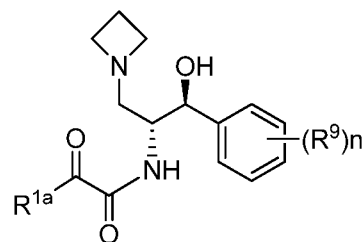
[000113] In some or any embodiments, the compound of Formula I is according to Formula I(z), Formula I(z'), or Formula I(z''):



Formula I(z)



Formula I(z')

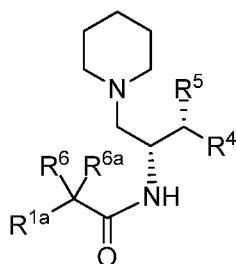


Formula I(z'')

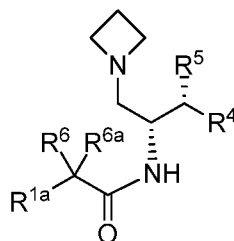
where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where at least one R^9 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where at least one R^9 is alkoxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(v), Formula I(v'), or Formula I(v'') is that where there are 2 R^9 groups, where one R^9 is halo and one R^9 is alkoxy, preferably cyclopropyloxy; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^{1a} is heteroaryl optionally

substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^{1a} is benzofuranyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^{1a} is benzothiophene optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^{1a} is aryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^{1a} is phenyl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where R^7 is phenyl or heteroaryl optionally substituted with at least one R^{7a} ; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(z), Formula I(z'), or Formula I(z'') is that where at least one R^{7a} is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

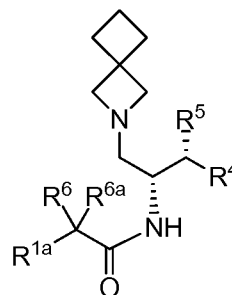
[000114] In some or any embodiments, the compound of Formula I is according to Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae):



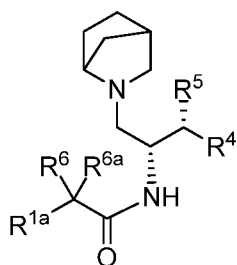
Formula I(aa)



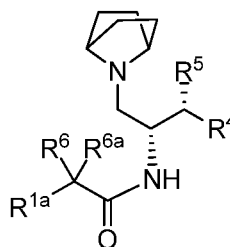
Formula I(ab)



Formula I(ac)



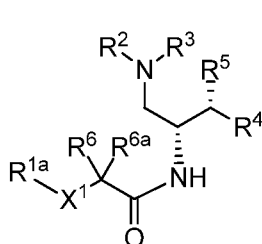
Formula I(ad)



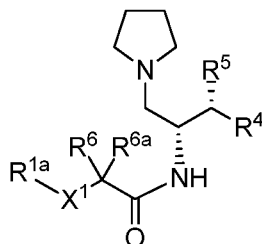
Formula I(ae)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R⁶ and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(aa), Formula I(ab), Formula I(ac), Formula I(ad), or Formula I(ae) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

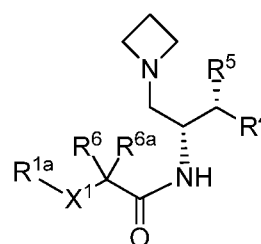
[000115] In some or any embodiments, the compound of Formula I is according to Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak):



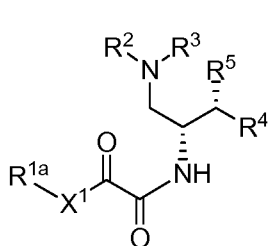
Formula I(af)



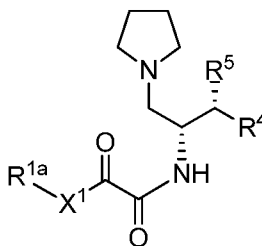
Formula I(ag)



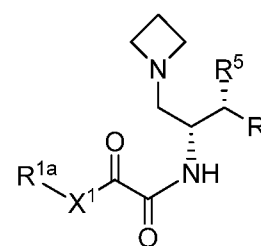
Formula I(ah)



Formula I(ai)



Formula I(aj)

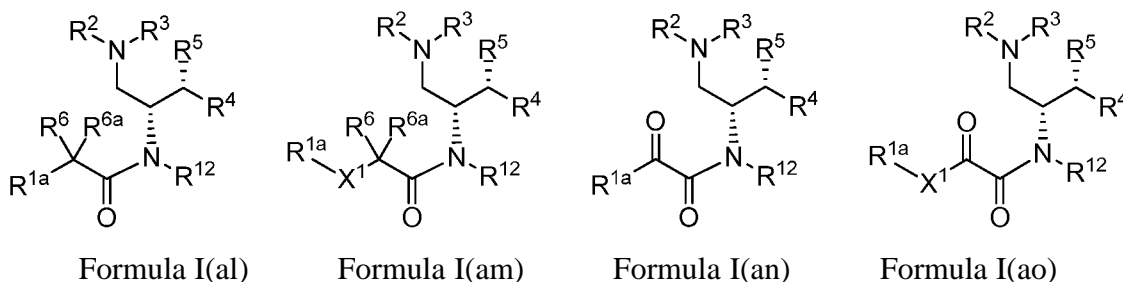


Formula I(ak)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where X¹ is alkylene or alkenylene; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where R⁵ is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where R⁴ is heteroaryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where R⁴ is aryl optionally substituted with 1, 2, or 3 R⁹ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af) or Formula I(ai) is that where R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af),

Formula I(ag), or Formula I(ah), is that where R^6 and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where R^{1a} is aryl or heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(af), Formula I(ag), Formula I(ah), Formula I(ai), Formula I(aj), or Formula I(ak) is that where at least one R^7 is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000116] In some or any embodiments, the compound of Formula I is according to Formula I(al), Formula I(am), Formula I(an), or Formula I(ao):



where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(am) or Formula I(ao) is that where X^1 is alkylene or alkenylene; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where R^5 is OH; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered

heterocycloalkyl ring which is optionally substituted with 1, 2, or 3 R⁸; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al) or Formula I(am) is that where R⁶ and R^{6a} are halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where R^{1a} is aryl or heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where at least one R⁷ is halo; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In another embodiment, the compound of Formula I(al), Formula I(am), Formula I(an), or Formula I(ao) is that where at least one R¹² is CH₃; and all other groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000117] In some or any embodiments, the compound is that of any one of Examples 1-74.

[000118] In some or any embodiments, the compound is that of any one of Examples 77-383.

[000119] In some or any embodiments, the compound is that of any one of Examples 384-478.

[000120] In some or any embodiments, the compound is selected from Table 1.

[000121] In some or any embodiments, the compound is selected from Table 2.

[000122] In some or any embodiments, the compound is selected from Table 3.

[000123] In some or any embodiments, the compound is selected from Table 1, where R^{1a} is aryl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000124] In some or any embodiments, the compound is selected from Table 1, where R^{1a} is heterocycloalkyl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000125] In some or any embodiments, the compound is selected from Table 1, where R^{1a} is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000126] In some or any embodiments, the compound is selected from Table 1, where R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000127] In some or any embodiments, the compound is selected from Table 1, where R² and R³ together with the nitrogen to which they are attached form a 7-8 membered bicyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000128] In some or any embodiments, the compound is selected from Table 1, where R⁴ is aryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000129] In some or any embodiments, the compound is selected from Table 1, where R⁴ is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000130] In some or any embodiments, the compound is selected from Table 1, where R⁵ is -OH.

[000131] In some or any embodiments, the compound is selected from Table 1, where R⁶ and R^{6a} together with the carbon to which they are attached form C(O).

[000132] In some or any embodiments, the compound is selected from Table 2, where R^{1a} is heterocycloalkyl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000133] In some or any embodiments, the compound is selected from Table 2, where R^{1a} is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000134] In some or any embodiments, the compound is selected from Table 2, where R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000135] In some or any embodiments, the compound is selected from Table 2, where R² and R³ together with the nitrogen to which they are attached form a 7-8 membered bicyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000136] In some or any embodiments, the compound is selected from Table 2, where R⁴ is aryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000137] In some or any embodiments, the compound is selected from Table 2, where R⁴ is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000138] In some or any embodiments, the compound is selected from Table 2, where R⁵ is -OH.

[000139] In some or any embodiments, the compound is selected from Table 2, where R⁶ and R^{6a} together with the carbon to which they are attached form C(O).

[000140] In some or any embodiments, the compound is selected from Table 3, where R^{1a} is heterocycloalkyl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000141] In some or any embodiments, the compound is selected from Table 3, where R^{1a} is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁷ groups.

[000142] In some or any embodiments, the compound is selected from Table 3, where R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000143] In some or any embodiments, the compound is selected from Table 3, where R² and R³ together with the nitrogen to which they are attached form a 7-8 membered bicyclic heterocycloalkyl ring, which is optionally substituted with 1 or 2 R⁸.

[000144] In some or any embodiments, the compound is selected from Table 3, where R⁴ is aryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000145] In some or any embodiments, the compound is selected from Table 3, where R⁴ is heteroaryl, which is optionally substituted with 1, 2, or 3 R⁹ groups.

[000146] In some or any embodiments, the compound is selected from Table 3, where R⁵ is -OH.

[000147] In some or any embodiments, the compound is selected from Table 3, where R⁶ and R^{6a} together with the carbon to which they are attached form C(O).

[000148] In some or any embodiments, provided is a pharmaceutical composition comprising 1) a Compound of Formula 1, 1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(j), I(k), I(m), I(n), I(p), I(q), I(r), I(s), I(t), I(u), I(v), I(v'), I(v''), I(w), I(w'), I(w''), I(x), I(x'), I(x''), I(y), I(y'), I(y''), I(z), I(z'), I(z''), I(aa), I(ab), I(ac), I(ad), I(ae), I(af), I(ag), I(ah), I(ai), I(aj), I(ak), I(al), I(am), I(an), or I(ao) or a compound in Table 1, 2, or 3, optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

Pharmaceutical Composition/Formulation

[000149] In some or any embodiments, optionally in combination with any or all of the above various embodiments, provided herein is a pharmaceutical composition comprising of a compound of Formula 1, 1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(j), I(k), I(m), I(n), I(p), I(q), I(r), I(s), I(t), I(u), I(v), I(v'), I(v''), I(w), I(w'), I(w''), I(x), I(x'), I(x''), I(y), I(y'), I(y''), I(z), I(z'), I(z''), I(aa), I(ab), I(ac), I(ad), I(ae), I(af), I(ag), I(ah), I(ai), I(aj), I(ak), I(al), I(am), I(an), or I(ao), or a compound of Table 1, 2, or 3, or stereoisomers, or a pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carrier(s), excipient(s), binder(s) or diluent(s). The pharmaceutical compositions can, moreover, contain

preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants.

[000150] In some or any embodiments, disclosed herein is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate of any of the compounds disclosed herein. In some embodiments, the pharmaceutical compositions further comprises a pharmaceutically acceptable diluent, excipient or binder.

[000151] In some or any embodiments, pharmaceutical compositions are formulated in any manner, including using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries which facilitate processing of the active compounds into pharmaceutical preparations. In some embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any techniques, carriers, and excipients are used as suitable.

[000152] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In some or any embodiments, a pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, includes administering or using a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. In specific embodiments, the methods of treatment provided for herein include administering such a pharmaceutical composition to a mammal having a disease or condition to be treated. In one embodiment, the mammal is a human. In some embodiments, the therapeutically effective amount varies widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In various embodiments, the compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[000153] In a some or any embodiment, it is provided a method of forming a composition, comprising providing a compound and forming the composition. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments of the composition, optionally in combination with any or all of the above various embodiments, the composition is formulated in a formulation for local or systemic delivery. Examples of such formulations are formulations for oral administration, injection,

topical administration, pulmonary administration, or implant. In some or any embodiments, the compound is according to any of the various embodiments described above or below.

[000154] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for intravenous injections. In certain aspects, the intravenous injection formulations provided herein are formulated as aqueous solutions, and, in some embodiments, in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, the pharmaceutical compositions provided herein are formulated for transmucosal administration. In some aspects, transmucosal formulations include penetrants appropriate to the barrier to be permeated. In certain embodiments, the pharmaceutical compositions provided herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, and in one embodiment, with physiologically compatible buffers or excipients.

[000155] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for oral administration. In certain aspects, the oral formulations provided herein comprise compounds described herein that are formulated with pharmaceutically acceptable carriers or excipients. Such carriers enable the compounds described herein to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[000156] In some or any embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. 1(f) desired, disintegrating agents are optionally added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[000157] In some or any embodiments, provided herein is a pharmaceutical composition formulated as dragee cores with suitable coatings. In some or any embodiments, concentrated sugar solutions are used in forming the suitable coating, and optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide,

lacquer solutions, and suitable organic solvents or solvent mixtures. In some embodiments, dyestuffs and/or pigments are added to tablets, dragees and/or the coatings thereof for, e.g., identification or to characterize different combinations of active compound doses.

[000158] In some or any embodiments, pharmaceutical preparations which are used include orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In some embodiments, the push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some or any embodiments, in soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers are optionally added. In some or any embodiments, the formulations for oral administration are in dosages suitable for such administration.

[000159] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for buccal or sublingual administration. In some or any embodiments, buccal or sublingual compositions take the form of tablets, lozenges, or gels formulated in a conventional manner. In some or any embodiments, parenteral injections involve bolus injection or continuous infusion. In some embodiments, formulations for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. In some embodiments, the pharmaceutical composition described herein is in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and optionally contains formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In some embodiments, suspensions of the active compounds are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In some or any embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspensions also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. In alternative embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[000160] In some embodiments, the compounds described herein are administered topically. In specific embodiments, the compounds described herein are formulated into a

variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives.

[000161] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for transdermal administration of compounds described herein. In some embodiments, administration of such compositions employs transdermal delivery devices and transdermal delivery patches. In some or any embodiments, the compositions are lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches include those constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In some embodiments, transdermal delivery of the compounds described herein is accomplished by use of iontophoretic patches and the like. In some or any embodiments, transdermal patches provide controlled delivery of the compounds provided herein, such as, for example, compounds of Formula (I). In some or any embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers are optionally used to increase absorption. Absorption enhancer and carrier include absorbable pharmaceutically acceptable solvents that assist in passage of the compound through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[000162] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for administration by inhalation. In some or any embodiments, in such pharmaceutical compositions formulated for inhalation, the compounds described herein are in a form as an aerosol, a mist or a powder. In some embodiments, pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain aspects of a pressurized aerosol, the dosage unit is determined by providing a valve to deliver a metered amount. In some or any embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator is

formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

[000163] In some embodiments, the compounds described herein are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas. In some or any embodiments, rectal compositions optionally contain conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In some or any suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[000164] In various embodiments provided herein, the pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into pharmaceutically acceptable preparations. In some or any embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any of the techniques, carriers, and excipients is used as suitable. In some embodiments, pharmaceutical compositions comprising a compound described herein are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[000165] In some or any embodiments, the pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound described herein described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds described herein exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, included herein are the solvated and unsolvated forms of the compounds described herein. Solvated compounds include those that are solvated with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In some embodiments, the pharmaceutical compositions described herein include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In additional embodiments, the

pharmaceutical compositions described herein also contain other therapeutically valuable substances.

[000166] Methods for the preparation of compositions containing the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. In various embodiments, the compositions are in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[000167] In some embodiments, a composition comprising a compound described herein takes the form of a liquid where the agents are present in solution, in suspension or both. In some embodiments, when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[000168] Useful aqueous suspension optionally contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Useful compositions optionally comprise an mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[000169] Useful compositions optionally include solubilizing agents to aid in the solubility of a compound described herein. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Solubilizing agents include certain acceptable nonionic surfactants, for example polysorbate 80, and ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[000170] Useful compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[000171] Useful compositions optionally include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[000172] Certain useful compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[000173] Some useful compositions optionally include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

[000174] Certain useful compositions optionally one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[000175] In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[000176] In various embodiments, any delivery system for hydrophobic pharmaceutical compounds is employed. Liposomes and emulsions are examples of delivery vehicles or carriers for hydrophobic drugs. In some or any embodiments, certain organic solvents such as *N*-methylpyrrolidone are employed. In some embodiments, the compounds are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are utilized in

the embodiments herein. In some or any embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. In some embodiments, depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[000177] In some or any embodiments, the formulations or compositions described herein benefit from and/or optionally comprise antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

Methods of Dosing and Treatment Regimens

[000178] In some or any embodiments, the method can be conducted in living bodies of mammals. In such a case, the compounds may be administered to the mammals.

[000179] In some or any embodiments, the compounds described herein are used in the preparation or manufacture of medicaments for the treatment of diseases or conditions that are mediated by the enzyme GCS or in which inhibition of the enzyme GCS ameliorates the disease or condition. In some embodiments, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[000180] In some or any embodiments, provided is a method of treating or ameliorating a medical condition, comprising administering to a subject in need thereof a compound according to any of the various embodiments described herein or a pharmaceutical composition according to any of the various embodiments described herein.

[000181] In some or any embodiments, provided herein is a method of treating or ameliorating a disease ameliorated by the inhibition of GCS comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of Formula I, 1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(j), I(k), I(m), I(n), I(p), I(q), I(r), I(s), I(t), I(u), I(v),

I(v'), I(v''), I(w), I(w'), I(w''), I(x), I(x'), I(x''), I(y), I(y'), I(y''), I(z), I(z'), I(z''), I(aa), I(ab), I(ac), I(ad), I(ae), I(af), I(ag), I(ah), I(ai), I(aj), I(ak), I(al), I(am), I(an), or I(ao), or a compound in Table 1, 2, or 3, optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof. In some or any embodiments, the disease is selected from glycolipid storage diseases (e.g., Tay Sachs, Sandhoffs, GM1 gangliosidosis and Fabry diseases); diseases associated with glycolipid accumulation (e.g., Gaucher disease); diseases that cause renal hypertrophy or hyperplasia such as diabetic nephropathy; diseases that cause hyperglycemia or hyperinsulemia; cancers in which glycolipid synthesis is abnormal; infectious diseases caused by organisms which use cell surface glycolipids as receptors or in which synthesis of glucosylceramide is essential or important; a metabolic disorder such as atherosclerosis, polycystic kidney disease, renal hypertrophy, diabetes mellitus, and obesity; cancer such as breast cancer, renal adenocarcinoma, brain cancer, neuroblastoma, lung cancer, intestinal cancer, pancreas and prostate cancer; neuronal disorders; neuronal injury; inflammatory diseases or disorders (e.g., rheumatoid arthritis, Crohn's disease, asthma and sepsis), and diabetes mellitus and obesity

[000182] In any of the aforementioned embodiments are further embodiments that include single administrations of the effective amount of the compound, including further embodiments in which the compound is administered to the subject (i) once; (ii) multiple times over the span of one day; (iii) continually; or (iv) continuously.

[000183] In any of the aforementioned embodiments are further embodiments in which administration is enteral, parenteral, or both, and wherein:

- (a) the effective amount of the compound is systemically administered to the subject;
 - (b) the effective amount of the compound is administered orally to the subject;
 - (c) the effective amount of the compound is intravenously administered to the subject;
 - (d) the effective amount of the compound administered by inhalation;
 - (e) the effective amount of the compound is administered by nasal administration;
 - (f) the effective amount of the compound is administered by injection to the subject;
 - (g) the effective amount of the compound is administered topically (dermal) to the subject;
 - (h) the effective amount of the compound is administered by ophthalmic administration;
- and/or
- (i) the effective amount of the compound is administered rectally to the subject.

[000184] In some or any embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In some or any therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. In some embodiments, amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. In certain instances, it is considered appropriate for the caregiver to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[000185] In some or any prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. In some embodiments, the amount administered is defined to be a "prophylactically effective amount or dose." In some or any embodiments of this use, the precise amounts of compound administered depend on the patient's state of health, weight, and the like. In some embodiments, it is considered appropriate for the caregiver to determine such prophylactically effective amounts by routine experimentation (*e.g.*, a dose escalation clinical trial). In some or any embodiments, when used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[000186] In some or any embodiments are further embodiments that include multiple administrations of the effective amount of the compound, including further embodiments wherein:

- (i) the compound is administered in a single dose;
- (ii) the time between multiple administrations is every 6 hours;
- (iii) the compound is administered to the subject every 8 hours.

[000187] In further or alternative embodiments, the method includes a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In some embodiments, the length of the drug holiday varies from 2 days to 1 year.

[000188] In certain instances, a patient's condition does not improve or does not significantly improve following administration of a compound or composition described

herein and, upon the doctor's discretion the administration of the compounds is optionally administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[000189] In certain cases wherein the patient's status does improve or does not substantially improve, upon the doctor's discretion the administration of the compounds are optionally given continuously; alternatively, the dose of drug being administered is optionally temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In some or any embodiments, the length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes a reduction from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[000190] In some or any embodiments, once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. In some embodiments, the dosage, *e.g.*, of the maintenance dose, or the frequency of administration, or both, are reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In some or any embodiments, however, patients are optionally given intermittent treatment on a long-term basis upon any recurrence of symptoms.

[000191] In some or any embodiments, the amount of a given agent that corresponds to an effective amount varies depending upon factors such as the particular compound, disease or condition and its severity, the identity (*e.g.*, weight) of the subject or host in need of treatment. In some embodiments, the effective amount is, nevertheless, determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent that is administered, the route of administration, the condition being treated, and the subject or host being treated. In some or any embodiments, however, doses employed for adult human treatment is in the range of about 0.02 to about 5000 mg per day, in a specific embodiment about 1 to about 1500 mg per day. In various embodiments, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[000192] In some or any embodiments, the pharmaceutical compositions described herein are in a unit dosage form suitable for single administration of precise dosages. In some instances, in unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. In some or any embodiments, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are, in some embodiments, presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[000193] In some or any embodiments, the daily dosages appropriate for the compounds described herein are from about 0.01 to about 2.5 mg/kg per body weight. In some embodiments, an indicated daily dosage in the larger subject, including, but not limited to, humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day or in extended release form. In some or any embodiments, suitable unit dosage forms for oral administration comprise from about 1 to about 50 mg active ingredient. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. In some or any embodiments, the dosages are altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[000194] In some or any embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. In some or any embodiments, compounds exhibiting high therapeutic indices are preferred. In some embodiments, the data obtained from cell culture assays and animal studies is used in formulating a range of dosage for use in human. In specific embodiments, the dosage of such

compounds lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In some or any embodiments, the dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

Kits/Articles of Manufacture

[000195] Articles of manufacture, comprising packaging material, a compound provided herein that is effective for modulating the activity of the enzyme GCS, or for treatment, prevention or amelioration of one or more symptoms of a GCS-mediated disease or condition, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for modulating the activity of GCS, or for treatment, prevention or amelioration of one or more symptoms of GCS-mediated disease or condition, are provided.

[000196] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. In various embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In some embodiments, the containers are formed from a variety of materials such as glass or plastic.

[000197] In some embodiments, the articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[000198] In some embodiments, the container(s) described herein comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example in some embodiments the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[000199] In some embodiments, a kit will comprises one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form,

and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but are not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions is optionally included.

[000200] In some or any embodiments, a label is on or associated with the container. In some embodiments, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In some or any embodiments, a label indicates that the contents are to be used for a specific therapeutic application. In some embodiments, the label indicates directions for use of the contents, such as in the methods described herein.

[000201] In some or any embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. In some embodiments, the pack contains a metal or plastic foil, such as a blister pack. The pack or dispenser device is optionally accompanied by instructions for administration. In some embodiments, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In some or any embodiments, such notice is, for example, the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein are formulated in a compatible pharmaceutical carrier and are placed in an appropriate container labeled for treatment of an indicated condition.

[000202] Any combination of the groups described above for the various variables is contemplated herein.

PREPARATION OF COMPOUNDS

[000203] The following are illustrative examples of how the compounds can be prepared and tested. Although the examples can represent only some embodiments, it should be understood that the following examples are illustrative and not limiting.

[000204] In a further aspect, it is provided a method of making a compound, comprising synthesizing a compound as any of the various embodiments described above or below.

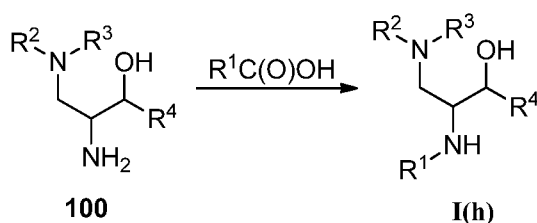
Examples of the method are further described in the Examples.

[000205] Compounds disclosed herein are commercially available or can be readily prepared from commercially available starting materials according to established methodology in the art of organic synthesis. General methods of synthesizing the compound can be found in, e.g., Stuart Warren and Paul Wyatt, Workbook for Organic Synthesis: The Disconnection Approach, second Edition, Wiley, 2010. Synthesis of some of the compounds are exemplified in detail below.

[000206] In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[000207] Materials were obtained from commercial suppliers and were used without further purification. Air or moisture sensitive reactions were conducted under argon atmosphere using oven-dried glassware and standard syringe/septa techniques. ¹H NMR spectra were measured at 400 MHz unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz).

General Scheme 1

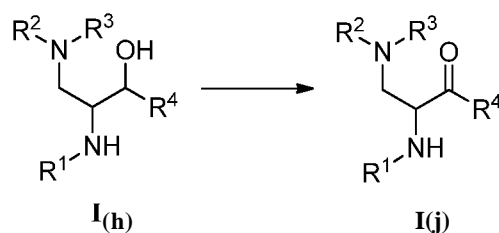


[000208] A Compound of Formula 1(h) (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 1.

[000209] A Compound of Formula 1(h) can be prepared using standard amide coupling conditions. More specifically, an intermediate of formula 100, which can be prepared using procedures disclosed herein or are known to one of ordinary skill in the art, is treated with in

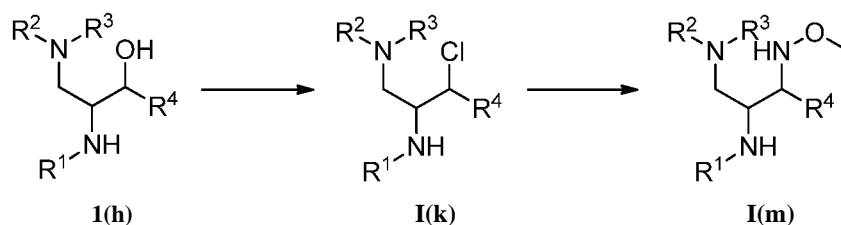
a solvent such as DMF, DCM or THF, optionally in the presence of a base such as DIPEA or TEA, and in the presence of a coupling agent such as EDCI and/or HOBt to yield a compound of Formula **1(h)**. The mixture can optionally be purified using procedures known to one of ordinary skill in the art. Alternatively, the intermediate of formula $R^1C(O)OH$ can be treated with a chlorinating agent such as oxalyl chloride in a solvent such as DMF followed by treatment with the intermediate of formula **100** to yield a compound of Formula **1(h)**. The mixture can optionally be purified using procedures known to one of ordinary skill in the art.

General Scheme 2



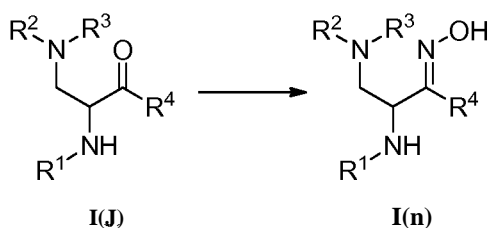
[000210] A Compound of Formula **I(j)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 2. A Compound of Formula **1(h)** is treated with a base such as NMP, in the presence of $NHCO_3$, and in a solvent such as DCM to yield a Compound of Formula **I(j)**.

General Scheme 3



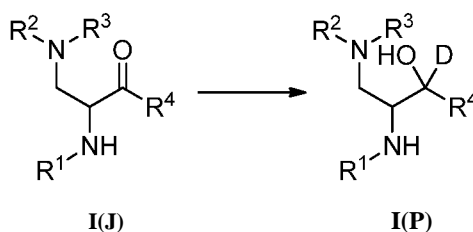
[000211] A Compound of Formula **I(k)** or **I(m)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 3. A Compound of Formula **1(h)** is treated with a chlorinating agent such as $SOCl_2$ in a solvent such as DCM to yield a Compound of Formula **I(k)**. A Compound of Formula **I(m)** is prepared by treating a Compound of Formula **I(k)** with NH_2OCH_3 in a solvent such as MeOH.

General Scheme 4



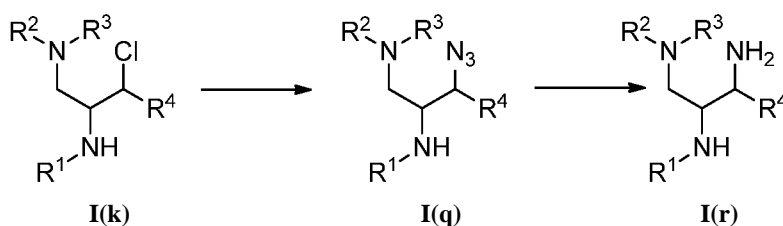
[000212] A Compound of Formula I(n) (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 4. A Compound of Formula I(j) is treated with hydroxylamine in a solvent such as MeOH to yield a Compound of Formula I(n).

General Scheme 5



[000213] A Compound of Formula I(p) (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 5. A Compound of Formula I(j) is treated with NaBD₄ in a deuterated solvent such as CD₃OD to yield a Compound of Formula I(p).

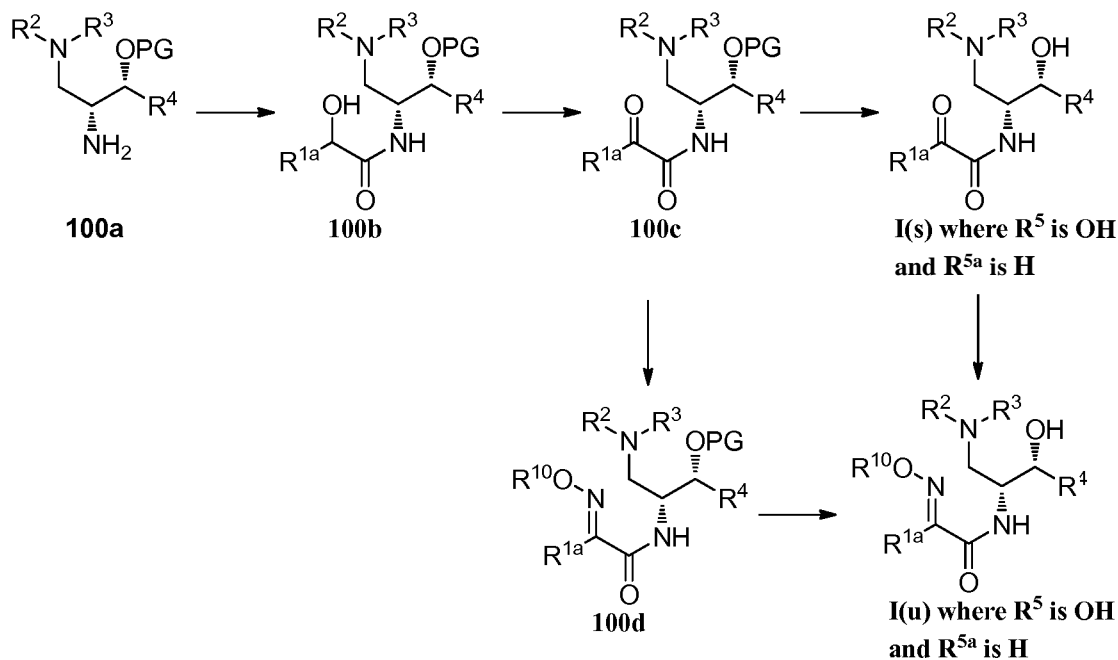
General Scheme 6



[000214] A Compound of Formula I(q) or I(r) (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 6. A Compound of Formula I(k) is treated with NaN₃ in a solvent such as DMF and heated to about 50 °C to yield a Compound of Formula I(q) which can be optionally worked up before proceeding to the next step. The Compound of Formula I(q) is then treated with PPh₃ in a solvent such as THF to yield the Compound of Formula I(r).

[000215] In some or any embodiments of General Schemes 1-6, intermediate of formula **100** or the Compound of Formula **1(h)**, **1(j)**, or **1(k)** is that where **R²** and **R³** together with the nitrogen to which they are attached form a 3-10-membered ring which is optionally substituted with 1, 2, or 3 **R⁸** groups.

General Scheme 7



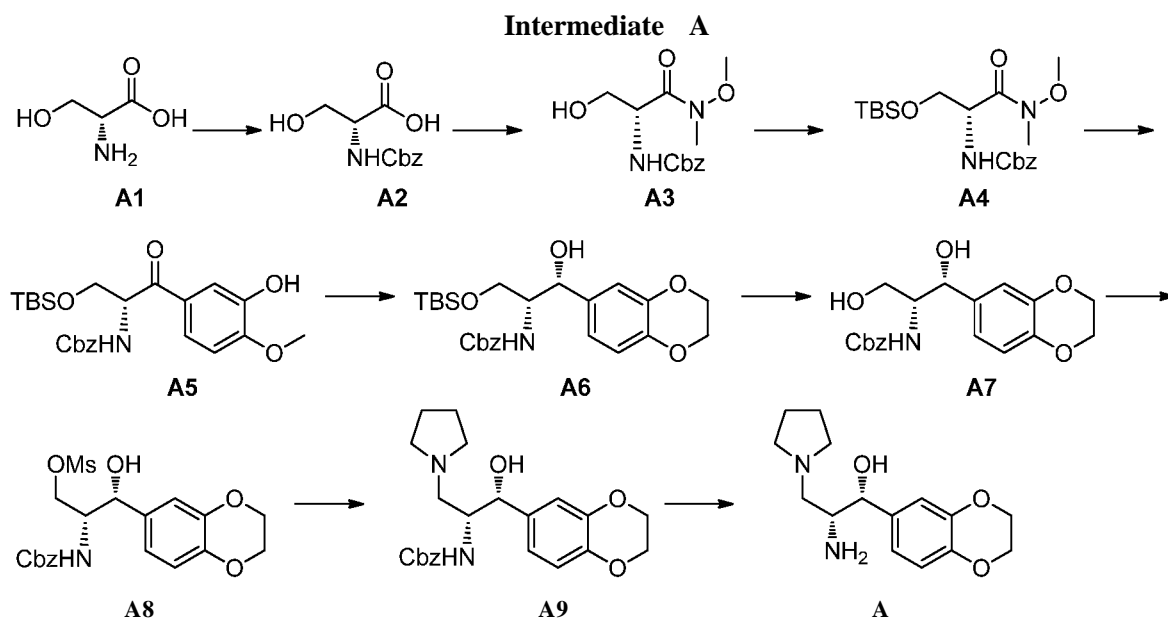
[000216] A Compound of Formula **I(s)** (where **R⁵** is hydroxy and **R^{5a}** is hydrogen and all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 7.

[000217] An intermediate of formula **100b** can be prepared using standard amide coupling conditions. More specifically, an intermediate of formula **100a**, which can be prepared using procedures disclosed herein or are known to one of ordinary skill in the art, is treated with in a solvent such as DMF, DCM or THF, optionally in the presence of a base such as DIPEA or TEA, and in the presence of a coupling agent such as EDCI and/or HOBt to yield an intermediate of formula **100c** (e.g., a compound of Formula **I(s)** where **R⁵** is -OTBS and **R^{5a}** is hydrogen). The protecting group in intermediate of formula **100c** is then removed in the presence of TBAF in a solvent such as THF. The mixture can optionally be purified using procedures known to one of ordinary skill in the art. Alternatively, a Compound of Formula **I(s)** (where **R⁵** is hydroxy and **R^{5a}** is hydrogen and all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) can be prepared by treating an intermediate of formula

100a with $R^{1a}C(0)C(0)OH$ using standard amide coupling procedures described herein or known to one of ordinary skill in the art. The mixture can optionally be purified using procedures known to one of ordinary skill in the art.

[000218] A Compound of Formula **I(u)** (where R^5 is hydroxy and R^{5a} is hydrogen and all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 7. The intermediate of formula **100c** is treated with an intermediate of formula $R^{1a}ONH_2$ in the presence of sodium acetate in a solvent such as ethanol or methanol to yield an intermediate of formula **100d** (e.g., a compound of Formula **I(u)** where R^5 is -OTBS and R^{5a} is hydrogen and all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein). The intermediate of formula **100d** is treated with TBAF in a solvent such as THF to yield a Compound of Formula **I(u)**. The mixture can optionally be purified using procedures known to one of ordinary skill in the art. Alternatively, the Compound of Formula **I(s)** (where R^5 is hydroxy and R^{5a} is hydrogen and all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) is treated with an intermediate of formula $R^{1a}ONH_2$ in a solvent such as ethanol or methanol to yield a Compound of Formula **I(u)**. The mixture can optionally be purified using procedures known to one of ordinary skill in the art.

SYNTHETIC EXAMPLES



[000219] Benzyl chloroformate (50 mL, 50 w.t.% solution in toluene, 148 mmol) was added to a solution of (i)-2-amino-3-hydroxypropanoic acid (**A1**) (10.5 g, 100 mmol) in sat.

aq NaHCO₃ solution (400 mL). The mixture was stirred vigorously for 4 h at 20 °C, and the aqueous solution was extracted with ether (400 mL x 2). The aqueous phase was acidified with cone. hydrochloric acid to pH = 2 and extracted with ethyl acetate (300 mL x 3). The combined organic phase was dried with Na₂SO₄ and concentrated to afford crude product Compound **A2** (20 g, yield 84%) as a white solid. LC-MS (m/z): 240 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) peaks: δ (ppm) 3.653 (m, 2H), 4.051 (m, 1H), 4.884 (m, 1H), 5.038 (s, 2H), 7.303-7.373 (m, 6H), 12.658 (s, 1H).

[000220] To a mixture of EDCI·HCl (2.4g, 12.5 mmol), HOBt (1.7 g, 12.5 mmol), DIPEA (2.7 g, 20 mmol) in DCM (50 mL) was added Compound **A2** (1 g, 4 mmol) and *N,N*-dimethylhydroxylamine hydrochloride (1.2 g, 12.5 mmol). The mixture was stirred at rt overnight. The mixture was washed with hydrochloric acid solution (1 M, 50 mL x 2), saturated aqueous NaHCO₃ (20 mL), brine (20 mL), and dried over Na₂SO₄. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum, 30% v/v) to give Compound **A3** (826 mg, yield 70%>) as a colorless liquid. LC-MS (m/z): 283 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 3.113 (s, 3H), 3.673 (s, 3H), 3.743 (t, *J* = 4.8 Hz, 2H), 4.766 (m, 1H), 4.959-5.044 (m, 2H), 6.046 (d, *J* = 8.0 Hz, 1H), 7.200-7.254 (m 5H).

[000221] TBDMS-Cl (800 mg, 5.31 mmol) in THF (10 mL) was added dropwise to a solution of Compound **A3** (500 mg, 1.77 mmol) and imidazole (602 mg, 8.86 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at rt for 2 h, and then filtered. The filtrate was washed with 1N HCl (50 mL x 2) and brine (50 mL), and dried over Na₂SO₄. The crude product was purified with silica gel column chromatography (ethyl acetate in petroleum, 13% v/v) to give Compound **A4** (526 mg, yield 75%>) as a colorless liquid. LC-MS (m/z): 396 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 0.012 (s, 3H), 0.085 (s, 6H), 0.852 (s, 9H), 3.211 (s, 3H), 3.756 (s, 3H), 3.794-3.896 (m, 2H), 4.809 (m, 1H), 5.085 (q, *J* = 11.2 Hz, 2H), 5.662 (d, *J* = 8.8 Hz, 1H), 7.286-7.351 (m 5H).

[000222] To a solution of 6-bromo-2,3-dihydrobenzo[*f*][1,4]dioxine (4.9 g, 23 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M, 15 mL) at -60 °C under N₂ and stirred for 0.5 h, before a solution of Compound **A4** (3 g, 7.6 mmol) in THF (50 mL) was added slowly. The mixture was stirred at -60 °C for 1 h, and followed by addition of a saturated NH₄Cl solution. The mixture was extracted with ethyl acetate (100 mL x 2), brine (100 mL), and then dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10%> v/v) to give Compound **A5** (3 g, yield 84%>) as a colorless liquid.

LC-MS (m/z): 472 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 0.000 (s, 3H), 0.024(s, 3H), 0.892 (s, 9H), 4.024-4.116 (m, 1H), 4.402-4.465 (m, 4H), 5.262(s, 2H), 5.421 (m, 1H), 6.066 (d, *J* = 8.0 Hz, 1H), 7.043 (d, *J* = 8.0 Hz, 1H), 7.444-7.505 (m, 5H), 7.618-7.639 (m, 2H).

[000223] Compound **A5** (2 g, 4.2 mmol) was dissolved in THF (30 mL) and the solution was cooled down to -70 °C under nitrogen atmosphere. L-Selectride (8.5 mL, 1M solution in THF, 8.5 mmol) was added dropwise while keeping the temperature at -70 °C. After an hour, the reaction was quenched with saturated NH₄Cl solution and extracted with ethyl acetate (50 mL x 2). The extract was dried over Na₂SO₄ to yield a crude product which was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to afford Compound **A6** (1.4 g, yield 70%) as a colorless oil. LC-MS (m/z): 474 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 0.08 (m, 6H), 0.85(s, 9H), 3.71 (m, 1H), 3.77 (m, 2H), 4.18 (s, 4H), 4.88 (m, 1H), 4.50 (m, 2H), 5.36 (d, *J* = 7.6 Hz, 1H), 6.76 (s, 2H), 6.83 (s, 1H), 7.28 (m, 5H).

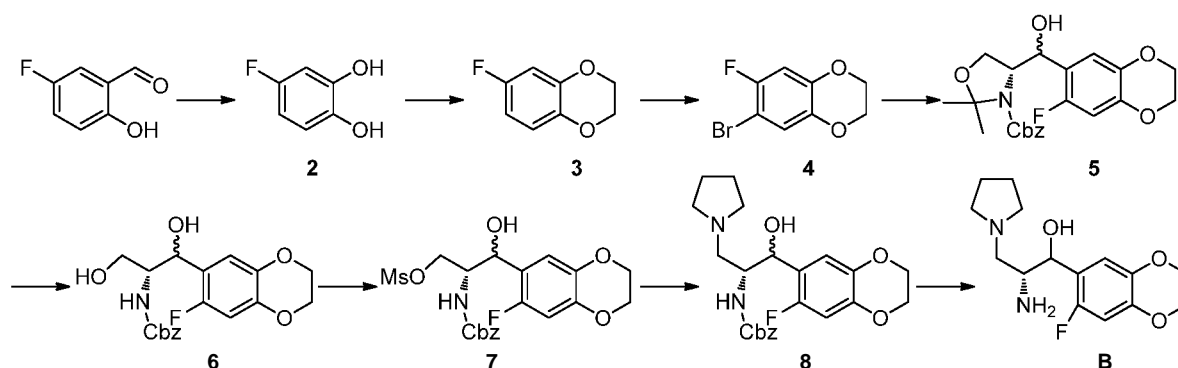
[000224] To a solution of Compound **A6** (1.4 g, 3 mmol) in THF (50 mL) was added a solution of TBAF (155 mg, 0.6 mmol) in THF (5 mL) at 0 °C, then the mixture was stirred at rt overnight. After removal of solvent by evaporation, water (50 mL) was added to the mixture which was then extracted with ethyl acetate (2 x 50 mL), washed with brine (1 x 100 mL), and dried over Na₂SO₄ to obtain Compound **A7** (1 g, crude). LC-MS (m/z): 342 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 3.620-3.737 (m, 3H), 3.772-3.814 (m, 1H), 4.014 (s, 1H), 4.224 (s, 4H), 4.867 (m, 1H), 5.024 (s, 2H), 5.607 (d, *J* = 8.8 Hz, 1H), 6.809 (s, 2H), 6.888 (s, 1H), 7.24 (m, 5H).

[000225] To a solution of Compound **A7** (3.6 g, 10 mmol) in THF (50 mL) was added Et₃N (3 g, 30 mmol), and then the mixture was cooled to -15 °C before adding MsCl (0.8 mL) slowly. The mixture was stirred at -15 °C about half an hour. The reaction mixture was taken up with water (30 mL), extracted with ethyl acetate (30 mL x 3), dried over anhydrous sodium sulfate, and evaporated to get Compound **A8**. To a solution of the resulting mesylate intermediate (**A8**) in THF (50 mL) was added pyrrolidine (5.7 g, 80 mmol), K₂CO₃ (11 g, 80 mmol) and NaI (3 g). The mixture was heated at 50 °C overnight. After filtration and evaporation, the crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **A9** (2.5 g, yield 61%) as a colorless oil. LC-MS (m/z): 413 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 1.756 (m, 4H), 2.534 (m, 1H), 2.660 (m, 4H), 2.877 (m, 1H), 4.019 (m, 1H), 4.236 (s, 4H), 4.924

(d, $J = 2.8$ Hz, 1H), 5.043 (s, 2H), 5.079 (m, 1H), 6.7756-6.892 (m, 3H), 7.266-7.361 (m, 5H).

[000226] To a solution of Compound **A9** (2.5 g, 6.1 mmol) in methanol (20 mL) was added $\text{Pd}(\text{OH})_2$ (250 mg), and then the mixture was stirred at rt under H_2 overnight. The mixture was filtered and the filtrate was evaporated to dryness to give Intermediate **A** (1.7 g). LC-MS (m/z): 279 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) peaks: δ (ppm) 1.70 (m, 4H), 2.53 (m, 6H), 3.05 (m, 1H), 4.18(s, 4H), 4.47 (d, $J = 3.6$ Hz, 1H), 6.75 (m, 3H).

Intermediate B



[000227] To a solution of 5-fluoro-2-hydroxybenzaldehyde (14.0 g, 0.1 mol) in THF (150 mL) was added dropwise sat. aq. NaOH solution (0.05 N, 300 mL, 15 mmol) at 0 °C, followed by 30% H_2O_2 solution (40 mL). After stirred for 2 h at rt, the second portion of 30% H_2O_2 (40 mL) was added dropwise and stirred for additional 4 h. The reaction mixture was cooled to 0 °C and pH was adjusted to 10-11 using aq. NaOH solution (2 N, 60 mL). The mixture was stirred for 0.5 h before it was quenched with cone. HCl at 0 °C to pH 2~3. The mixture was extracted with DCM (150 mL x 3) and washed with brine (150 mL x 1), dried over sodium sulfate, and evaporated to dryness to yield Compound **B1** (12.8 g, yield 100%) as a yellow oil. $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 6.38-6.56 (m, 1H), 6.53-6.56 (m, 1H), 6.66-6.70 (m, 1H), 8.83 (s, 1H), 9.30 (s, 1H).

[000228] A mixture of Compound **B1** (12.8 g, 0.1 mol), Cs_2CO_3 (81.5 g, 0.25 mol) in DMF (200 mL) was first stirred for 0.5 h at 40 °C and then 1,2-dibromoethane (11.7 mL, 0.135 mol) was added and the mixture was stirred for 16 h at 80 °C. After it was cooled down to rt, the mixture was filtered and the cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (400 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with water (200 mL x 5) and brine (200 mL x 1), dried over sodium sulfate, concentrated, and purified by column chromatography on silica gel (ethyl acetate/PE = 1/20, v/v) to get Compound **B2** (4.3 g, yield 30%) as a yellow oil. $^1\text{H-NMR}$

NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.20-4.25 (m, 4H), 6.51-6.56 (m, 1H), 6.58-6.61 (m, 1H), 6.76-6.80 (m, 1H).

[000229] To a solution of Compound **B2** (4.1 g, 26.5 mmol) and NBS (7.1 g, 40 mmol) in ACN (30 mL) was added TFA (302 mg, 2.65 mmol) at rt and the mixture was kept at rt with stirring overnight. Upon removal of the solvents, the residue was purified by column chromatography on silica gel (ethyl acetate/PE = 1/25, v/v) to yield Compound **B3** (4.9 g, yield 79%) as a white solid. ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.21-4.26 (m, 4H), 6.67-6.69 (d, *J* = 9.2 Hz, 1H), 7.02-7.04 (d, *J* = 6.8 Hz, 1H).

[000230] To a solution of Compound **B3** (700 mg, 53.7 mmol) in THF (10 mL) was added n-BuLi (2.5M, 1.24 mL, 3.1 mmol) at -60 °C under N₂. After 30 min, a solution of (i?)-benzyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (263 mg, 1 mmol) in THF (3 mL). The mixture was stirred at -60 °C under N₂ for an additional 30 min, before it was quenched with saturated aqueous NH₄Cl solution (20 mL). The mixture was extracted with ethyl acetate (20 mL x 3), washed with brine (20 mL x 1), dried over anhydrous Na₂SO₄, and purified by column chromatography on silica (ethyl acetate in petroleum, 30% v/v) to yield Compound **B4** (120 mg, yield 29%) as a white foam. LCMS (m/z): 440 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.41-1.70 (m, 6H), 3.63-3.94 (m, 1.5H), 4.09 (m, 0.5H), 4.19 (m, 4H), 4.29-4.41 (m, 1H), 4.95-4.98 (m, 1H), 5.09-5.22 (m, 2H), 6.54 (m, 1H), 6.98 (m, 1H), 7.35 (m, 5H).

[000231] To a solution of Compound **B4** (2 g, 4.8 mmol) in THF (20 mL) was added 3 N HCl (8 mL) and stirred at 50 °C for 6 h. The mixture was diluted with water (50 mL), extracted with ethyl acetate (30 mL x 3), washed with brine (30 mL x 1), dried over anhydrous Na₂SO₄, and concentrated to obtain Compound **B5** (1.8 g, yield 100%) as a yellow oil. LCMS (m/z): 400 [M+23]⁺.

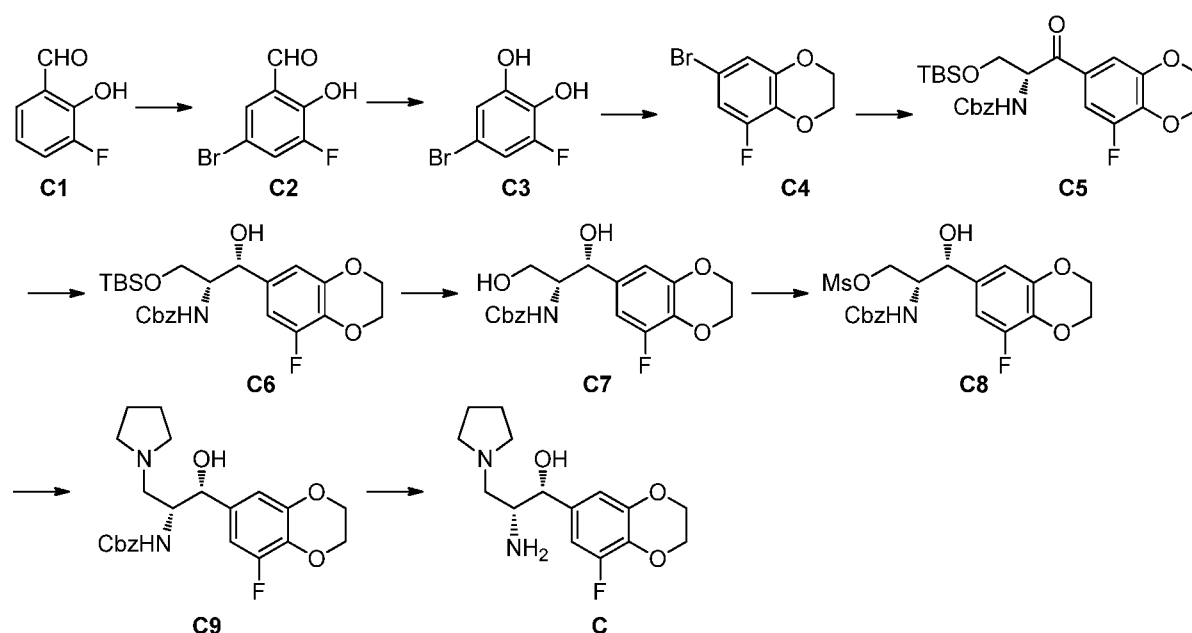
[000232] To a solution of Compound **B5** (1.8 g, 4.8 mmol) and Et₃N (1 mL, 7.2 mmol) in THF (40 mL) was added MsCl (1.44 mL) at -50 °C. Stirred at this temperature for 2 h under N₂, the reaction was quenched with sat. aqueous NaHCO₃ solution (50 mL). It was extracted with ethyl acetate (50 mL x 3), washed with brine (30 mL x 1), dried with anhydrous Na₂SO₄, purified with a silica gel column (MeOH in DCM, 3% v/v) to give Compound **B6** (1.2 g, yield 55%) as a colorless oil. LCMS (m/z): 478 [M+23]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.94-3.09 (m, 3H), 4.13-4.55 (m, 7H), 5.00-5.31 (m, 4H), 6.56-6.60 (m, 1H), 6.94-6.98 (m, 1H), 7.27-7.37 (m, 5H).

[000233] To a solution of Compound **B6** (1.2 g, 2.6 mmol) in THF (40 mL) was added pyrrolidine (2 mL, 23.7 mmol) and stirred at 50 °C overnight. After the mixture was cooled

down, the mixture was diluted with water (100 mL), extracted with ethyl acetate (50 mL x 3), washed with water (100 mL x 3), brine (100 mL x 1), dried over anhydrous Na_2SO_4 , and purified using silica gel column chromatography (MeOH in DCM, 4% v/v) to obtain Compound **B7** (0.4 g, 36%) as a white solid. LCMS (m/z): 431 [M+]⁺.

[000234] To a solution of Compound **B7** (400 mg, 0.93 mmol) in EtOH (20 mL) and water (2 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (120 mg, 2.79 mmol). The mixture was stirred at reflux for 4 h, followed by addition of water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3), washed with brine (50 mL x 1), dried over anhydrous Na_2SO_4 , and concentrated to give Intermediate B (300 mg, yield 100%) as a yellow solid. LCMS (m/z): 297 [M+]⁺.

Intermediate C



[000235] To a solution of Compound **C1** (50 g, 357 mmol) in ACN (400 mL) was added NBS (60.08 g, 360 mmol) and $\text{HC(O)O}^- \text{NH}_4^+$ (2.47 mg, 39 mmol) at rt and then the mixture was stirred at rt for 2 h. After removal of the solvent and diluted with ethyl acetate (200 mL), the mixture was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated to give Compound **C2** (78 g, yield 100%) as a yellow solid. ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 7.48-7.23 (m, 2H), 9.87 (s, 1H), 10.89 (s, 1H).

[000236] To a solution of Compound **C2** (40 g, 183 mmol) in THF (260 mL) was added dropwise aq. NaOH solution (0.05 N, 720 mL, 37 mmol) at 0 °C, and then 30% H_2O_2 solution (90 mL). The mixture was stirred for 2 h at rt and followed by the addition of a second portion of 30% H_2O_2 (90 mL). After stirred for 4 h, it was cooled to 0 °C and aq. NaOH solution (2 N, 112 mL) was added until pH10~11 was reached, and then the mixture was stirred for 0.5 h and quenched with cone. HCl at 0 °C to pH2~3. It was extracted with

dichloromethane (250 mL x 3) and washed with brine (300 mL x 2), dried over Na₂SO₄, and concentrated to give Compound **C3** (37 g, yield 98%) as a yellow oil. LC-MS (m/z): 205 [M+1].

[000237] To a mixture of Compound **C3** (30 g, 146 mol), K₂CO₃ (60.3 g, 437 mol) in DMF (450 mL) was added 1,2-dibromoethane (63 mL, 730 mol). The mixture was stirred at 80 °C for 4 h. After cooled to rt, it was filtered and the cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (900 mL) and extracted with ethyl acetate (400 mL x 3). The organic layer was washed with water (900 mL x 5) and brine (900 mL x 1), dried, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 5 % v/v) to afford Compound **C4** (20.4 g, yield 60%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.35 (s, 4H), 6.91 (t, *J* = 8 Hz, 2H), 7.33 (s, 1H).

[000238] To a solution of Compound **C4** (10.5 g, 45 mmol) in THF (300 mL) was added n-BuLi (2.4 M, 20 mL, 46.5 mmol) at - 60 °C under N₂ and it was stirred at under this condition for 0.5 h. It was added a solution of Compound **A4** (6 g, 15 mmol) in THF (10 mL). The mixture was stirred at - 60 °C under N₂ for 20 min, quenched with saturated aqueous NH₄Cl solution (200 mL), extracted with ethyl acetate (200 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na₂SO₄, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to obtain Compound **C5** (4.87 g, yield 66%) as a colorless oil. LC-MS (m/z): 490 [M+1]⁺.

[000239] To a solution of Compound **C5** (4 g, 8.1 mmol) in THF (50 mL) was added L-Selectride (16.3 mL) at - 60 °C under N₂. The mixture was stirred under the same condition for 1 h before quenched with saturated aqueous NH₄Cl solution (50 mL). It was extracted with ethyl acetate (50 mL x 3), washed with brine, dried over anhydrous Na₂SO₄, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 9% v/v) to yield Compound **C6** (4 g, yield 100%) as a colorless oil. LC-MS (m/z): 474 [M+1-18]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.77-3.83 (m, 2H), 4.28 (t, *J* = 8 Hz, 4H), 4.92-5.05 (m, 2H), 5.11 (m, 1H), 5.38-5.57 (m, 1H), 6.67-6.74 (m, 2H), 7.29-7.36 (m, 5H).

[000240] To a solution of Compound **C6** (4.15 g, 8.4 mmol) in THF (150 mL) was added TBAF (1.1g, 4.2 mmol) at 0 °C and it was stirred at rt overnight. The mixture was added water (100 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, and concentrated to give Compound **C7** (3.18 g, yield 100%) as a colorless oil. LC-MS (m/z): 360 [M+1-18]⁺; ¹H-NMR (CDCl₃, 400 MHz) major

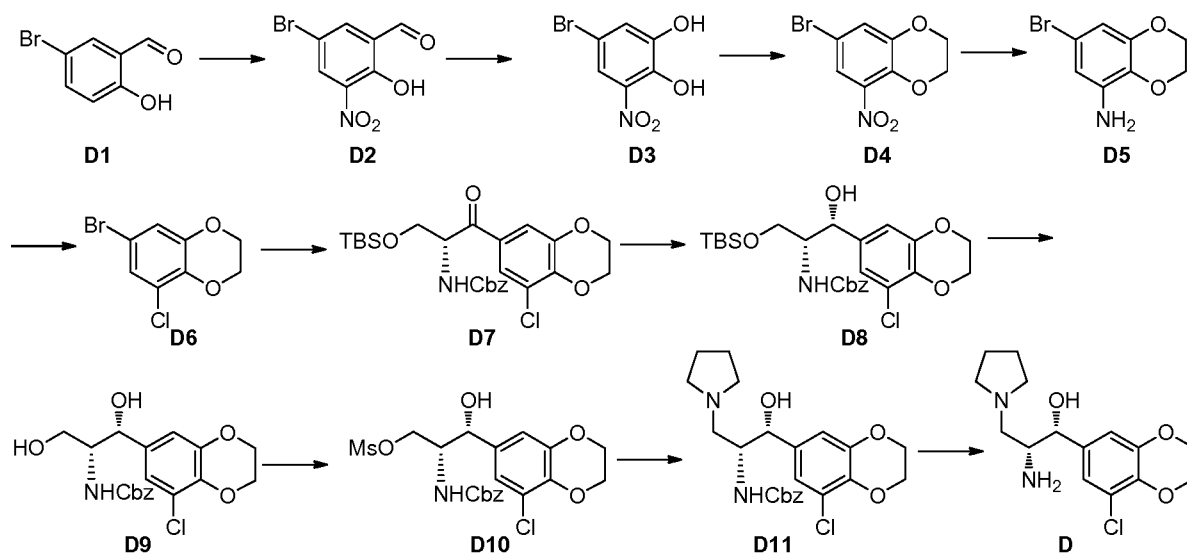
characteristic peaks: δ (ppm) 4.14-4.16 (m, 6H), 4.91 (s, 2H), 4.98 (s, 1H), 5.47 (d, $J = 8$ Hz, 2H), 6.55-6.63 (m, 2H), 7.17-7.26 (m, 5H).

[000241] To a solution of Compound **C7** (3.18 g, 8.4 mmol) and Et_3N (3.5 mL, 25.3 mmol) in THF (80 mL) was added MsCl (0.71 mL, 9.3 mmol) at -40 °C and the mixture was stirred at -40 °C for 4 h. It was added water (100 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 1), dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica gel (ethyl acetate in petroleum, 30% v/v) to give Compound **C8** (1.35 g, yield 35%) as a colorless oil. LC-MS (m/z): 438 [$\text{M}+1-18$]⁺.

[000242] To a solution of Compound **C8** (1 g, 3 mmol) in THF (20 mL) was added pyrrolidine (2.66 mL, 30 mmol). The mixture was stirred at 60 °C overnight. It was added water (20 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (30 mL x 1), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give Compound **C9** (900 mg, crude) as a yellow oil. LC-MS (m/z): 431 [$\text{M}+1$]⁺.

[000243] To a solution of Compound **C9** (900 mg, 2.1 mmol) in EtOH/water (20 mL, 9:1, v/v) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (264 mg, 6.3 mmol). The mixture was refluxed for 36 h and then diluted with water (20 mL). It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give Intermediate **C** (800 mg, crude) as a yellow oil. LC-MS (m/z): 297 [$\text{M}+1$]⁺.

Intermediate D



[000244] To a solution of Compound **D1** (80 g, 266 mmol) in $\text{CH}_3\text{CO}_2\text{H}$ (400 mL) was added fuming HNO_3 (24 mL) at 10 °C and the mixture was stirred at 32 °C for 1 h. Water (200 mL) was added and the mixture filtered. The filtrate was washed with water to remove

CH₃CO₂H and was dried to give Compound **D2** (80 g, yield 82%) as a yellow solid. LC-MS (m/z): 244 [M-1]⁻.

[000245] To a solution of Compound **D2** (40 g, 163 mmol) in THF (260 mL) was added dropwise aq. NaOH solution (0.05 N, 640 mL, 33 mmol) at 0 °C and 30% H₂O₂ solution (80 mL). The mixture was stirred for 2 h at rt. The second portion of 30% H₂O₂ (80 mL) was added dropwise and the mixture was stirred for 4 h. After cooling to 0 °C, aq. NaOH solution (2 N, 98 mL) was added dropwise until pH 10~11. The mixture was stirred for 0.5 h and quenched with cone. HCl at 0 °C until pH 2~3. The mixture was extracted with dichloromethane (250 mL x 3) and washed with brine (300 mL x 2), dried over Na₂SO₄, and concentrated to give Compound **D3** (37 g, yield 98%>) as a yellow solid. LC-MS (m/z): 232 [M-1]⁻; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 7.17 (s, 1H), 7.48 (s, 1H), 10.59 (s, 2H).

[000246] To a mixture of Compound **D3** (32 g, 137 mol) and K₂CO₃ (73 g, 549 mol) in DMF (500 mL) was added 1,2-dibromoethane (147 mL, 343 mol). The mixture was stirred at 80 °C for 4 h. After cooling to rt, the mixture was filtered and the cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (900 mL) and extracted with ethyl acetate (400 mL x 3). The organic layer was washed with water (900 mL x 5) and brine (900 mL x 1), dried, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 5 %>v/v) to yield Compound **D4** (30 g, yield 84%>) as a colorless oil. 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.35 (s, 4H), 6.91 (t, J = 8 Hz, 2H), 7.33 (s, 1H).

[000247] To a solution of Compound **D4** (11 g, 42.5 mmol) in EtOH (200 mL) was added HCl (7 mL). Fe (7.1 g, 127 mmol) was added over 0.5 h. Then HCl was added to reach pH 3-4. The mixture was stirred at 100 °C for 2 h. After cooling to rt, 10% NaOH aq was added dropwise until pH 10-11. The mixture was filtered and the cake was washed with THF. The filtrate was condensed and extracted with ethyl acetate (100 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to obtain Compound **D5** (9 g, yield 93%) as a white solid. LC-MS (m/z): 230 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.23-4.27 (m, 4H), 6.46 (d, J = 8 Hz, 2H).

[000248] A solution of **D5** (3.3 g, 14.7 mmol) in H₂O (15 mL) and concentrated HCl (4 mL, 48 mmol) was cooled to 5 °C. A solution of NaNO₂ (1.09 g, 15.8 mmol) in H₂O (7 mL) was added dropwise. The brown solution of the diazonium salt was then added dropwise to a solution of CuCl (2.96 g, 28.4 mmol) in concentrated HCl (5 mL), maintaining the internal

temperature around 10 °C. The mixture was then diluted with H₂O (120 ml) and the solution was stirred for an additional 1 h at rt. The product was extracted into ethyl acetate (50 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to obtain Compound **D6** (1.9 g, yield 53%) as a white solid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.26 (t, *J* = 8 Hz, 2H), 4.34 (t, *J* = 8 Hz, 2H), 6.95 (s, 1H), 7.08 (s, 1H).

[000249] To a solution of Compound **D6** (8.05 g, 32 mmol) in THF (300 mL) was added n-BuLi (2.4 M, 14 mL, 29.4 mmol) at - 60 °C under N₂ and stirred for 0.5 h. Then it was added a solution of Compound **A6** (4.3 g, 11 mmol) in THF (10 mL). The mixture was stirred at - 60 °C under N₂ for 20 min, quenched with saturated aqueous NH₄Cl solution (200 mL), extracted with ethyl acetate (200 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na₂SO₄, purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to yield Compound **D7** (4.87 g, yield 66%) as a colorless oil. LC-MS (m/z): 506 [M+1]⁺.

[000250] To a solution of Compound **D7** (4.5 g, 8.8 mmol) in THF (50 mL) was added L-selectride (17.7 mL) at - 60 °C under N₂. After stirred for 1 h, the mixture was quenched with saturated aqueous NH₄Cl solution (50 mL), extracted with ethyl acetate (50 mL x 3), washed with brine, dried over anhydrous Na₂SO₄, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 20 % v/v) to give Compound **D8** (3.8 g, yield 85 %) as a white solid. LC-MS (m/z): 490 [M+1-18]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.90 (s, 9H), 3.77-3.85(m, 2H), 4.25 (s, 2H), 4.34 (s, 2H), 4.90 (s, 1H), 5.01-5.12 (m, 2H), 5.40 (d, *J* = 8 Hz, 1H), 6.80 (s, 1H), 6.97 (s, 1H), 7.32-7.36 (m, 5H).

[000251] To a solution of Compound **D8** (3.8 g, 7.5 mmol) in THF (150 mL) was added TBAF (1 g, 3.8 mmol) at 0 °C and it was stirred at rt overnight. The mixture was added water (100 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, and concentrated to yield **D9** (2.81 g, yield 100%) as a colorless oil. LC-MS (m/z): 376 [M+1-18]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.72-3.80 (m, 2H), 4.23 (s, 2H), 4.31 (s, 2H), 4.69-4.86 (m, 1H), 5.02-5.15 (m, 2H), 5.51 (d, *J* = 8 Hz, 1H), 6.75-6.96 (m, 2H), 7.29-7.36 (m, 5H).

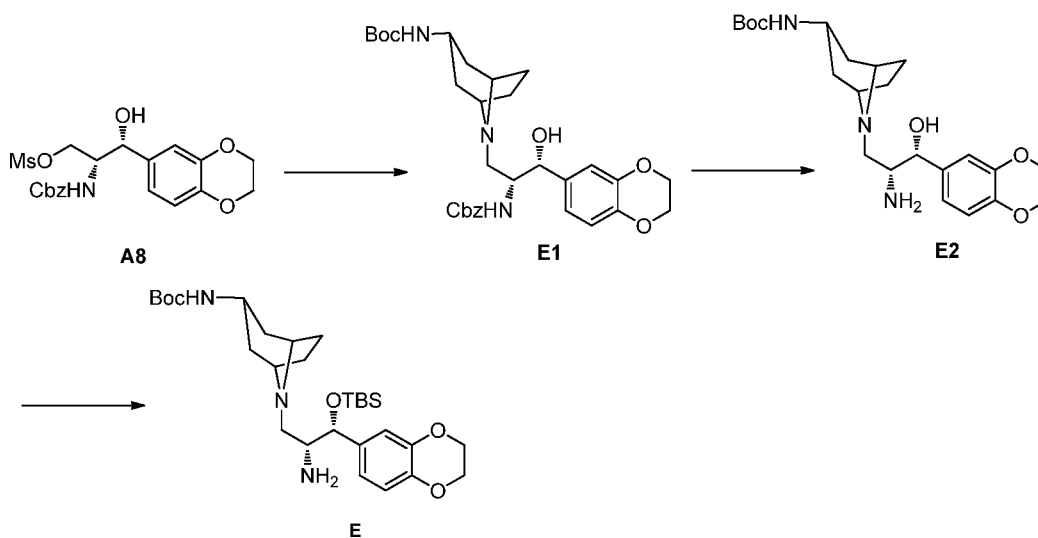
[000252] To a solution of Compound **D9** (1.4 g, 3.6 mmol) and TEA (1.5 mL, 10.8 mmol) in THF (30 mL) was added MsCl (0.31 mL, 3.9 mmol) at - 40 °C. After stirring at - 0 °C for 4 h, water (50 mL) was added and the product was extracted into ethyl acetate (50 mL

x 3) which was washed with brine (100 mL x 1) and dried over anhydrous Na_2SO_4 . The product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 50% v/v) to give Compound **D10** (756 mg, yield 45%) as a white solid. LC-MS (m/z): 454 [M+18]⁺.

[000253] To a solution of Compound **D10** (756 mg, 1.6 mmol) in THF (20 mL) was added pyrrolidine (1.4 mL, 16 mmol). The mixture was stirred at 60 °C overnight. It was added water (20 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (30 mL x 1), dried over anhydrous Na_2SO_4 , and concentrated in vacuum to give crude product Compound **D11** (715 mg, crude) as a white solid. LC-MS (m/z): 447 [M+1]⁺.

[000254] To a solution of Compound **D11** (714 mg, 1.6 mmol) in EtOH/water (24 mL, 2:1, v/v) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (672 mg, 16 mmol). The mixture was refluxed for 24 h before added water (20 mL). It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give crude product **Intermediate D** (620 mg, crude) as a yellow oil. LC-MS (m/z): 313 [M+1]⁺.

Intermediate E



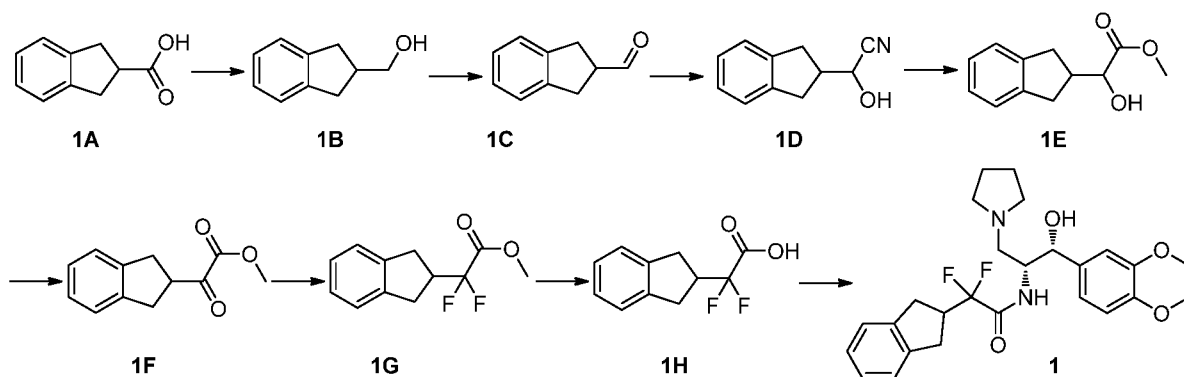
[000255] A suspension of Compound **A8** (1.00 g, 2.29 mmol), *tert*-butyl-8-aza-bicyclo[3.2.1]octan-3-ylcarbamate (1.96 g, 6.86 mmol) and K_2CO_3 (1.58 g, 11.45 mmol) in ACN (30 mL) was stirred at 60 °C overnight. The mixture was diluted with ethyl acetate (150 mL) and evaporated to give Compound **E1** (1.20 g, yield 92%>) as a colorless oil. LCMS (m/z): 568 [M+1]⁺.

[000256] A mixture of Compound **E1** (1.20 g, 2.12 mmol) and NaOH (423 mg, 10.58 mmol) in $\text{H}_2\text{O}/\text{EtOH}$ (10/50 mL) was stirred at 80 °C overnight. The mixture was diluted with

ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to yield Compound **E2** (980 mg, yield 100%) as a colorless oil. LCMS (m/z): 433 [M+1]⁺.

[000257] To a solution of Compound **E2** (980 mg, 2.26 mmol) and imidazole (461 mg, 6.78 mmol) in THF (10 mL) was added TBDMSC1 (678 mg, 4.53 mmol) at rt. The mixture was stirred at rt for 2 h. It was diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂SO₄, and evaporated to afford Intermediate **E** (1.10 g, yield 89%>) as a colorless oil, which was used for next step directly. LCMS (m/z): 548 [M+1]⁺.

Example 1



[000258] To a stirred solution of Compound **1A** (2.75 g, 17 mmol) in DCM (40 mL) was added THF-borane (1 M, 20 mL, 20 mmol) at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was allowed to warm up to rt over 1 h. To the mixture was added MeOH (8 mL) and it was heated to reflux for 2 h. Diluted with aq. NaHCO_3 (20 mL), the mixture was poured into crash ice slowly with stirring. The mixture was then extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product which was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 25% v/v) to yield compound **1B** (2.4 g, yield 96%) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.79-2.75 (m, 3H), 3.01-3.08 (m, 2H), 3.61-3.64 (m, 2H), 7.10-7.23 (m, 4H).

[000259] A solution of Compound **1B** (200 mg, 1.4 mmol) and Dess-Martin reagent (688 mg, 1.6 mmol) in dichloromethane (20 mL) was stirred at rt for 4 h. The resulting solution was poured into a saturated solution of sodium hydrogen carbonate (20 mL) in which beforehand sodium thiosulfate pentahydrate had been dissolved. After 15 min of vigorous stirring, the organic phase was collected and the aqueous phase was extracted with diethyl ether (10 mL x 3). The combined organic layers were dried and evaporated to give a crude product which was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 4% v/v) to afford Compound **1C** (190 mg, yield 96%+) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.05-3.23 (m, 5H), 7.06-7.15 (m, 4 H), 9.67 (s, 1H).

[000260] Compound **1C** (292 mg, 2 mmol) was added to a solution of sodium metabisulfite (196 mg, 4 mmol) in water (3 mL). The mixture was vigorously stirred for 2 h at rt and after the addition of sodium cyanide (380 mg, 2 mmol), and then stirred for 1 h. The mixture was extracted with diethyl ether (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated to give a crude product **1D**

(316 mg, yield 91%) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.89-3.01 (m,3H), 3.14-3.24 (m, 2H), 4.41-4.43 (d, *J* = 8 Hz, 1H), 7.16-7.26 (m,4H).

[000261] A solution of Compound **ID** (300 mg, 1.7 mmol) in HCl/MeOH (3 M, 2 mL) was heated to reflux for 18 h. The mixture was concentrated by evaporation and purified by column chromatography on silica gel to give Compound **IE** (116 mg, yield 32%). ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.85-3.01 (m,6H), 3.75(s,3H), 4.28 (s,1H), 7.11-7.19 (m, 4H).

[000262] A solution of Compound **IE** (550mg, 2.70 mmol) and Dess-Martin reagents (1.3 g, 3.2 mmol) in dichloromethane (20 mL) was stirred at rt for 4 h. The suspension was diluted with diethyl ether (60 mL) before being slowly poured into a saturated solution of sodium hydrogen carbonate (20 mL) in which contained a pre-dissolved sodium thiosulfate pentahydrate (1.6 g, 6.4 mmol). After 15 min of vigorous stirring, the organic phase was collected and the aqueous phase was extracted with diethyl ether (10 mL x 3). The combined organic layers were dried and evaporated to give a crude product **IF** (500 mg, yield 92%>) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.24-3.26 (d, *J* = 4 Hz, 4H), 3.89-3.91(m,3H), 4.01-4.05 (m,1H), 7.14-7.20 (m, 4H).

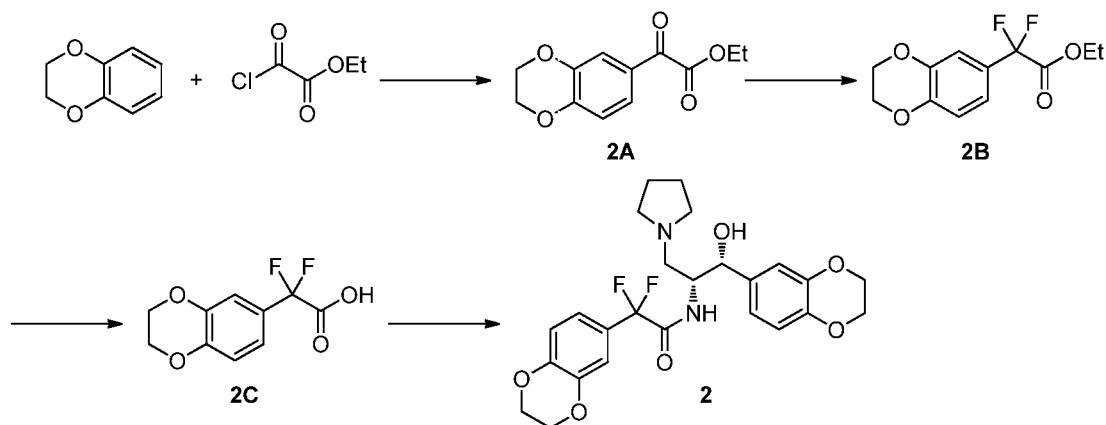
[000263] To a stirred solution of Compound **IF** (200 mg, 1 mmol) in DCM (4 mL) was added DAST (0.8 mL, 6 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 h. The mixture was poured into crash ice slowly with stirring. The mixture was stirred for 30 min, and then extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂S₄, and concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether as the eluent) to give Compound **IG** (80 mg, yield 36%). ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.98-3.19 (m,5H), 3.74 (s,3H), 7.07-7.17 (m, 4H).

[000264] To a stirred solution of Compound **IG** (140mg, 0.6mmol) in EtOH (2 mL) and H₂O (2 mL) was added LiOH·H₂O (50 mg, 1.2 mmol) in ice bath. The resulting mixture was stirred at rt for 2 h and followed by acidification to pH 2 with 2 M HCl. The mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na₂S₄, and concentrated to give Compound **IH** (130 mg, yield 100%) as yellow oil. LC-MS (m/z): 211 [M-1]⁻; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.09-3.12 (m,5H),7.13-7.18 (m, 4 H).

[000265] To a stirred mixture of Compound **IH** (31.8mg, 0.15mmol) and Intermediate **A** (62.55 mg, 0.23 mmol) in DMF (3 mL) was added HOBt (30 mg, 0.25 mmol) and EDCI (43.2 mg, 0.23 mmol). The resulting mixture was stirred at rt overnight. The mixture was

diluted with water (15 mL), and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , and concentrated to give a crude product. The crude product was purified by prep-HPLC to afford trifluoroacetic acid salt of Compound **1** (11.1 mg, yield 15.5%) as a white solid. LC-MS(*m/z*): 473 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.62 (s, 4H), 2.16 (s, 4H), 2.58-2.64 (m, 2H), 2.85-3.09 (m, 4H), 3.52-3.57 (m, 1H), 3.52-3.57 (m, 1H), 4.11-4.21 (m, 4H), 4.39-4.41 (m, 1H), 5.16 (s, 1H), 6.80-6.90 (m, 3H), 7.13-7.15 (t, *J* = 4 Hz, 4H), 7.37-7.39 (d, *J* = 8 Hz, 1H).

Example 2



[000266] To a stirred suspension of AlCl_3 (26.7 g, 200 mmol) in DCM (100 mL) was added dropwise ethyl 2-chloro-2-oxoacetate (27.3 g, 200 mmol) at 0 °C. After stirred at 0 °C for 30 min, 2,3-dihydrobenzo[b][1,4]dioxine (13.6 g, 100 mmol) was added dropwise at 0 °C to the mixture. The resulting mixture was stirred at rt for 3 h, poured into ice water (300 mL), and then extracted with DCM (150 mL x 3). The combined organic layers were washed with aq. NaHCO_3 (200 mL), brine (200 mL), dried over Na_2SO_4 , and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to yield Compound **2A** (18 g, yield 76%) as a yellow solid. LC-MS (*m/z*): 162 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.40-1.43 (t, *J* = 7.2 Hz, 3 H), 4.28-4.33 (m, 2 H), 4.34-4.36 (m, 2 H), 4.40-4.45 (m, 2 H), 6.94-6.96 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.54-7.56 (m, 2 H).

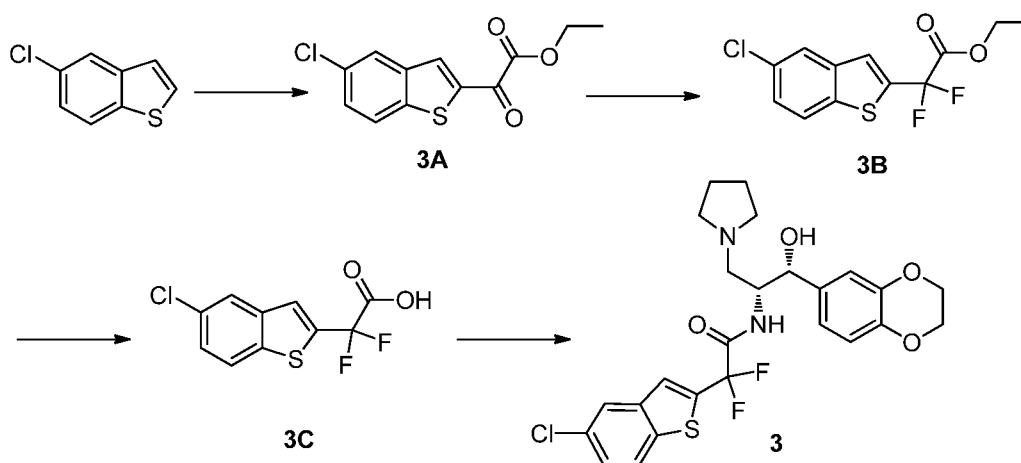
[000267] To a stirred solution of Compound **2A** (4.72 g, 20 mmol) in DCM (50 mL) was added DAST (16.1 g, 100 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 h and poured into crash ice slowly with stirring. The mixture was stirred for 30 min, and then extracted with DCM (40 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated to give crude product. The crude product was

purified by column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 3% v/v) to afford Compound **2B** (4.28 g, yield 83%) as a yellow oil. LC-MS (m/z): 259 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.29-1.33 (t, *J* = 7.2 Hz, 3H), 4.26-4.32 (m, 6H), 6.90-6.92 (d, *J* = 8.0 Hz, 1H), 7.07-7.12 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.12-7.13 (d, *J* = 2.0 Hz, 1H).

[000268] To a stirred solution of Compound **2B** (4.28 g, 16.59 mmol) in THF (20 mL) and H₂O (20 mL) was added LiOH·H₂O (1.393 g, 33.18 mmol) in an ice bath. The resulting mixture was stirred at rt for 16 h. THF was removed under reduced pressure. The residue was diluted with water (20 mL), acidified to pH 2 with 2 M HCl, and then extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated to give Compound **2C** (3.8 g, yield 98%) as light yellow solid. LC-MS (m/z): 211 [M-19]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.28-4.30 (t, *J* = 4.4 Hz, 4H), 6.98-7.04 (m, 3H).

[000269] To a stirred mixture of Compound **2C** (23 mg, 0.1 mmol) and Intermediate A (41.7 mg, 0.15 mmol) in DMF (1 mL) was added HOBT (20 mg, 0.15 mmol) and EDCI (30mg, 0.15 mmol). The resulting mixture was stirred at rt overnight. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated to give crude product. The crude product was purified by prep-HPLC to give trifluoroacetic acid salt of Compound **2** (18.9 mg, yield 39%) as a white solid. LC-MS (m/z): 491 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.07(s, 3 H), 2.86 (s, 1 H), 3.00 (s, 1H), 3.46 (s, 2H), 3.76 (s, 2H), 4.20-4.25 (m, 8H), 4.37 (s, 1 H), 5.05 (s, 1 H), 6.72-6.81 (m, 4H), 6.91 (s, 1H), 7.65 (s, 1H), 11.67 (s, 1H).

Example 3



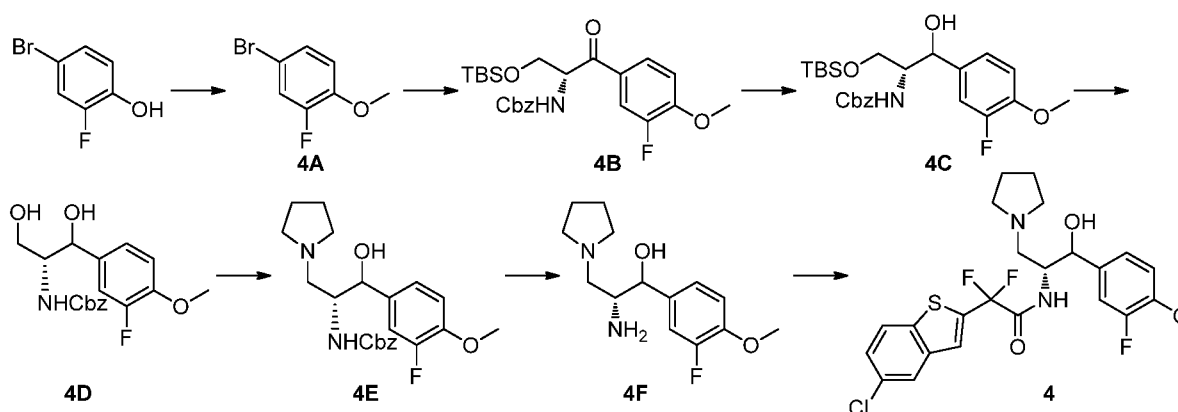
[000270] To a solution of 5-chlorobenzo[6]thiophene (2.00 g, 11.83 mmol) in THF (50 mL) was added dropwise n-BuLi in THF (5.20 mL, 13.01 mmol) at -78 °C. Then it was stirred at -50 °C for 1 h. Diethyl oxalate (4.32 g, 29.58 mmol) was added to the mixture quickly at -78 °C. The mixture was stirred at -50 °C for 1 h. It was quenched with acetic acid, diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na₂S₂O₄, and evaporated to give a residue which was washed with petroleum ether to obtain Compound **3A** (2.60 g, yield 82%) as a light yellow solid. LCMS: 269 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.46 (t, *J* = 7.6 Hz, 3H), 4.45-4.51 (m, 2H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.92 (s, 1H), 8.37 (s, 1H).

[000271] To a solution of Compound **3A** (600 mg, 2.25 mmol) in DCM (120 mL) was added dropwise DAST (1.5 mL, 11.19 mmol) at rt. The mixture was stirred at rt overnight. It was then quenched with ice, diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂S₂O₄, and evaporated to yield Compound **3B** (420 mg, yield 64%) as a yellow oil. LCMS: 291 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.37 (t, *J* = 7.2 Hz, 3H), 4.35-4.41 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.58 (s, 1H), 7.77-7.82 (m, 2H).

[000272] A solution of Compound **3B** (420 mg, 1.45 mmol) and LiOH·H₂O (122 mg, 2.90 mmol) in THF/MeOH/H₂O (10/10/5 mL) was stirred at rt for 2 h. The mixture was adjusted to pH 2 with cone. HCl, diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂S₂O₄, and evaporated to give Compound **3C** (400 mg, yield 100%) as a white solid. LCMS: 261 [M-]⁻.

[000273] A mixture of Intermediate **A** (80 mg, 0.29 mmol), Compound **3C** (94 mg, 0.34 mmol), EDCI (84 mg, 0.44 mmol), HOBt (59 mg, 0.44 mmol) and DIPEA (0.2 mL) in DCM (5 mL) was stirred at rt overnight. Then it was diluted with ethyl acetate (150 mL) washed with water and brine, purified by prep-HPLC to afford Compound **3** (50 mg, yield 33%>) as a white solid. LCMS: 523 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.14 (br s, 4H), 2.59 (br s, 4H), 2.89-3.03 (m, 2H), 3.45-3.51 (m, 2H), 3.82 (br s, 2H), 4.00-4.16 (m, 4H), 4.44 (br s, 1H), 5.15 (s, 1H), 6.72-6.82 (m, 3H), 7.10 (s, 1H), 3.37 (d, *J* = 10.4 Hz, 1H), 7.70-7.78 (m, 2H), 11.95 (s, 1H).

Example 4



[000274] To a solution of 4-bromo-2-fluorophenol (15 g, 78.5 mmol) in DMF (200 mL) was added K_2CO_3 (32.25 g, 235.6 mmol), CH_3I (12.3 mL, 96.3 mmol). The mixture was stirred at rt overnight. Water (500 mL) was added to the mixture and the mixture was extracted with ethyl acetate (200 mL x 3), dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica gel (petroleum 100%) to obtain Compound **4A** (11.3 g, 70%) as a colorless oil. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 3.86 (s, 3H), 6.83 (t, $J = 8.8$ Hz, 1H), 7.20 (m, 2H).

[000275] To a solution of Compound **4A** (11 g, 53.7 mmol) in THF (250 mL) was added *n*-BuLi (2.5M, 22.2 mL, 55.5 mmol) at $-60^\circ C$ under N_2 . The mixture was stirred at $-60^\circ C$ under N_2 for 0.5 h. Then it was added a solution of Intermediate **A4** (7.1 g, 17.9 mmol) in THF (50 mL). The mixture was stirred at $-60^\circ C$ under N_2 for another 5 min before quenched with saturated aqueous NH_4Cl solution (200 mL). The mixture was extracted with ethyl acetate (200 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica (ethyl acetate in petroleum, 9% v/v) to yield Compound **4B** (7.1 g, 86%) as a colorless oil. LCMS: 462 $[M+1]^+$; 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) -0.14 (s, 3H), -0.12 (s, 3H), 0.75 (s, 9H), 3.89 (m, 1H), 3.96 (m, 4H), 5.13 (s, 2H), 5.29 (m, 1H), 5.89 (m, 1H), 7.01 (m, 1H), 7.35 (m, 5H), 7.73 (m, 2H).

[000276] To a solution of Compound **4B** (7.1 g, 15.4 mmol) in THF (100 mL) was added *L*-Selectride (31 mL) at $-60^\circ C$ under N_2 and stirred at $-60^\circ C$ under N_2 for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with ethyl acetate (100 mL x 3), washed with brine, dried over anhydrous Na_2SO_4 , and then purified by column chromatography on silica gel (ethyl acetate in petroleum, 9% v/v) to give Compound **4C** (6.7 g, 94%) as a colorless oil. LCMS: 446 $[M+1-18]^+$; 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 0.03 (m, 6H), 0.90 (d, 9H), 3.68 (m, 1H), 3.88 (m,

5H), 4.89 (m, 1H), 5.04 (m, 2H), 5.39 (m, 1H), 6.88 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.30 (m, 5H).

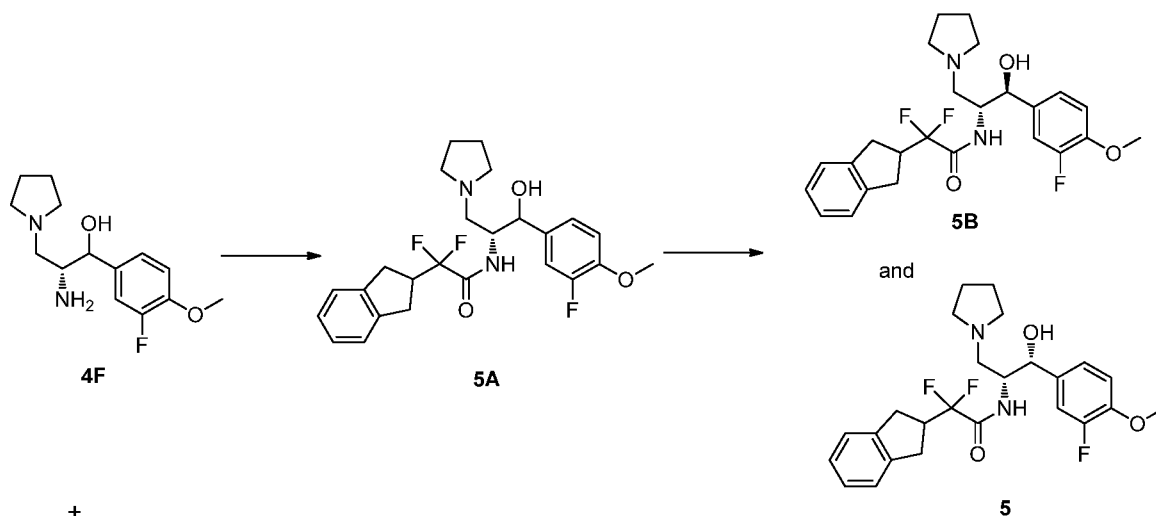
[000277] To a solution of Compound **4C** (6.7 g, 13.6 mmol) in THF (250 mL) was added TBAF (1.8 g, 6.8 mmol) at 0°C and stirred at rt overnight. The mixture was added water (200 mL), extracted with ethyl acetate (100 mL x 3), washed with brine (200 mL x 1), dried over anhydrous Na₂SO₄, concentrated to obtain Compound **4D** (5 g, 98%) as a yellow oil. LCMS: 332 [M+18]⁺.

[000278] To a solution of Compound **4D** (5 g, 14.3 mmol) and TEA (6 mL, 42.9 mmol) in THF (80 mL) was added MsCl (1.2 mL) at -60°C and stirred at -60°C for 2 h. The mixture was added pyrrolidine (12 mL, 143 mmol) and stirred at 50°C overnight. After the mixture was cooled down, water (200 mL) was added. The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL x 1), and dried over anhydrous Na₂SO₄. The crude product was purified by prep-HPLC to obtain Compound **4E** (1.9 g, 33%) as a colorless oil. LCMS: 403 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.78 (m, 4H), 2.64 (m, 6H), 3.88 (m, 4H), 5.03 (m, 4H), 6.89 (m, 1H), 6.70 (m, 1H), 7.11 (m, 1H), 7.28 (m, 5H).

[000279] To a solution of Compound **4E** (1.9 g, 4.7 mmol) in MeOH (30 mL) was added Pd(OH)₂ (660 mg, 4.7 mmol). The mixture was stirred at rt overnight under H₂. The mixture was filtered and the filtrate was concentrated to obtain Compound **4F** (1.2 g, 95%) as a colorless oil. LCMS: 269 [M+1]⁺.

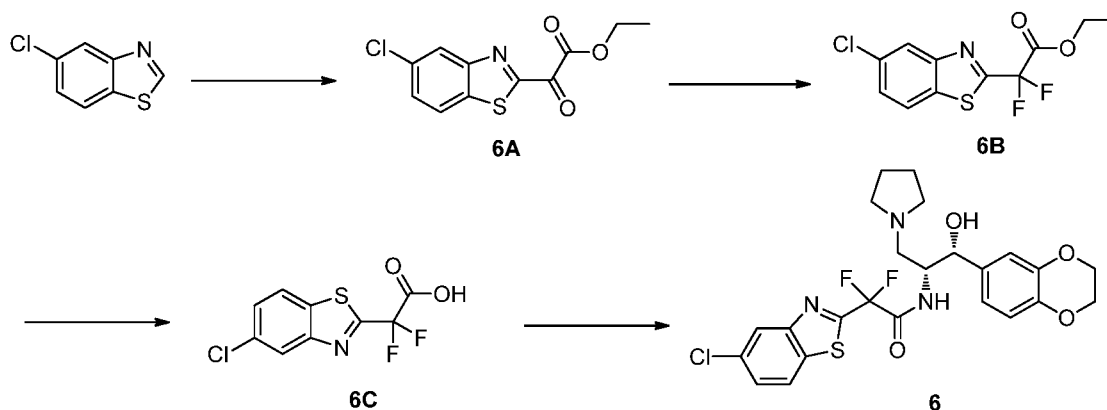
[000280] To a mixture of Compound **4F** (194 mg, 0.74 mmol) in DCM (10 mL) was added EDCI (213 mg, 1.1 mmol), HOBt (150 mg, 1.1 mmol) and Compound **3C** (200 mg, 0.74 mmol) and stirred at rt for overnight. Then it was added water (50 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na₂SO₄, purified by prep-HPLC to give **4** (50 mg, 14%) as a white solid. LCMS: 514 [M+1]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 2H), 2.02 (m, 2H), 3.12 (m, 2H), 3.49 (s, 3H), 3.56 (m, 4H), 4.28 (m, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 6.06 (br, 1H), 6.71 (t, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 7.05 (dd, 1H), 7.20 (s, 1H), 7.52 (dd, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 9.23 (m, 1H), 9.78 (br, 1H).

Example 5



[000281] To a mixture of Compound 4F (157 mg, 0.74 mmol) in DCM (10 mL) was added EDCI (213 mg, 1.1 mmol), HOBT (150 mg, 1.1 mmol) and Compound 1H (200 mg, 0.74 mmol) and stirred at rt overnight. Water (50 mL) was added to the mixture, which was then extracted with DCM (20 mL x 3). The combined organic phases were dried over anhydrous Na₂SO₄ and evaporated to remove solvents. The residues were purified by prep-HPLC to yield **5** (30 mg, yield 9%) as a white solid. LCMS: 463 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 2H), 2.03 (m, 2H), 3.10 (m, 2H), 3.54 (m, 5H), 3.76 (s, 3H), 4.31 (m, 1H), 4.50 (d, *J* = 7.2 Hz, 1H), 6.09 (br, 1H), 7.13 (m, 7H), 8.86 (d, *J* = 8.8 Hz, 1H), 9.51 (br, 1H).

Example 6



[000282] To a solution of 5-chlorobenzo[1,2-b:4,5-b']thiazole (500 mg, 2.95 mmol) in THF (20 mL) was added *n*-BuLi (1.42 mL, 3.54 mmol) at -78 °C under the protection of nitrogen. The mixture was stirred at -78 °C for 1 h, and then diethyl oxalate (1.08 g, 7.37 mmol) was added to the mixture and stirred for additional one hour at -78 °C. The reaction was quenched with sat. aqueous NH₄Cl. The organic phase was separated and washed with brine,

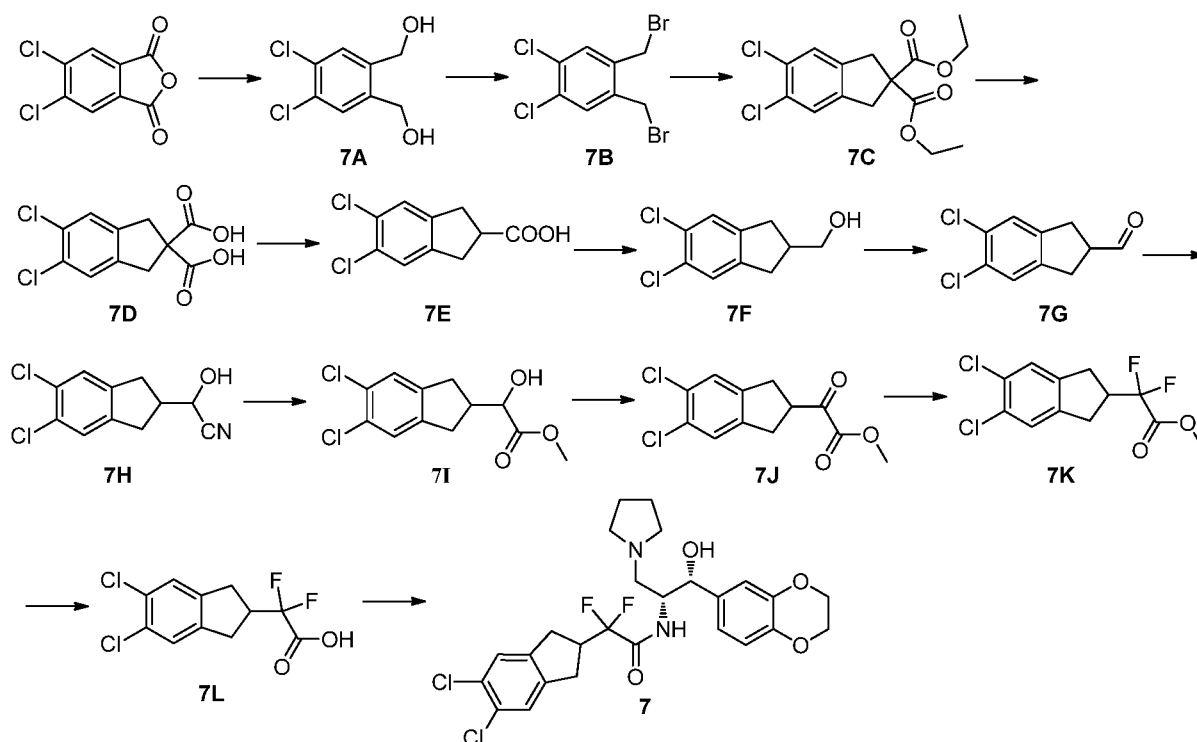
dried over anhydrous Na_2SO_4 , and purified with column chromatography on silica gel (ethyl acetate in petroleum 20% v/v) to give Compound **6A** (200 mg, yield 25%) as a yellow solid. LCMS (m/z): 288 $[\text{M}+18]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.46 (t, $J = 7.2$ Hz, 3H), 4.54 (q, $J = 7.2$ Hz, 2H), 7.57 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 8.27 (d, $J = 2.0$ Hz, 1H).

[000283] To a solution of Compound **6A** (170 mg, 0.63 mmol) in DCM (10 mL) was added DAST (305 mg, 1.89 mmol) at 0 °C under N_2 and stirred at 15 °C overnight. The reaction mixture was poured into 100 mL of ice-water and extracted with DCM (50 mL x 3). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica gel (ethyl acetate in petroleum, 9% v/v) to yield Compound **6B** (105 mg, yield 52%) as a yellow oil. LCMS (m/z): 292 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.27 (t, $J = 7.2$ Hz, 3H), 4.43 (q, $J = 7.2$ Hz, 2H), 7.72 (dd, $J = 2.0, 8.8$ Hz, 1H), 8.36 (m, 2H).

[000284] To a solution of Compound **6B** (105 mg, 0.36 mmol) in THF/MeOH/water (6 mL, 1:1:1, v/v) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (15 mg). The mixture was stirred at 25 °C for 2 h. After removal of the solvents and adjust pH to 7 with 1 N HCl, the mixture was diluted with ethyl acetate (100 mL), washed with water, brine, and dried over anhydrous Na_2SO_4 . The crude product was used for next step without further purification. Compound **6C** (95 mg, yield 99%) was obtained as a yellow oil. LCMS (m/z): 264 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 7.51 (dd, $J = 1.6, 8.8$ Hz, 1H), 7.90 (d, $J = 8.84$ Hz, 1H), 8.14 (d, $J = 1.6$ Hz, 1H).

[000285] To a mixture of Compound **6C** (95 mg, 0.36 mmol) in DCM (10 mL) was added EDCI (104 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol) and Intermediate **A** (100 mg, 0.36 mmol) and stirred at 25 °C overnight. Diluted with water (5 mL), the mixture was extracted with DCM (20 mL x 3). The organic phase was dried over anhydrous Na_2SO_4 and purified with prep-HPLC to afford Compound **6** (10 mg, yield 6%>) as a colorless oil. LCMS (m/z): 524 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.91 (m, 4H), 2.75 (m, 2H), 2.93-3.01 (m, 6H), 3.23 (m, 2H), 4.24 (s, 4H), 4.63 (d, $J = 9.6$ Hz, 1H), 6.80 (m, 2H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 2.0$ Hz, 1H).

Example 7



[000286] To a solution of 5,6-dichloroisobenzofuran-1,3-dione (12.00 g, 55.30 mmol) in THF (300 mL) was added LiAlH_4 (3.15 g, 82.95 mmol) carefully at 0 °C. The mixture was stirred at rt overnight. It was then quenched with water (13 mL), 15% aqueous NaOH (3.2 mL). After filtration, the filtrate was evaporated to dryness to yield Compound **7A** (11.20 g, yield 98%) as a white solid. LCMS: 207 $[\text{M}+1]^+$, $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 4.47 (d, $J = 5.6$ Hz, 4H), 5.34 (t, $J = 5.6$ Hz, 2H), 7.57 (s, 2H).

[000287] A suspension of Compound **7A** (4.80 g, 23.2 mmol) in conc. HBr (100 mL) was stirred at 90 °C overnight. The mixture was diluted with ethyl acetate (100 mL) and petroleum ether (100 mL), washed with water and brine, concentrated, and then purified by silica chromatography on silica gel (ethyl acetate in petroleum ether, 8% v/v) to give Compound **7B** (5.20 g, yield 68%) as a light yellow solid. LCMS: 333 $[\text{M}+1]^+$, $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 4.55 (s, 4H), 7.47 (s, 2H).

[000288] To a solution of Compound **7B** (5.88 g, 36.8 mmol) in THF (300 mL) was added NaH (882 mg, 36.8 mmol). The mixture was stirred at rt for 10 min. Then diethyl malonate (12.20 g, 36.75 mmol) was added to the mixture. After stirring for 20 min, an additional portion of NaH (882 mg, 36.8 mmol) was added. After stirring at rt overnight, the mixture was evaporated to dryness to give Compound **7C** (12.6 g, yield 100%) as a white solid. LCMS: 331 $[\text{M}+1]^+$.

[000289] A mixture of Compound **7C** (12.6 g, 38.2 mmol) and LiOH·H₂O (5.80 g, 0.15 mol) in THF/MeOH/H₂O (100/100/50 mL) was stirred at rt overnight. The mixture was condensed by removal of solvents and adjusted to pH 1 with cone. HCl. The precipitate was filtered to obtain Compound **7D** (11.2 g, yield 100%) as a white solid. LCMS: 273 [M-1]⁻, 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 3.47 (s, 4H), 7.57 (s, 2H), 13.16 (s, 2H).

[000290] A mixture of Compound **7D** (4.80 g, 17.5 mmol) and NaCl (4.80 g) in DMSO (100 mL) was stirred at 130 °C for 5 h. Diluted with ethyl acetate (200 mL), the mixture was washed with water and brine, dried with anhydrous Na₂SO₄, and evaporated to dryness to give Compound **7E** (3.40 g, yield 84%) as a white solid. LCMS: 229 [M-1]⁻, 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 3.12-3.23 (m, 4H), 3.34-3.42 (m, 1H), 7.55 (s, 2H), 12.45 (s, 1H).

[000291] To a solution of Compound **7E** (3.40 g, 1.47 mmol) in THF (100 mL) was added LiAlH₄ (554 mg, 1.47 mmol). The mixture was stirred at rt overnight. After being quenched with water (2.4 mL) and aqueous NaOH (15%, 0.56 mL), the precipitate was filtered off and the filtrate was evaporated to give Compound **7F** (2.80 g, yield 88%>) as a white solid. LCMS: 217 [M+1]⁺; 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 2.50-2.60 (m, 1H), 2.89-2.95 (m, 2H), 3.32 (s, 4H), 4.65-4.68 (m, 1H), 7.44 (s, 2H).

[000292] To a solution of Compound **7F** (2.80 g, 12.96 mmol) in DCM (100 mL) was added DMP (6.60 g, 15.6 mmol). The mixture was stirred at rt for 2 h. The solids were filtered off and the filtrate was diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel chromatography (ethyl acetate in PE, 15% v/v) to give Compound **7G** (2.10 g, yield 76%) as a light yellow solid. LCMS: 215 [M+1]⁺; 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 3.06-3.12 (m, 2H), 3.19-3.24 (m, 2H), 3.37-3.44 (m, 1H), 7.51 (s, 2H), 9.68 (s, 1H).

[000293] A suspension of Compound **7G** (2.70 g, 12.6 mmol) and Na₂O₅S₂ (1.24 g, 25.2 mmol) in EtOH/H₂O (20/20 mL) was stirred at rt for 2 h before NaCN (1.24 g, 25.24 mmol) was added. The mixture was stirred at rt overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, purified by silica gel chromatography (ethyl acetate in petroleum ether, 30%> v/v) to yield Compound **7H** (2.10 g, yield 69%>) as a white solid. LCMS: 242 [M+1]⁺; 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 2.79-2.87 (m, 3H), 3.01-3.08 (m, 2H), 4.57 (t, *J* = 6.8 Hz, 1H), 6.60 (d, *J* = 6.4 Hz, 1H), 7.50 (s, 2H).

[000294] A solution of Compound **7H** (2.10 g, 8.71 mmol) in MeOH (100 mL) was stirred at rt overnight in the presence of HCl gas. After the addition of water (20 mL), the mixture was stirred at rt for 2 h and then diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na₂SO₄. Removal of solvents by evaporation gave Compound **7I** (1.80 g, yield 75%) as a white solid. LCMS: 275 [M+]⁺; 1H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 2.76-2.92 (m, 5H), 3.63 (s, 3H), 4.08 (t, *J* = 5.6 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H), 7.44 (s, 2H).

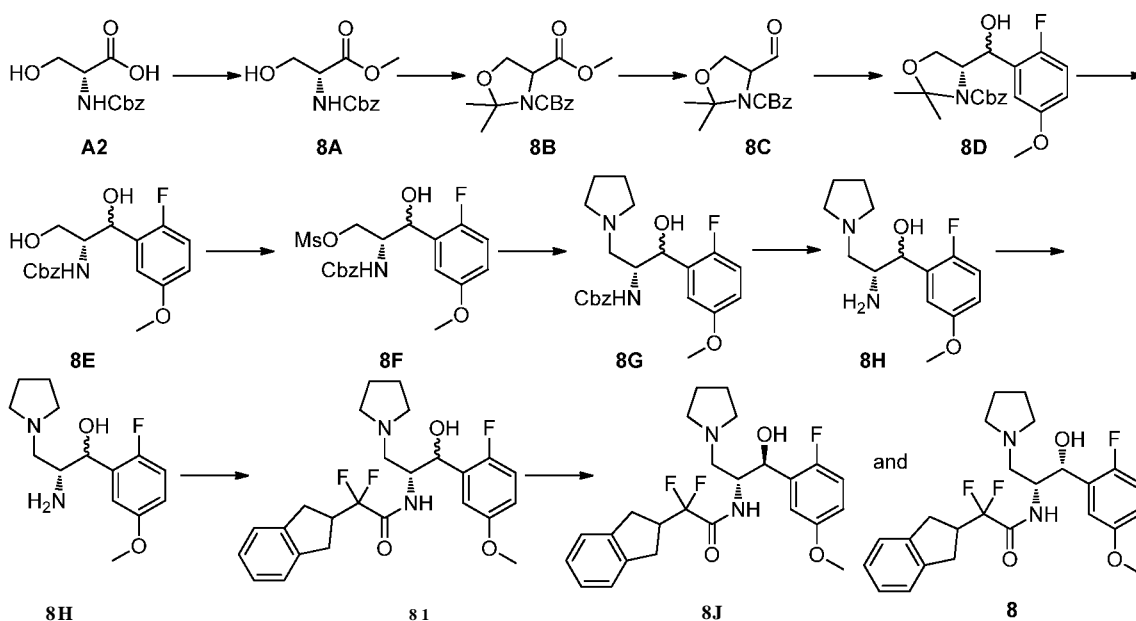
[000295] To a solution of Compound **7I** (1.00 g, 3.65 mmol) in DCM (30 mL) was added DMP (1.55 g, 3.65 mmol). The mixture was stirred at rt for 2 h. It was then diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel chromatography (ethyl acetate in petroleum ether, 25% v/v) to afford Compound **13** (880 mg, yield 87%) as a white solid. LCMS: 273 [M+]⁺.

[000296] To a solution of Compound **13** (272 mg, 1.00 mmol) in DCM (10 mL) was added DAST (0.66 mL, 5.00 mmol). The mixture was stirred at 25 °C overnight. It was then diluted with ethyl acetate (150 mL), washed with water and brine, and purified by silica gel chromatography (ethyl acetate in PE, 10% v/v) to yield Compound **7K** (210 mg, yield 71%) as a white solid. LCMS: 295 [M+]⁺.

[000297] A mixture of Compound **7K** (120 mg, 0.41 mmol) and LiOH·H₂O (52 mg, 1.23 mmol) in THF/MeOH/H₂O (5/5/2 mL) was stirred at rt for 2 h. After removal of solvents, the residues were purified by prep-HPLC to give Compound **7L** (90 mg, yield 78%) as a white solid. LCMS: 279 [M-]⁻.

[000298] A mixture of Intermediate A (100 mg, 0.36 mmol), Compound **7L** (100 mg, 0.36 mmol), EDCI (103 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol) and Et₃N (0.2 mL) in DCM (5 mL) was stirred at 25 °C overnight. It was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to afford **7** (50 mg, yield 37%) as a white solid. LCMS: 541 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.14 (br s, 4H), 2.52-2.59 (m, 2H), 2.65-2.87 (m, 3H), 2.93-3.11 (m, 3H), 3.38-3.50 (m, 2H), 3.82 (br s, 2H), 4.14-4.25 (m, 4H), 4.42 (br s, 1H), 5.12 (s, 1H), 6.80-6.88 (m, 3H), 7.21 (s, 2H), 7.45 (br s, 1H), 11.99 (s, 1H).

Example 8



[000299] Acetyl chloride (10 g, 130 mmol) was added to methanol (100 mL) at 0 °C in an ice-water bath under N₂. The mixture was stirred for 5 min before Compound **A2** (10 g, 42 mmol) was added. The mixture was heated to reflux and stirred for 2 h. Removal of the solvent by evaporation gave Compound **8A** (9 g, yield 85%) as a white solid, which was used for the next step without further purification.

[000300] To a solution of Compound **8A** (10 g, 40 mmol) in acetone (100 mL) was added 2,2-dimethoxypropane (37 g, 0.36 mol) and BF₃·Et₂O (2 mL). The resulting orange solution was stirred at rt for 3 h. The mixture was treated with TEA (4 mL) and then evaporated to dryness. The resulted residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine, and then evaporated to give a crude product, which was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **8B** (7.5 g, yield 80%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.49-1.57 (d, 3H), 1.64-1.71 (d, 3H), 3.64, 3.77 (s, 3H), 4.08-4.19 (m, 2H), 4.47-4.57 (m, 1H), 5.03-5.20 (m, 2H), 7.28-7.37 (m, 5H).

[000301] To a solution of Compound **8B** (6 g, 20 mmol) in toluene (50 mL) at -78 °C was added 1.0 M DIBAL (30 mL). The mixture was stirred at this temperature for 2 h, quenched with menthol (6 mL), diluted with 1 N aq HCl (25 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and evaporated to remove the volatiles. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to give Compound **8C** (2.7 g, yield 51%) as a colorless oil. ¹H-NMR (CDCl₃,

400 MHz) major characteristic peaks: δ (ppm) 1.51-1.58 (d, 3H), 1.60-1.68 (d, 3H), 4.08-4.16 (m, 2H), 4.31-4.36 (m, 1H), 5.10 (m, 2H), 7.28-7.37 (m, 5H), 9.56-9.63 (s, 1H).

[000302] To a solution of 2-bromo-1-fluoro-4-methoxybenzene (3.5 g, 34 mmol) in THF (60 mL) was added n-BuLi (9.2 mL, 2.5 M) under N₂ at -60 °C. Stirred for 1 h, Compound **8C** (3 g, 11.4 mmol) in THF (10 mL) was added to the mixture. After stirring for an additional 3 h at rt, the mixture was diluted with sat. aq. NH₄Cl (40 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and then evaporated to give a crude product, which was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 30% v/v) to yield Compound **8D** (1.8 g, yield 41%>) as colorless oil. LC-MS (m/z): 390 [M+1]⁺.

[000303] A solution of Compound **8D** (0.39 g, 1 mmol) in THF (10 mL) and 1 N aq HCl (2 mL) was stirred at rt for 5 h. The mixture was quenched with water (10 mL), extracted with ethyl acetate (20 mL x 2), washed with brine (30 mL x 2), and evaporated to remove solvents. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to give Compound **8E** (283 mg, yield 81%>) as a colorless oil. LC-MS (m/z): 350 [M+1]⁺.

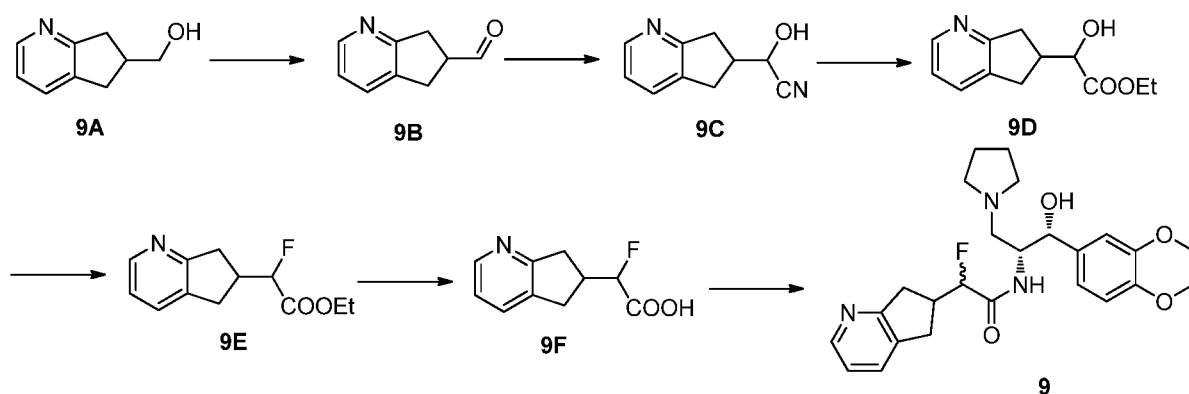
[000304] To a solution of Compound **8E** (1 g, 2.9 mmol) in THF (25 mL) was added triethylamine (0.44 g, 4.4 mmol) and MsCl (0.4 g, 3.5 mmol) under N₂ at -40 °C. The mixture was stirred at this temperature for 3 h before quenched with water (40 mL). It was extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), and evaporated to give a crude product, which was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to yield Compound **8F** (0.85 g, yield 69%>) as a colorless oil. LC-MS (m/z): 410 [M-17]⁺.

[000305] To a solution of Compound **8F** (0.8 g, 2.3 mmol) in THF (25 mL) was added pyrrolidine (1.5 g, 21 mmol). The mixture was stirred at 60 °C overnight, quenched with water (40 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), and evaporated to remove solvents. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **8G** (0.5 g, 54%) as colorless oil. LC-MS (m/z): 403 [M+1]⁺.

[000306] A solution of Compound **8G** (0.5 g, 1.2 mmol) and LiOH·H₂O (157 mg, 3.6 mmol) in ethanol (20 mL) was heated to reflux overnight. The mixture was quenched with water (40 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), and evaporated to yield Compound **8H** (0.3 g, 93%>) as a colorless oil. LC-MS (m/z): 269 [M+1]⁺

[000307] To a solution of Compound **8H** (0.2 g, 0.75 mmol) in dichloromethane (15 mL) was added Compound **1H** (191 mg, 0.9 mmol), EDCI (216 mg, 1.13 mmol), HOBT (152 mg, 1.13 mmol). The mixture was stirred at rt overnight, quenched with water (20 mL), extracted with DCM (20 mL x 2), washed with brine (50 mL x 2), and evaporated. The crude product was purified by prep-HPLC to give **8I** and followed by chiral-prep-HPLC to afford two isomers **8J** (5 mg) as a white solid and **8K** (105 mg) as a white solid. For **8J**: LC-MS (m/z): 463 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.87 (m, 4H), 2.80 (m, 3H), 2.86 (m, 2H), 2.96 (m, 3H), 3.10 (m, 3H), 3.72 (s, 3H), 3.81 (s, 1H), 4.34 (s, 1H), 5.46 (s, 1H), 6.80 (m, 1H), 6.96 (m, 2H), 7.14 (m, 5H). For **8K**: LC-MS (m/z): 463 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.84 (s, 4H), 2.80 (m, 7H), 3.02 (m, 3H), 3.18 (m, 1H), 3.81 (s, 3H), 4.21 (s, 1H), 5.16 (m, 1H), 6.81 (m, 1H), 6.94 (m, 1H), 7.16 (m, 5H).

Example 9



[000308] To a solution of Compound **9A** (2.18 g, 15 mmol) in DCM (50 mL) was added DMP (7.44 g, 18 mmol). The mixture was stirred at rt for 2 h, followed by filtration. The filtrate was washed with sat.aq. NaHCO₃ (50 mL x 2), extracted with DCM (50 mL x 2), washed with brine (1 x 50 mL), dried over Na₂S₂O₄, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **9B** (1.2 g, yield 56%) as a white solid. LC-MS (m/z): 148 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.17 (m, 1H), 3.38 (m, 4H), 7.09 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 4.4 Hz, 1H), 9.82 (s, 1H).

[000309] Compound **9B** (1.2 g, 8.2 mmol) was added to a solution of sodium metabisulfate (1.55 g, 8.2 mmol) in water (35 mL). The mixture was vigorously stirred for 2 h at rt before the addition of NaCN (800 mg, 16 mmol). Stirred overnight, the mixture was diluted with water (30 mL) and THF (10 mL). The mixture was extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na₂S₂O₄, and concentrated to give

Compound **9C** (1.15 g, yield 81%) as a white solid. LC-MS (m/z): 175 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.86 (m, 3H), 3.08 (m, 2H), 4.62 (m, 1H), 6.63 (t, *J* = 3.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 4.8 Hz, 1H).

[000310] A solution of Compound **9C** (1.15 g, 6.6 mmol) in EtOH (20 mL) was bubbled with a gentle stream of HCl (gas) (dried over cone. H₂SO₄) for 5 h at 0 °C. The mixture was added water (20 mL), stirred at rt for 2 h, and then adjusted pH to 7 with dilute NaOH (2M). It was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to yield Compound **9D** (1 g, yield 69%) as a colorless oil. LC-MS (m/z): 222 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.29 (m, 3H), 3.055 (m, 5H), 4.24 (m, 3H), 7.03 (m, 1H), 7.46 (m, 1H), 8.33 (d, *J* = 4.4 Hz, 1H)

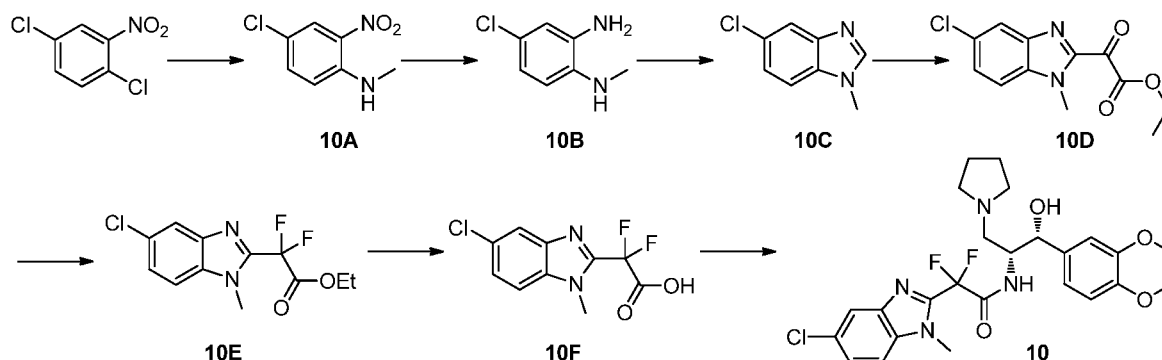
[000311] To a solution of Compound **9D** (500 mg, 2.26 mmol) in DCM (20 mL) was added DAST (1.1 g, 6.78 mmol) at 0 °C, then the mixture was stirred at rt overnight. The mixture was poured into ice-water, added sat. aq NaHCO₃ (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄ and evaporated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to render Compound **9E** (170 mg, yield 34%) as a colorless oil. LC-MS (m/z): 224 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.29 (t, *J* = 7.2 Hz, 3H), 3.12 (m, 5H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.01 (m, 1H), 7.06 (m, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 8.35 (d, *J* = 5.2 Hz, 1H).

[000312] To a solution of Compound **9E** (170 mg, 0.76 mmol) in EtOH (5 mL) was added LiOH (96 mg, 2.29 mmol) in water (5 mL). The mixture was stirred at rt overnight and concentrated to remove EtOH. After adjusted pH to 7 with diluted aq HCl, a lyophilization of the solution led to Compound **9F** (148 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 196 [M+]⁺.

[000313] A mixture of Compound **9F** (100 mg, 0.51 mmol), EDCI (148 mg, 0.77 mmol), HOBt (105 mg, 0.77 mmol), DIPEA (198 mg, 1.54 mmol), Intermediate **A** (142 mg, 0.51 mmol) in THF (20 mL) was stirred at rt overnight. After addition of aq sat. NaHCO₃, the mixture was extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **9** (39 mg, yield 18%) as a white solid. LC-MS (m/z): 456 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.73 (s, 4H), 2.86 (m, 11H), 4.16 (m,

5H), 4.76 (s, 0.5H), 4.87 (m, 1H), 4.98 (s, 0.5H), 6.75 (m, 4H), 6.95 (m, 1H), 7.35 (m, 1H), 8.24 (m, 1H).

Example 10



[000314] A solution of 1,4-dichloro-2-nitrobenzene (5 g, 26 mmol) in 30% methylamine alcohol solution (50 mL) was stirred at 50 °C for 4 h. The mixture was quenched with water (50 mL) and extracted with ethyl acetate (80 mL x 3). The organic layer was washed with brine (150 mL x 2) and then evaporated to give Compound **10A** (4 g, yield 84%) as a red solid. LC-MS (m/z): 187 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.95 (d, *J* = 4.8 Hz, 3H), 7.04 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 8.05 (s, 1H), 8.24 (s, 1H).

[000315] To a solution of Compound **10A** (3 g, 16 mmol) in ethanol (100 mL) was added 10 N aq HCl (2 mL) and Fe (9 g, 0.16 mmol). The mixture was stirred at 80 °C overnight. After filtration, the filtrate was washed with 3 N aq NaOH (50 mL), extracted with ethyl acetate (100 mL x 2), and dried over Na₂SO₄. Filtration and solvent evaporation led to crude Compound **10B** (2.7 g, crude) as a red solid, which was used to next step without purified. LC-MS (m/z): 157 [M+]⁺.

[000316] To a solution of Compound **10B** (2.5 g, 16 mmol) in methanol (50 mL) was added triethoxymethane (2.8 g, 19 mmol) and sulfamic acid (155 mg, 1.6 mmol). The mixture was stirred at rt for 5 h. After removal of solvents, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was dried over Na₂SO₄. Filtration and evaporation of solvents gave a crude product Compound **10C** (2.3 g, crude) as a red solid, which was used to next step without purification. LC-MS (m/z): 167 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.84 (s, 3H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 8.25 (s, 1H).

[000317] Ethyl oxalyl chloride (2.7 g, 20 mmol) was added dropwise over 20 mins to a stirred solution of Compound **10C** (2.5 g, 15 mmol) in dichloromethane (60 mL) at -20 °C. Then DIPEA (3.9 g, 30 mmol) was added and the mixture was warmed to rt and kept stirring

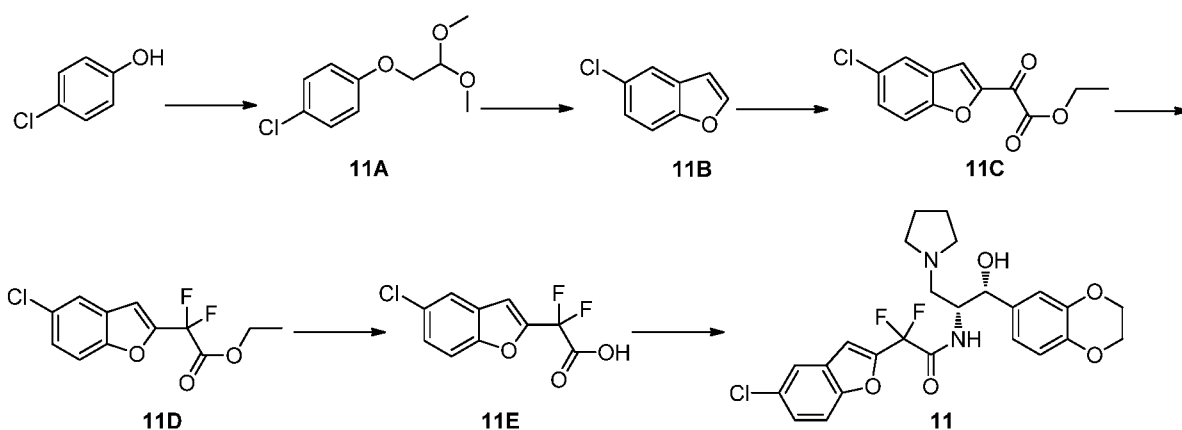
overnight. The mixture was quenched with water (50 mL) and extracted with dichloromethane (50 mL x 2). The organic layer was dried over Na₂S₀₄ before filtered and concentrated, giving a crude product. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **10D** (3.3 g, yield 83%) as yellow solid. LC-MS (m/z): 267 [M+]⁺.

[000318] To a solution of Compound **10D** (1.5 g, 5.6 mmol) in dichloromethane (30 mL) was added DAST (2.7 g, 17 mmol). The mixture was stirred at rt overnight, quenched with water (30 mL), and extracted with dichloromethane (50 mL x 2). After dried over Na₂S₀₄, the organic layer was filtered and concentrated to give the crude product Compound **10E** (0.9 g, crude) as a colorless oil, which was used for the next step without purification. LC-MS (m/z): 289 [M+]⁺.

[000319] To a solution of Compound **10E** (1 g, 3.5 mmol) in methanol (20 mL) and H₂O (10 mL) was added LiOH·H₂O (294 mg, 7 mmol). The mixture was stirred at rt for 5 h, quenched with water (30 mL), and extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na₂S₀₄. Filtration and removal of solvents led to the crude product Compound **10F** (0.4 g, crude) as a colorless oil, which was used for the next step without purification. LC-MS (m/z): 261 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 3.97(s, 3H), 7.47 (d, *J* = 10.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.86 (s, 1H).

[000320] To a solution of Intermediate **A** (0.16 g, 0.58 mmol) in dichloromethane (15 mL) was added Compound **10F** (150 mg, 0.58 mmol), EDCI (167 mg, 0.87 mmol), HOBT (116 mg, 0.87 mmol). The mixture was stirred at rt overnight, quenched with water (20 mL), extracted with dichloromethane (20 mL x 2), washed with brine (50 mL x 2), and evaporated. The crude product was purified by prep-HPLC to afford Compound **10** (29 mg, yield 9.6%) as a white solid. LC-MS (m/z): 521 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.95 (m, 4H), 3.47 (m, 6H), 3.89 (s, 3H), 4.16 (s, 4H), 4.42 (s, 1H), 4.69 (s, 1H), 5.91 (s, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 10.4 Hz, 1H), 6.81 (s, 1H), 7.50 (d, *J* = 11.2 Hz, 1H), 7.80 (d, *J* = 10.8 Hz, 2H), 8.96 (d, *J* = 9.2 Hz, 1H), 9.37 (s, 1H).

Example 11



[000321] A mixture of 4-chlorophenol (10 g, 78 mmol), 2-bromo-1,1-dimethoxyethane (13.1 g, 78 mmol), K_2CO_3 (14 g, 101 mmol), KI (100 mg) in DMF (50 mL) was stirred at reflux for 3 h. The mixture was cooled to rt and filtered. The filtrate was added water (200 mL), extracted with ethyl acetate (100 mL x 2), washed with water (100 mL x 3), brine (100 mL x 1), dried over Na_2SO_4 , concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **11A** (15 g, yield 89 %) as a colorless liquid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 3.45 (s, 6H), 3.96 (d, $J = 5.2$ Hz, 2H), 4.70 (t, $J = 5.6$ Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 2H).

[000322] A solution of polyphosphoric acid (90 g) in toluene was heated to 90 °C. To this solution was added Compound **11A** (15.4 g, 71 mmol) in toluene (20 mL), followed by stirring at 90 °C for 3 h. The mixture was poured into ice and stirred for 30 min. It was extracted with ethyl acetate (2 x 100 mL), washed with brine (100 mL x 1), dried over Na_2SO_4 , concentrated and purified by column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **11B** (4.5 g, yield 50%) as a red liquid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 6.72 (m, 1H), 7.24 (dd, $J_1, J_2 = 8.8, 2.4$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.63 (d, $J = 2.4$ Hz, 1H).

[000323] To a solution of Compound **11B** (4.5 g, 30 mmol) in THF (20 mL) was added n-BuLi (14 mL) at -78 °C under N_2 . Stirred for 30 min, to the mixture was added diethyl oxalate (10.8 g, 74 mmol). The mixture was stirred at -78 °C for 1 h before the addition of aq sat. NH_4Cl . It was extracted with ethyl acetate (50 mL x 2), washed with sat. $NaHCO_3$ (50 mL x 2), brine (50 mL x 1), dried over Na_2SO_4 , concentrated and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to give Compound **11C** (3.5 g, yield 47%) as a yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) major characteristic peaks: δ

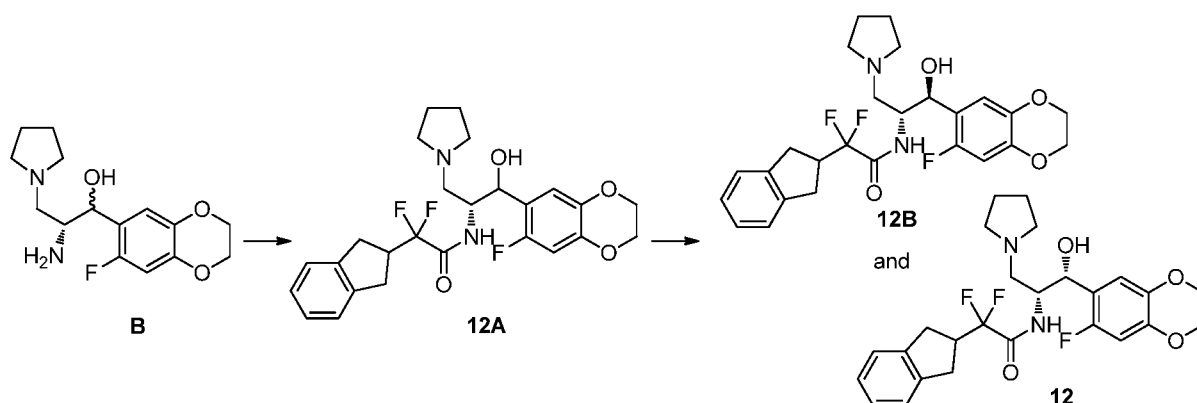
(ppm) 1.37 (t, $J = 6.8$ Hz, 3H), 4.41 (q, $J = 6.8$ Hz, 2H), 7.64 (m, 1H), 7.82 (d, $J = 8.8$ Hz, 1H), 8.03 (d, $J = 2.4$ Hz, 1H), 8.19 (s, 1H).

[000324] To a solution of Compound **11C** (1 g, 3.95 mmol) in DCM (50 mL) was added DAST (3.18 g, 18 mmol) at 0 °C, then the mixture was stirred at rt overnight. The reaction was quenched by addition of ice-water and sat. aq NaHCO₃ (20 mL). It was then extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and evaporated to remove solvents. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **11D** (700 mg, yield 65%) as a yellow liquid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.37 (t, $J = 6.8$ Hz, 3H), 4.41 (q, $J = 6.8$ Hz, 2H), 7.10 (s, 1H), 7.36 (m, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H).

[000325] To a solution of Compound **11D** (120 mg, 0.44 mmol) in EtOH (5 mL) was added LiOH (46 mg, 1.09 mmol) in water (5 mL). The mixture was stirred at rt overnight, followed by removal of EtOH. It was adjusted to pH 7 with diluted HCl and freeze-dried to give Compound **HE** (100 mg, crude) which was used for the next step without further purification. LC-MS (m/z): 245 [M-1]⁻.

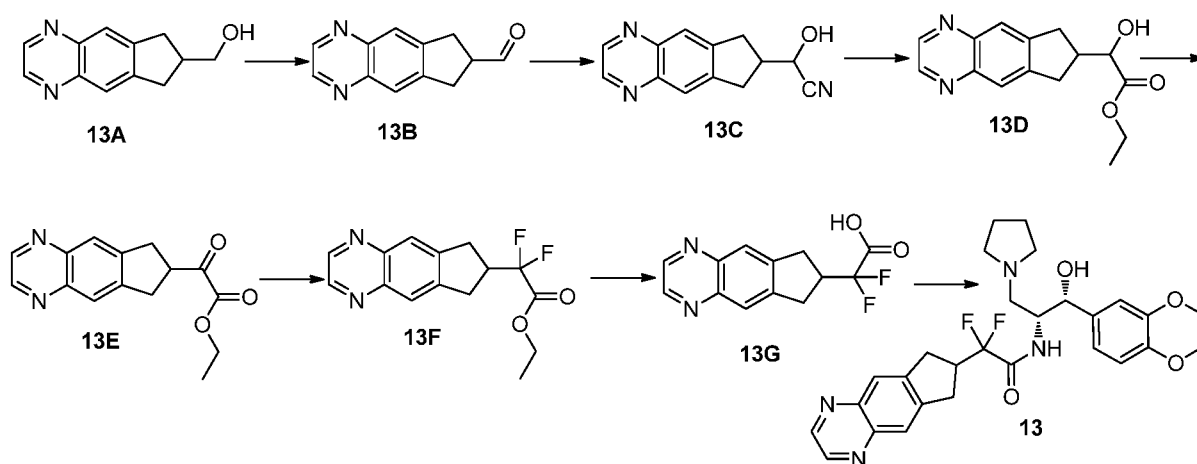
[000326] A mixture of Compound **HE** (100 mg, 0.41 mmol), EDCI (117 mg, 0.61 mmol), HOBT (83 mg, 0.61 mmol), Intermediate **A** (115 mg, 0.41 mmol) in DCM (20 mL) was stirred at rt overnight. The reaction was quenched by addition of sat. NaHCO₃. The resulting mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by prep-HPLC to give Compound **11** (49 mg, yield 24%) as a white solid. LC-MS (m/z): 507 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 2.91 (m, 2H), 3.48 (s, 2H), 3.84 (s, 2H), 4.15 (m, 4H), 4.46 (m, 1H), 5.13 (s, 1H), 6.77 (s, 3H), 6.84 (s, 1H), 7.35 (m, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 2.0$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 11.68 (s, 1H).

Example 12



[000327] To a mixture of Intermediate **B** (300 mg, 1 mmol) in DCM (15 mL) was added EDCI (400 mg, 2 mmol), HOBt (264 mg, 2 mmol) and Compound **1H** (300 mg, 1.5 mmol) and stirred at rt overnight. The reaction mixture was poured into water (50 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford a crude product **12A** (100 mg, yield 20%) as a white solid. The chiral resolution on Compound **12A** was achieved using chiral-prep-HPLC to give Compound **12B** (70 mg) and **12** (1.2 mg). For Compound **12B**, LCMS: 491 $[\text{M}+\text{I}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.82 (m, 4H), 2.82 (m, 7H), 3.04 (m, 3H), 3.19 (m, 1H), 4.16 (m, 1H), 4.26 (m, 4H), 5.05 (m, 1H), 6.56 (d, $J = 10.8$ Hz, 1H), 6.69 (m, 1H), 7.06 (d, $J = 7.2$ Hz, 1H), 7.16 (m, 4H). For Compound **12**, LCMS: 491 $[\text{M}+\text{I}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.23 (m, 4H), 2.67 (m, 1H), 2.82 (m, 1H), 2.97 (m, 2H), 3.12 (m, 2H), 3.65 (m, 1H), 3.81 (m, 1H), 3.89 (m, 1H), 4.03 (m, 1H), 4.12 (m, 1H), 4.18 (m, 1H), 4.47 (m, 1H), 5.43 (m, 1H), 6.60 (d, $J = 11.2$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 1H), 7.16 (m, 5H).

Example 13



[000328] To a solution of Compound **13A** (2.00 g, 10 mmol) in DCM (50 mL) was added DMP (7.44 g, 18 mmol). The mixture was stirred at rt for 2 h and filtered. The filtrate was washed with sat. aq NaHCO₃ (50 mL x 2), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to get Compound **13B** (1.2 g, yield 56%) as a white solid. LC-MS (m/z): 199 [M+]⁺.

[000329] Compound **13B** (1.13 g, 5 mmol) was added to a solution of sodium metabisulfate (1.55 g, 8.2 mmol) in water (35 mL). The mixture was vigorously stirred for 2 h at rt, before the addition of NaCN (800 mg, 16 mmol). After stirred overnight, the reaction mixture was poured to a mixture of water (30 mL) and THF(10 mL). It was then extracted with ethyl acetate (100 mL x 2), washed with brine (00 mL), dried over Na₂SO₄, and concentrated to give Compound **13C** (1.15 g, 81%) as a white solid. LC-MS (m/z): 226 [M+]⁺.

[000330] To a solution of Compound **13C** (1.15 g, 5 mmol) in EtOH (20 mL) was bubbled with a gentle stream of HCl (gas) (dried over con.H₂SO₄) at 0 °C for 5 h. Water (20 mL) was added to the mixture and stirred at rt for 2 h. It was adjusted to pH = 7 with diluted NaOH (2M), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to get Compound **13D** (1 g, yield 69%) as a colorless oil. LC-MS (m/z): 273 [M+]⁺.

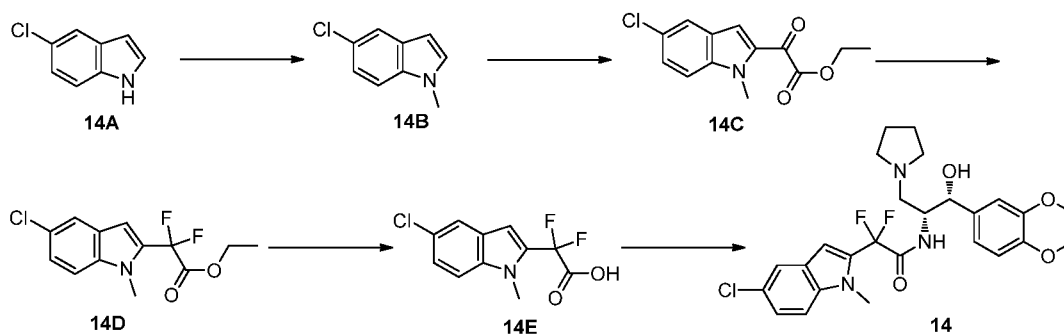
[000331] To a solution of Compound **13D** (2.72 g, 10 mmol) in DCM (50 mL) was added DMP (7.44 g, 18 mmol). The mixture was stirred at rt for 2 h and filtered. The filtrate was washed with sat. aq NaHCO₃ (50 mL x 2), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to get Compound **13E** (1.2 g, yield 56%) as a white solid. LC-MS (m/z): 271 [M+]⁺.

[000332] To a solution of Compound **13E** (540 mg, 2 mmol) in DCM (20 mL) was added DAST (1.1 g, 6.78 mmol) at 0 °C, then the mixture was stirred at rt overnight. The reaction mixture was quenched by pouring into ice-water. After neutralized with sat. NaHCO₃ (20 mL), the mixture was extracted with DCM (2 x 50 mL), washed with brine (1 x 50 mL), dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to yield Compound **13F** (170 mg, yield 34%) as a colorless oil. LC-MS (m/z): 293 [M+]⁺.

[000333] To a solution of Compound **13F** (293 mg, 1 mmol) in EtOH (5 mL) was added LiOH (96 mg, 2.29 mmol) in water (5 mL). The mixture was stirred at rt overnight, concentrated to remove EtOH, and adjusted to pH 7 with diluted HCl. It was then lyophilized to give Compound **13G** (148 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 265 [M+]⁺.

[000334] A mixture of Compound **13G** (132 mg, 0.51 mmol), EDCI (148 mg, 0.77 mmol), HOBT (105 mg, 0.77 mmol), DIPEA (198 mg, 1.54 mmol), Intermediate **A** (142 mg, 0.51 mmol) in THF (20 mL) was stirred at rt overnight. After the addition of sat. aq NaHCO₃, the mixture was extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by prep-HPLC to give Compound **13** (39 mg, yield 18%) as a white solid. LC-MS (m/z): 525 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.84 (m, 4H), 2.75 (m, 4H), 3.03 (m, 6H), 4.22 (m, 6H), 5.11 (m, 1H), 6.90 (m, 4H), 7.85 (s, 2H), 8.76 (s, 2H).

Example 14



[000335] To a solution of Compound **14A** (1.21 g, 8 mmol) in THF (20 mL) was added NaH (480 mg, 12 mmol) under N₂ atmosphere. The mixture was stirred at 0 °C for 1 h. CH₃I (0.47 mL, 16 mmol) was added. The mixture was stirred at 25 °C for additional 2 h. It was diluted with NH₄Cl (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (60 mL), dried over Na₂SO₄, and concentrated to give a crude product, which was purified by column chromatography on silica gel (ethyl acetate in petroleum 10% v/v) to yield Compound **14B** (1.2 g, yield 90%) as a red oil. LCMS (m/z): 166 [M+]⁺. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.76 (s, 3H), 6.40 (d, *J* = 3.2 Hz, 1H), 7.05 (d, *J* = 3.2 Hz, 1H), 7.16 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 1.6 Hz, 1H).

[000336] To a solution of Compound **14B** (1.04 g, 6 mmol) in THF (20 mL) was added *n*-BuLi (3 mL, 8 mmol) at -78 °C under the protection of nitrogen. Then it was allowed to warm up to rt over one hour. At this point, diethyl oxalate (2.1 mL, 16 mmol) was added to

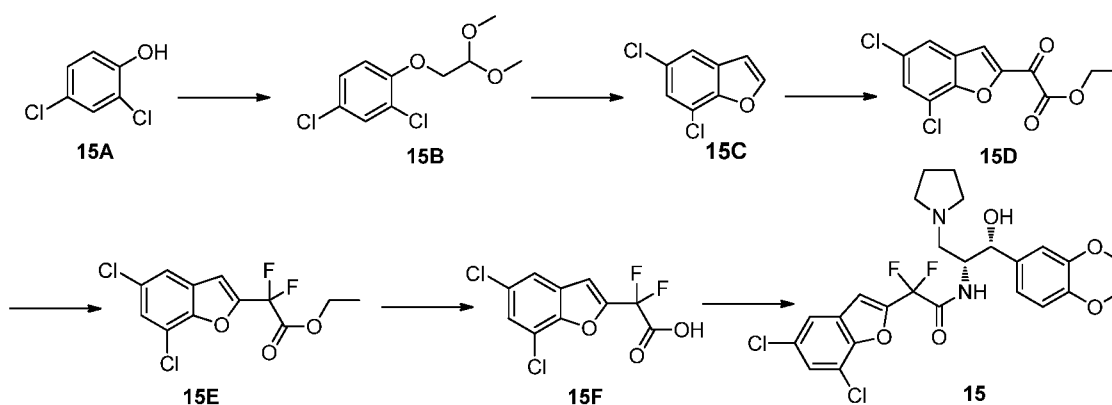
the mixture at - 78 °C and then it was allowed to warm up to rt over one hour. The mixture was quenched with sat. aq NH₄Cl. The organic phase was washed with brine, dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (ethyl acetate in petroleum 3% to 10 % v/v) to afford Compound **14C** (1.38 g, yield 86%) as a yellow solid. LCMS (m/z): 266 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.45 (t, *J* = 7.2 Hz, 3H), 4.08 (s, 3H), 4.45 (q, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.53 (s, 1H), 7.69 (d, *J* = 1.6 Hz, 1H).

[000337] To a solution of Compound **14C** (530 mg, 2 mmol) in DCM (20 mL) was added DAST (1.6 mL, 12 mmol) at 0 °C under N₂ and stirred at 25 °C overnight. It was poured into 50 mL of ice-water and extracted with DCM (20 mL x 3). The combined organic phase was washed with brine, and dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (ethyl acetate in petroleum, 10% v/v) to yield Compound **14D** (195 mg, yield 33%) as yellow oil. LCMS (m/z): 288[M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.37 (t, *J* = 8.8 Hz, 3H), 3.86 (s, 3H), 4.40 (q, *J* = 8.8 Hz, 2H), 6.73 (s, 1H), 7.28 (s, 2H), 7.60 (s, 1H).

[000338] To a solution of Compound **14D** (195 mg, 0.68 mmol) in THF/MeOH/water (6 mL, 1:1:1, v/v) was added LiOH·H₂O (34 mg, 0.81mmol). The mixture was stirred at 25 °C for 1 h. After removal of the solvents, it was adjust pH to 6 with 1N HCl. The mixture was dissolved ethyl acetate (100 mL), washed with water, brine, and dried over anhydrous Na₂SO₄. Removal of solvent by evaporation led to a crude product Compound **14E** (140 mg, yield 80%) was got as a yellow solid, which was used for the next step without purification. LCMS (m/z): 260 [M+1]⁺.

[000339] To a mixture of Compound **14E** (70 mg, 0.27 mmol) in DCM (20 mL) was added EDCI (78 mg, 0.40 mmol), HOBt (54 mg, 0.40 mmol) and Intermediate **A** (66 mg, 0.27 mmol) and stirred at 25 °C for overnight. The reaction was quenched with addition of water (10 mL). The mixture was extracted with DCM (20 mL x 3), dried over anhydrous Na₂SO₄, and purified by prep-HPLC to give a trifluoroacetic acid salt of Compound **14** (80 mg, yield 56%) as a colorless solid. LCMS (m/z): 529 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (m, 4H), 2.70-2.91 (m, 2H), 3.06-3.43 (s, 2H), 3.73 (s, 3H), 3.86 (s, 2H), 4.00-4.09 (m, 1H), 4.09-4.21 (m, 2H), 4.49 (s, 1H), 5.17 (s, 1H), 6.09 (s, 1H), 6.76-6.80 (m, 2H), 6.83 (s, 1H), 7.23-7.24 (m, 2H), 7.54 (s, 2H).

Example 15



[000340] A mixture of Compound **15A** (12.64 g, 78 mmol), 2-bromo-1,1-dimethoxyethane (13.6 g, 79 mmol), K_2CO_3 (14 g, 101 mmol), KI (100 mg) in DMF (50 mL) was stirred at reflux for 3 h, and then cooled to rt, and filtered. The filtrate was diluted with water (200 mL), extracted with ethyl acetate (100 mL x 2), washed with water (100 mL x 3), brine (100 mL x 1), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **15B** (17.2 g, yield 88%) as a red liquid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 3.49 (s, 6H), 4.02 (d, $J = 5.2$ Hz, 2H), 4.73 (t, $J = 5.6$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 1H), 7.15-7.18 (dd, $J = 2.8, 8.8$ Hz, 1H), 7.36 (d, $J = 2.8$ Hz, 1H).

[000341] A solution of polyphosphoric acid (90 g) in toluene was stirred to 90°C, then to the solution was added Compound **15B** (15 g, 60 mmol) in toluene (20 mL). The mixture was stirred at 90 °C for 3 h before it was poured into ice and stirred for 30 min. It was then extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (petroleum ether, 100% v/v) to give Compound **15C** (2.6 g, yield 23%) as a white solid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 6.76 (d, $J = 2.4$ Hz, 1H), 7.30 (d, $J = 2.0$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.69 (d, $J = 2.4$ Hz, 1H).

[000342] To a solution of Compound **15C** (1.6 g, 8.6 mmol) in THF (10 mL) was added *n*-BuLi (4.2 mL) at -78 °C under N_2 . After stirred for 30 min, to the mixture was added diethyl oxalate (10.8 g, 74 mmol). It was stirred at -78 °C for 1 h before it was quenched by addition of aq sat. NH_4Cl . The mixture was sequentially extracted with ethyl acetate (50 mL x 2), washed with sat. $NaHCO_3$ (50 mL x 2), brine (50 mL x 1), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to yield Compound **15D** (1.64 g, yield 67%) as a yellow solid. 1H -NMR

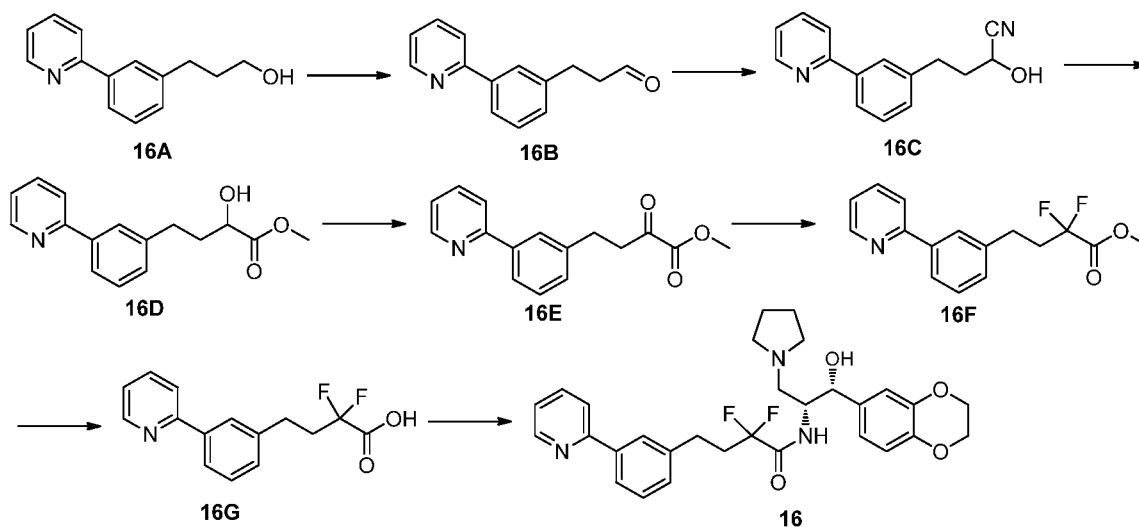
(CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.46 (t, $J = 7.2$ Hz, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.54 (m, 1H), 7.66 (d, $J = 1.6$ Hz, 1H), 8.04 (s, 1H).

[000343] To a solution of Compound **15D** (500 mg, 1.75 mmol) in DCM (15 mL) was added DAST (1.15 g, 8.74 mmol) at 0 °C. The mixture was stirred at rt overnight before it was poured into ice-water, and followed by addition of aq sat. aq NaHCO₃ (20 mL). The resulted mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated to give a crude product, which was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **15E** (269 mg, yield 50%) as a red liquid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.37 (t, $J = 6.8$ Hz, 3H), 4.44 (q, $J = 7.2$ Hz, 2H), 7.14 (s, 1H), 7.41 (m, 1H), 7.54 (m, 1H).

[000344] To a solution of Compound **15E** (260 mg, 0.88 mmol) in EtOH (0.5 mL) was added LiOH (46 mg, 1.09 mmol) in water (0.5 mL). The mixture was stirred at rt overnight, evaporated to remove EtOH, and neutralized with diluted HCl. This aqueous solution was lyophilized to yield a crude Compound **15F** (193 mg), which was used for the next step without further purification. LC-MS (m/z): 279 [M-1]⁻.

[000345] A mixture of Compound **15F** (70 mg, 0.25 mmol), EDCI·HCl (71 mg, 0.37 mmol), HOBT (50 mg, 0.37 mmol), Intermediate **A** (61 mg, 0.25 mmol) in DCM (10 mL) was stirred at 28 °C overnight. The reaction was quenched by addition of aq sat. NaHCO₃. The mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated to give a crude product, which was purified by prep-HPLC to afford Compound **15** (46.3 mg, yield 23%) as a white solid. LC-MS (m/z): 541 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.12-2.17 (m, 4H), 2.93-2.99 (m, 2H), 3.45-3.55 (m, 2H), 3.82-3.92 (m, 3H), 4.10-4.16 (m, 4H), 4.52 (s, 1H), 5.05 (s, 1H), 6.70-6.83 (m, 4H), 7.40 (s, 1H), 7.49 (s, 1H), 7.94-7.96 (d, $J = 8.0$ Hz, 1H), 11.53 (s, 1H).

Example 16



[000346] The mixture of Compound **16A** (4.10 g, 19.25 mmol) in DCM (100 mL) was added DMP (9.79 g, 23.09 mmol) at rt. After stirred at rt for 1 h the mixture was diluted with ethyl acetate (200 mL), filtered to remove solid, washed with water and brine, and purified by silica gel chromatography (ethyl acetate in petroleum ether, 20% v/v) to give Compound **16B** (3.10 g, yield 76%) as a colorless oil. LCMS (m/z): 212 [M+]⁺, ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.90 (t, *J* = 9.2 Hz, 2H), 3.06 (t, *J* = 9.2 Hz, 2H), 7.25-7.32 (m, 2H), 7.43 (t, *J* = 12.8 Hz, 1H), 7.78-7.93 (m, 4H), 8.74 (s, 1H), 9.86 (s, 1H).

[000347] A mixture of Compound **16B** (3.00 g, 14.22 mmol) and 2NaO₅S₂ (2.70 g, 14.22 mmol) in H₂O/dioxane (50/10 mL) was stirred at rt for 2 h. After the addition of NaCN (1.39 g, 28.43 mmol), the mixture was stirred at rt overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to yield Compound **16C** (2.00 g, yield 59%) as a colorless oil. LCMS (m/z): 239 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.05-2.26 (m, 2H), 2.83-2.96 (m, 2H), 4.36 (t, *J* = 6.8 Hz, 1H), 4.97 (s, 1H), 7.22-7.31 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.69-7.82 (m, 4H), 8.68 (s, 1H).

[000348] A solution of Compound **16C** (2.00 g, 8.40 mmol) in MeOH (50 mL) was stirred at rt for 6 h with HCl gas bubbling. The reaction was quenched with H₂O (10 mL) and stirred at rt for 1 h. It was diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂SO₄, and evaporated to give Compound **16D** (1.90 g, yield 83%) as colorless oil. LCMS (m/z): 272 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.96-2.06 (m, 1H), 2.14-2.23 (m, 1H), 2.83-2.90 (m, 2H), 3.75 (s, 3H), 4.21-

4.24 (m, 1H), 7.21-7.29 (m, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.22-7.80 (m, 3H), 7.87 (s, 1H), 8.70 (s, 1H).

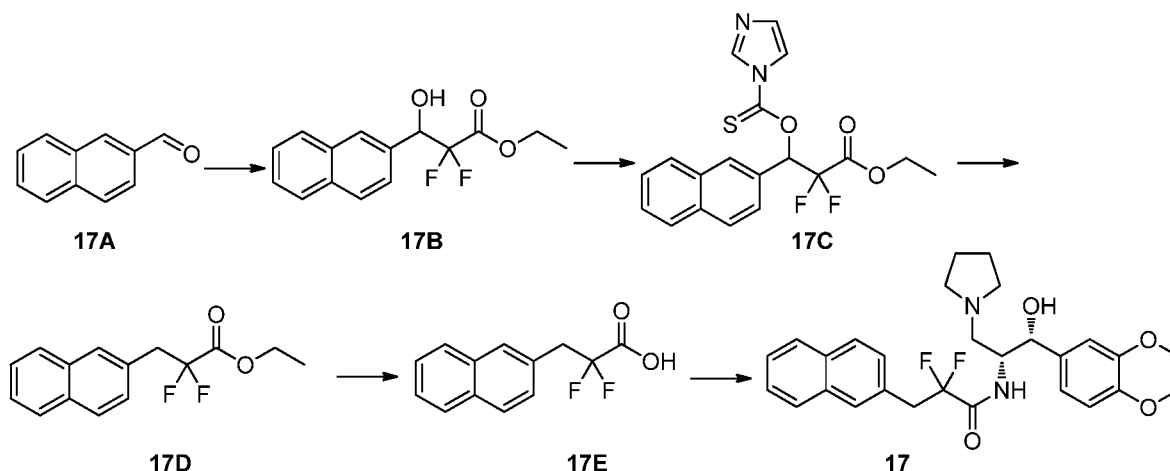
[000349] To a solution of Compound **16D** (800 mg, 2.95 mmol) in DCM (20 mL) was added DMP (1.50 g, 3.54 mmol). The mixture was stirred at rt for 2 h. It was then diluted with ethyl acetate (150 mL), filtered to remove solid, washed with water and brine, dried with anhydrous Na_2SO_4 , and purified by silica gel column chromatography (ethyl acetate in PE, 30% v/v) to yield Compound **16E** (300 mg, yield 38%) as a colorless oil. LCMS (m/z): 270 [M+]⁺, 1H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.07 (t, $J = 7.2$ Hz, 2H), 3.28 (t, $J = 7.2$ Hz, 2H), 3.86 (m, 3H), 7.25-7.35 (m, 2H), 7.43 (t, $J = 7.2$ Hz, 1H), 7.78-7.93 (m, 4H), 8.74 (s, 1H).

[000350] To a solution of Compound **16E** (400 mg, 1.48 mmol) in DCM (15 mL) was added DAST (1.23 g, 7.43 mmol) at rt. The mixture was stirred at rt overnight. It was then diluted with ethyl acetate (150 mL), washed with saturated NaHCO_3 , water and brine, purified by silica gel column chromatography (ethyl acetate in petroleum ether, 40% v/v) to afford Compound **16F** (120 mg, yield 28%) as a white solid. LCMS (m/z): 292 [M+]⁺.

[000351] A mixture of Compound **16F** (120 mg, 0.41 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (52 mg, 1.24 mmol) in THF/MeOH/ H_2O (5/5/2 mL) was stirred at rt for 2 h. It was adjusted to pH 6 with 1 M HCl and purified by prep-HPLC to give Compound **16G** (80 mg, yield 70%>) as white solid. LCMS (m/z): 278 [M+]⁺; 1H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.40-2.53 (m, 2H), 2.89-2.93 (m, 2H), 7.26-7.37 (m, 2H), 7.42 (t, $J = 7.2$ Hz, 1H), 7.73-7.88 (m, 4H), 8.72 (s, 1H).

[000352] A solution of Intermediate **A** (80 mg, 0.29 mmol), Compound **16G** (80 mg, 0.29 mmol), EDCI (83 mg, 0.44 mmol) and HOBt (59 mg, 0.44 mmol) in DCM (5 mL) was stirred at rt overnight. It was then diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to afford Compound **16** (50 mg, yield 32%>) as a white solid. LCMS (m/z): 538 [M+]⁺; 1H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.58 (br s, 2H), 1.86 (s, 4H), 2.21-2.42 (m, 3H), 2.56-2.64 (m, 1H), 2.75-2.85 (m, 3H), 3.02 (s, 2H), 3.88-4.06 (m, 4H), 4.21 (s, 1H), 5.12 (s, 1H), 6.78-6.87 (m, 4H), 7.14 (d, $J = 7.6$, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.72-7.82 (m, 4H), 8.69 (s, 1H).

Example 17



[000353] To a solution of Compound **17A** (3.12 g, 20 mmol) in anhydrous tetrahydrofuran (80 mL) was added zinc (2.1 g, 26 mmol). The mixture was heated at 75 °C under N₂ atmosphere and ethyl 2-bromo-2,2-difluoroacetate (3.2 mL, 29 mmol) was slowly added. The mixture was heated under the same conditions for 2 h. After cooling, it was filtered. The filtrate was concentrated to give a crude product which was purified by column chromatography on silica gel (ethyl acetate in petroleum 5% to 20% v/v) to yield Compound **17B** (3.9 g, yield 70%) as a white solid. LCMS (m/z): 281 [M+]⁺. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.26 (t, *J* = 7.2 Hz, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 5.34 (q, *J* = 8 Hz, 1H), 7.50-7.56 (m, 3H), 7.83-7.88 (m, 3 3H), 7.91 (s, 1H)

[000354] To a solution of Compound **17B** (280 mg, 1 mmol) in DCM (20 mL) was added dropwise *N,N'*-thiocarbonyldiimidazole (25.0 g, 126 mmol) in DCM (10 mL) at 72 °C. After stirring for 3 h, the reaction mixture was cooled to rt and concentrated in vacuum to give a crude product. It was purified by silica gel column chromatography (ethyl acetate in petroleum 5% to 20% v/v) to afford Compound **17C** (310 mg, yield 79%) as a yellow oil. LCMS (m/z): 391 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.24 (t, *J* = 7.2 Hz, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 6.98 (m, 1H), 7.10 (s, 1H), 7.53-7.55 (m, 3H), 7.70 (s, 1H), 7.84-7.90 (m, 3H), 7.94 (s, 1H), 8.43 (s, 1H).

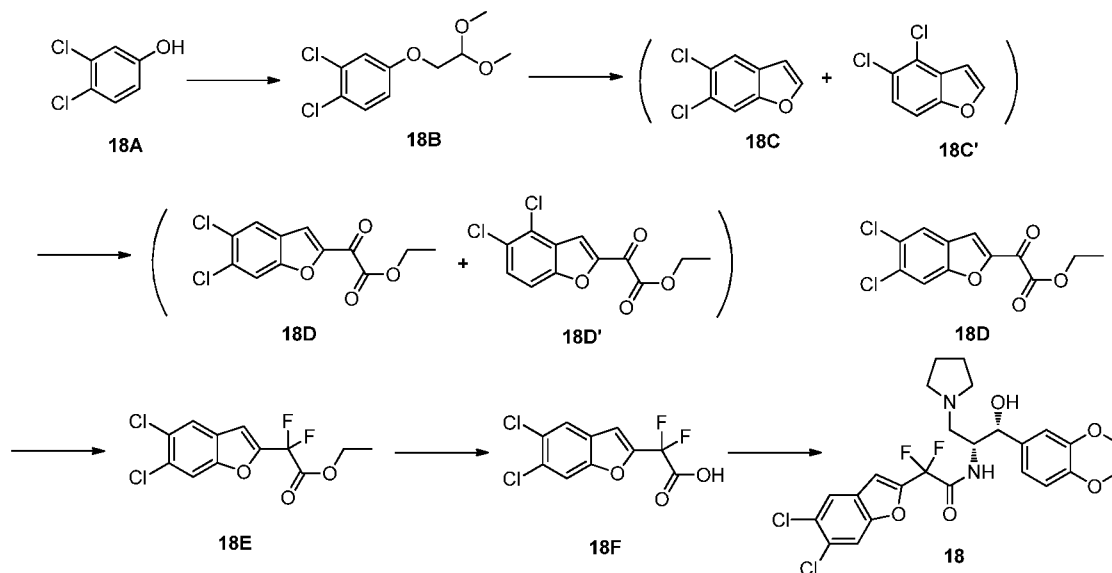
[000355] To a solution of n-Bu₃SnH (922 mg, 1.59 mmol) and AIBN (2 mg, cat.) in refluxing toluene (10 ml) was added dropwise the Compound **17C** (310 mg, 0.79 mmol) in toluene (10 ml). After stirred for 3 h at 110 °C, the reaction mixture was cooled to rt and concentrated in vacuum to give a crude product Compound **17D** (500 mg, crude) as a yellow oil. It was used for the next step without purification. LCMS (m/z): 265 [M+]⁺.

[000356] To a solution of Compound **17D** (500 mg, 0.79 mmol) in THF/MeOH/water (3 mL, 1:1:1, v/v) was added LiOH·H₂O (60 mg, 1.5 mmol). The mixture was stirred at 25 °C

for 1 h. After the addition of water (20 mL), the mixture was extracted with ethyl acetate (20 mL x 2). The water phase was adjusted pH to 6 with 1 N HCl and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a crude product Compound **17E** (169 mg, yield 80%) as a white solid. LCMS (m/z): 235 $[\text{M}-1]^-$; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 3.59 (t, $J = 17.2$ Hz, 2H), 7.42 (d, $J = 8$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 7.82 (s, 1H), 7.90 (t, $J = 8$ Hz, 3H), 14.75 (s, 1H).

[000357] To a mixture of Compound **17E** (67 mg, 0.25 mmol) in DCM (10 mL) was added EDCI (72 mg, 0.38 mmol), HOBT (51 mg, 0.38 mmol) and Intermediate **A** (61 mg, 0.25 mmol) and stirred at 25 °C overnight. After the addition of water (10 mL), the mixture was extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford trifluoroacetic acid salt of Compound **17** (47 mg, yield 27%) as a white solid. LCMS (m/z): 496 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.62-2.03 (m, 4H), 2.53 (s, 1H), 2.95 (s, 1H), 3.33-3.56 (m, 4H), 3.94 (s, 2H), 4.19 (s, 4H), 4.25 (s, 1H), 4.89 (s, 1H), 6.60 (d, $J = 8$ Hz, 1H), 6.71 (d, $J = 8$ Hz, 1H), 6.78 (s, 1H), 7.34 (t, $J = 8$ Hz, 2H), 7.48 (d, $J = 8$ Hz, 2H), 7.70 (s, 1H), 7.77-7.83 (m, 3H), 11.31 (s, 1H).

Example 18



[000358] A mixture of Compound **18A** (30 g, 184 mmol), 2-bromo-1,1-dimethoxyethane (37 g, 221 mmol), K_2CO_3 (38 g, 276 mmol), KI (600 mg) in DMF (150 mL) was stirred at reflux overnight. Cooling to rt, it was filtered. The filtrate was diluted with water (500 mL), extracted with ethyl acetate (250 mL x 2), washed with water (250 mL x 3) and brine (250 mL), dried over Na_2SO_4 , and evaporated to dryness to yield a crude

Compound **18B** (46 g, yield 100%), which was used for the next step without further purification.

[000359] A solution of polyphosphoric acid (75 g) in toluene was stirred to 90 °C, then to the solution was added Compound **18B** (46 g) in toluene (20 mL). The mixture was stirred at 90 °C for 4 h, then poured into ice, and stirred for 30 min. Cooling to rt, the mixture was extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL), dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (petroleum ether, 100% v/v) to yield a mixture of Compound **18C** and Compound **18C** (7 g, yield 21%) as a white solid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 6.69 (d, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 7.34 (s, 2H), 7.61 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.65 (s, 1H).

[000360] To a solution of Compound **18C** and **18C** (8 g, 42.8 mmol) in THF (60 mL) was added n-BuLi (20 mL) at -78 °C under N₂. After stirred for 30 min, diethyl oxalate (6 g, 51 mmol) was added to the mixture and it was stirred at -78 °C for 1 h, followed by the addition of aq sat. NH₄Cl. The resulting mixture was extracted with ethyl acetate (100 mL x 2), washed with aq sat. NaHCO₃ (100 mL x 2), brine (100 mL), dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to give Compound **18D** (2.5 g, yield 19%) and Compound **18D'** (250 mg, yield 1.9%) as a yellow solid. Compound **18D**: LC-MS (m/z): 287 [M]⁻; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.45 (t, *J* = 6.8 Hz, 3H), 4.45 (q, *J* = 6.8 Hz, 2H), 6.79 (d, *J* = 2.4 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.83 (s, 1H). Compound **18D'**: LC-MS (m/z): 287 [M+1T]; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.47 (t, *J* = 6.8 Hz, 3H), 4.50 (q, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 8.12 (s, 1H).

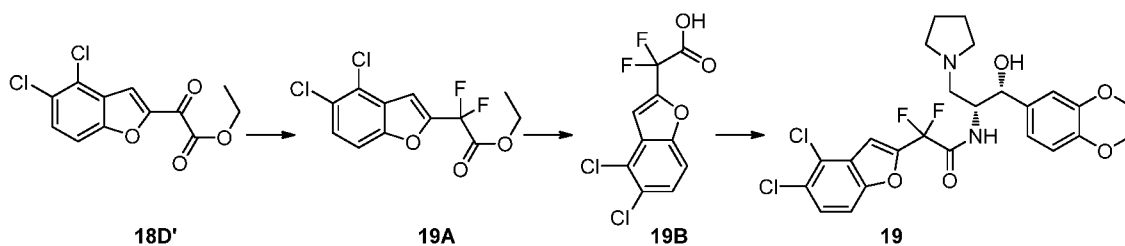
[000361] To a solution of Compound **18D** (750 mg, 2.6 mmol) in DCM (50 mL) was added DAST (2.5 g, 15.7 mmol) at 0 °C and the mixture was stirred at rt overnight. It was poured into ice-water, followed by addition of aq sat. aq NaHCO₃ (20 mL). The resulted mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to render Compound **18E** (350 mg, yield 51%) as a yellow liquid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.26 (t, *J* = 6.8 Hz, 3H), 4.31 (q, *J* = 6.8 Hz, 2H), 6.71 (d, *J* = 1.6 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.76 (s, 1H).

[000362] To a solution of Compound **18E** (150 mg, 0.5 mmol) in THF (20 mL) was added LiOH (24 mg, 0.6 mmol) in water (5 mL) and the mixture was stirred at rt 3 h. It was

concentrated by removal of EtOH and adjusted to pH 7 with diluted HCl. Lyophilization of the solution led to Compound **18F** (124 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 280 [M-1]⁻; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 7.17 (s, 1H), 8.24 (s, 1H), 8.26 (s, 1H).

[000363] A mixture of Compound **18F** (124 mg, 0.44 mmol), EDCI (117 mg, 0.61 mmol), HOBt (83 mg, 0.61 mmol), Intermediate **A** (115 mg, 0.41 mmol) in DCM (20 mL) was stirred at rt overnight. To the mixture was added dropwise aq sat. NaHCO₃. It was then extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **18** (78 mg, yield 26%) as a white solid. LC-MS (m/z): 541 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 2.89 (m, 2H), 3.09 (brs, 1H), 3.37 (brs, 1H), 3.62 (brs, 1H), 3.87 (brs, 2H), 4.25 (s, 4H), 4.36 (m, 1H), 5.21 (s, 1H), 6.75 (s, 1H), 6.83 (s, 2H), 6.89 (s, 1H), 7.62 (d, *J* = 2 Hz, 1H), 7.68 (d, *J* = 2 Hz, 1H), 7.80 (s, 1H), 11.41 (s, 1H).

Example 19

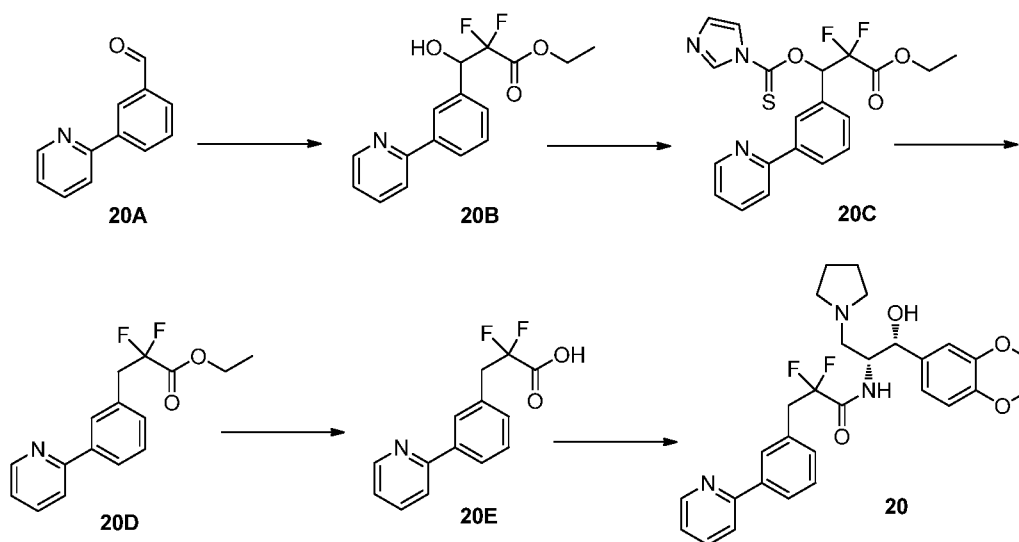


[000364] To a solution of Compound **18D'** (240 mg, 0.84 mmol) in DCM (11 mL) was added DAST (740 mg, 4.59 mmol) at 0 °C and the mixture was stirred at rt overnight. The reaction was quenched by pouring the mixture into ice-water, and followed with addition of sat. aq NaHCO₃ (20 mL). It was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to render Compound **19A** (245 mg, yield 94.8%) as a yellow liquid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.35-1.40 (m, 3H), 4.35-4.44 (m, 2H), 7.23 (s, 1H), 7.40-7.42 (d, *J* = 8.8 Hz, 1H), 7.46-7.48 (d, *J* = 8.8 Hz, 1H).

[000365] To a solution of Compound **19A** (245 mg, 0.795 mmol) in THF (10 mL) was added LiOH (63 mg, 1.49 mmol) in water (5 mL) and the mixture was stirred at rt for 4 h. The mixture was concentrated by removal of solvent and then adjusted pH to 6 with diluted HCl. Lyophilization of the solution gave rise to Compound **19B** (210 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 279 [M-1]⁻.

[000366] A mixture of Compound **19B** (135 mg, 0.48 mmol), EDCI (135 mg, 0.70 mmol), HOBT (94 mg, 0.69 mmol), Intermediate **A** (130 mg, 0.47 mmol) in DCM (20 mL) was stirred at rt overnight. The mixture was diluted with aq sat. NaHCO_3 , extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC to give **19** (83 mg, yield 32%) as a white solid. LC-MS (m/z): 541.2 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.11 (s, 4H), 2.91-2.99 (m, 2H), 3.41-3.42 (m, 1H), 3.56-3.62 (m, 1H), 3.78 (s, 1H), 3.94-3.80 (m, 2H), 4.11-4.15 (m, 4H), 4.48 (s, 1H), 5.03 (s, 1H), 6.69-6.77 (m, 2H), 6.80 (s, 1H), 7.35-7.38 (d, $J = 9.2$ Hz, 1H), 7.44-7.46 (d, $J = 8.8$ Hz, 1H), 8.02-8.04 (d, $J = 8.8$ Hz, 1H), 11.70 (s, 1H).

Example 20



[000367] To a solution of Compound **20A** (2.2 g, 12 mmol) in anhydrous tetrahydrofuran (80 mL) was added zinc (1.01 g, 15.6 mmol). The mixture was heated at 75 °C under N_2 atmosphere and ethyl 2-bromo-2,2-difluoroacetate (1.9 mL, 15 mmol) was slowly added. The mixture was heated under the same conditions for 2 h. After cooling, it was filtered. The filtrate was concentrated to give a crude product, which was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **20B** (1.9 g, yield 58%) as a colorless oil. LCMS (m/z): 309 $[\text{M}+1]^+$.

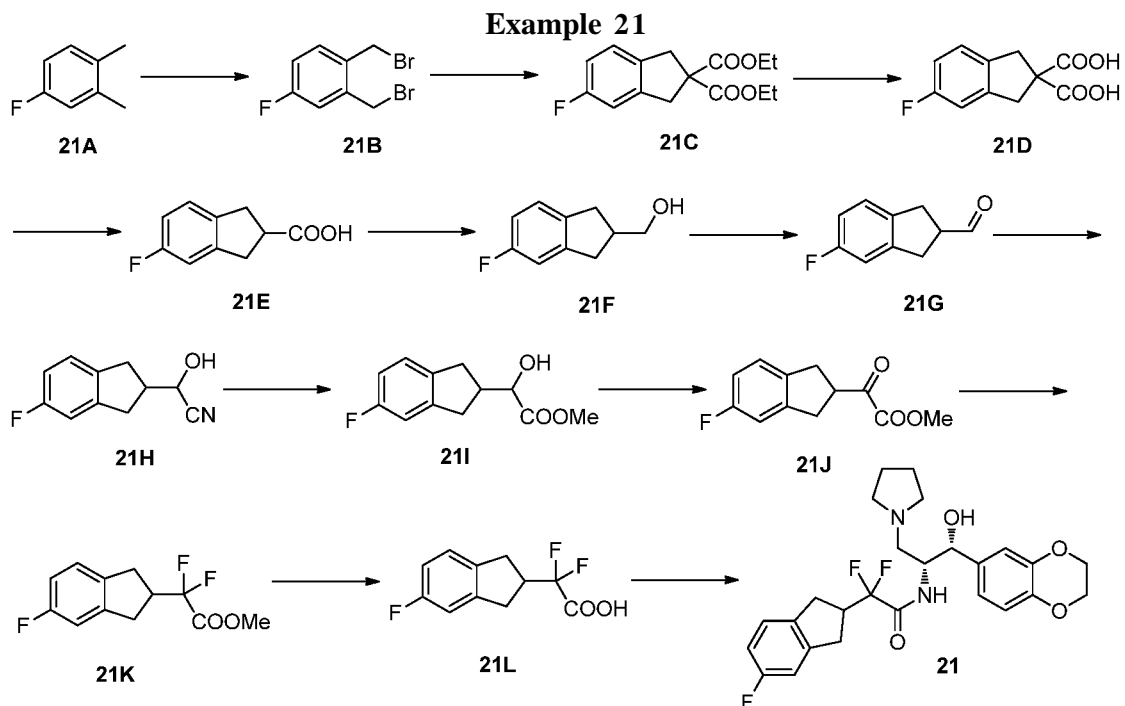
[000368] To a solution of Compound **20B** (500 mg, 1.63 mmol) in DCM (20 mL) was added dropwise *N,N*'-thiocarbonyldiimidazole (349 mg, 1.95 mmol) in DCM (10 mL) at 72 °C. After 3 h, the reaction mixture was cooled to rt and concentrated in vacuum to give a crude product. It was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to render Compound **20C** (590 mg, yield 87%) as a colorless oil.

LCMS (m/z): 418 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.26 (t, *J* = 6.8 Hz, 3H), 4.31 (q, *J* = 6.8 Hz, 2H), 6.92 (m, 1H), 7.09 (s, 1H), 7.28 (m, 1H), 7.60 (m, 2H), 7.70-7.81 (m, 3H), 8.07 (d, *J* = 7.2 Hz, 1H), 8.13 (s, 1H), 8.41 (s, 1H), 8.70 (d, *J* = 4.4 Hz, 1H).

[000369] To a solution of «-Bu₃SnH (821 mg, 2.8 mmol) and AIBN (2 mg, cat.) in refluxing toluene (10 ml) was added dropwise the Compound **20C** (590 mg, 1.4 mmol) in toluene (10 ml). After stirred for 3 h at 110 °C, the reaction mixture was cooled to rt and concentrated in vacuum to purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **20D** (200 mg, yield 50%) as a colorless oil. LCMS (m/z): 392 [M+1]⁺.

[000370] To a solution of Compound **20D** (100 mg, 0.34 mmol) in THF/MeOH/water (3 mL, 1:1:1, v/v) was added LiOH·H₂O (36 mg, 1.5 mmol). The mixture was stirred at 25 °C for 1 h. After the completion of the reaction, water (20 mL) was added. It was extracted with ethyl acetate (20 mL x 2). The aqueous phase was adjusted pH to 6 with 1 N HCl and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuum to give crude product Compound **20E** (90 mg, crude) as a yellow solid. LCMS (m/z): 264 [M+1]⁺.

[000371] To a mixture of Compound **20E** (80 mg, 0.3 mmol) in DCM (10 mL) was added EDCI (88 mg, 0.45 mmol), HOBt (62 mg, 0.45 mmol) and Intermediate **A** (85 mg, 0.3 mmol) and stirred at 25 °C overnight. After the addition of water (10 mL), the mixture was extracted with DCM (20 mL x 3), dried over anhydrous Na₂SO₄, purified by prep-HPLC to render Compound **20** (35 mg, yield 22%) as a white solid. LCMS (m/z): 524 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.99 (s, 4H), 2.72 (m, 2H), 3.19 (s, 1H), 3.42-3.66 (m, 6H), 4.20 (s, 4H), 4.40 (s, 1H), 4.77 (s, 1H), 4.89 (s, 1H), 6.68 (m, 1H), 6.76 (m, 2H), 7.45-7.54 (m, 2H), 7.70 (m, 1H), 7.77-7.85 (m, 3H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.28 (t, *J* = 7.6 Hz, 1H), 8.90 (s, 1H), 1.43 (s, 1H).



[000372] To a solution of Compound **21A** (2.5 g, 20 mmol) in CCl_4 (100 mL) was added NBS (7.12 g, 40 mmol), BPO (100 mg) and it was stirred at reflux overnight. The mixture was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to render Compound **21B** (2.34 g, yield 41%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 4.60 (s, 2H), 4.62 (s, 2H), 6.98 (m, 1H), 7.08 (m, 1H), 7.33 (m, 1H).

[000373] To a solution of diethyl malonate (1.52 mL, 10 mmol) in THF (100 mL) was added NaH (60%, 400 mg, 10 mmol) at 0 °C and stirred at 0°C for 15 min. To the mixture was added Compound **21B** (2.8 g, 10 mmol) at 0°C and stirred for 15 min and then followed by addition of NaH (60%, 400 mg, 10 mmol) at 0°C. The mixture was stirred at rt for 2 h and was filtered to remove the salt. The filtrate was concentrated and purified by flash column (ethyl acetate in petroleum ether, 10% v/v) to give Compound **21C** (2.2 g, yield 79%) as a colorless oil. LC-MS (m/z): 281 [$\text{M}+1$]⁺; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.26 (t, $J = 7.0$ Hz, 6H), 3.53 (s, 2H), 3.56 (s, 2H), 4.20 (m, 4H), 6.87 (m, 2H), 7.12 (m, 1H).

[000374] To a solution of Compound **21B** (2.2 g, 7.9 mmol) in ethanol (30 mL) was added a solution of LiOH (1.26 g, 31.4 mmol) in water (30 mL) and stirred at rt overnight. The mixture was concentrated to remove ethanol, acidified with cone. aqueous HCl solution, extracted with ethyl acetate (100 mL x 3) and concentrated to render Compound **21D** (1 g, yield 62%) as a yellow solid. LC-MS (m/z): 247 [$\text{M}+23$]⁺; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz)

major characteristic peaks: δ (ppm) 3.38 (s, 2H), 3.42 (s, 2H), 6.93 (m, 1H), 7.05 (m, 1H), 7.21 (m, 1H), 12.93 (s, 2H).

[000375] To a solution of Compound **21D** (1 g, 4.5 mmol) in DMSO (15 mL) was added NaCl (1 g). The mixture was stirred at 130 °C for 6 h. After the addition of ethyl acetate (100 mL), the mixture was washed with water (200 mL x 3) and brine (200 mL x 1), dried over anhydrous Na₂S₂O₄, and concentrated to yield Compound **21E** (0.6 g, yield 74%) as a brown solid. ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 3.08 (m, 4H), 3.29 (m, 1H), 6.92 (m, 1H), 7.03 (m, 1H), 7.21 (m, 1H), 12.37 (s, 1H).

[000376] To a solution of Compound **21E** (0.6 g, 3.3 mmol) in DCM (10 mL) was added B₂H₆ in THF solution (1M, 4 mL, 4 mmol) at -78 °C under N₂ and stirred at rt for 1 h. MeOH (2 mL) was added to the mixture and it was stirred at the same temperature overnight. After removal of the solvents, the residues were purified with flash column chromatography (ethyl acetate in petroleum ether, 35% v/v) to give Compound **21F** (250 mg, yield 46%>) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.70 (m, 3H), 3.04 (m, 2H), 3.65 (d, *J* = 6.4 Hz, 2H), 6.80 (m, 1H), 6.87 (m, 1H), 7.11 (m, 1H).

[000377] To a solution of Compound **21F** (6.3 g, 38 mmol) in DCM (300 mL) was added DMP (19 g, 45.5 mmol) at 0 °C and it was stirred at rt for 3 h. The mixture was concentrated and purified by flash column chromatography (ethyl acetate in petroleum ether, 20% v/v) to give Compound **21G** (6 g, yield 96%) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.23 (m, 5H), 6.88 (m, 2H), 7.15 (m, 1H), 9.77 (d, *J* = 0.8 Hz, 1H).

[000378] To a solution of Na₂S₂O₅ (3.6 g, 73.2 mmol) in water (100 mL) was added Compound **21G** (6 g, 36.6 mmol) and it was stirred at rt for 2 h and followed by the addition of NaCN (3.6 g, 73.2 mmol). The mixture was stirred at rt overnight. It was extracted with ethyl acetate (100 mL x 3), dried over anhydrous Na₂S₂O₄, purified by flash column chromatography (ethyl acetate in petroleum ether, 30%> v/v) to give Compound **21H** (3.3 g, 47%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.96 (m, 3H), 3.16 (m, 2H), 4.45 (m, 1H), 6.86 (m, 2H), 7.14 (m, 1H).

[000379] To a solution of Compound **21H** (3.3 g, 17.3 mmol) in MeOH (100 mL) was bubbled with a gentle stream of HCl gas (dried over cone. H₂S₂O₄) for 6 h and was allowed to stand overnight at 4 °C. To the mixture was added water (50 mL) and it was stirred at rt for 3 h. Saturated aqueous NaHCO₃ solution was added to adjust pH > 7, the mixture was then extracted with ethyl acetate (100 mL x 3), washed with brine (100 mL x 1), dried over anhydrous Na₂S₂O₄, and purified by flash column chromatography (ethyl acetate in petroleum

ether, 25% v/v) to give Compound **211** (1.9 g, yield 49%) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.90 (m, 5H), 3.77 (d, *J* = 2.4 Hz, 3H), 4.27 (d, *J* = 3.6 Hz, 1H), 6.81 (m, 2H), 7.07 (m, 1H).

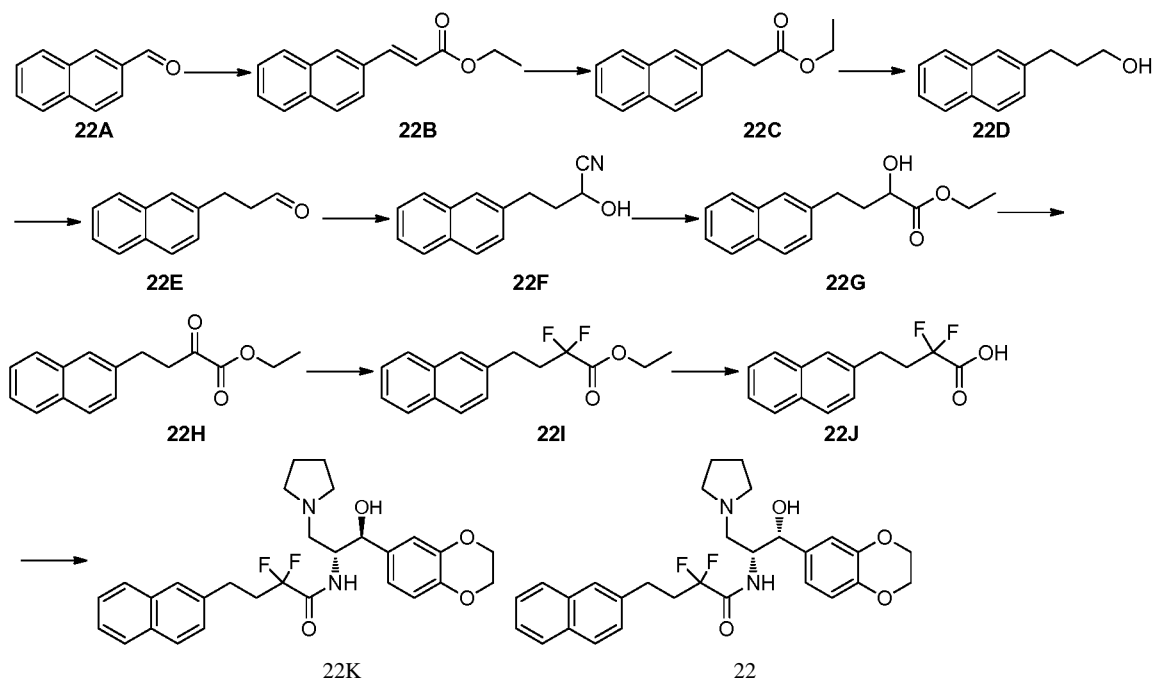
[000380] To a solution of Compound **211** (1.9 g, 8.5 mmol) in DCM (100 mL) was added DMP (5.4 g, 12.7 mmol) at 0 °C and it was stirred at rt for 3 h. After removal of the solvent, the residues were purified by flash column chromatography (ethyl acetate in petroleum ether, 10% v/v) to give Compound **21J** (1.7 g, yield 90%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.19 (m, 4H), 3.91 (s, 3H), 4.07 (m, 1H), 6.83 (m, 2H), 7.10 (m, 1H).

[000381] To a solution of Compound **21J** (444 mg, 2 mmol) in DCM (10 mL) was added DAST (1 mL, 8 mmol) and it was stirred at 25 °C overnight. The mixture was purified by flash column chromatography (ethyl acetate in petroleum ether, 2% v/v) to give **21K** (300 mg, 61%) as a yellow oil. LC-MS (m/z): 225 [M-19]⁺.

[000382] To a solution of Compound **21K** (300 mg, 1.23 mmol) in MeOH (5 mL) was added a solution of LiOH (100 mg, 2.46 mmol) in water (5 mL) and it was stirred at rt overnight. The mixture was acidified using 1M aqueous HCl solution, extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated to give Compound **21L** (200 mg, yield 35%) as a colorless oil. LC-MS (m/z): 229 [M-1]⁻.

[000383] To a solution of Compound **21L** (230 mg, 0.87 mmol) in DCM (10 mL) was added EDCI (250 mg, 1.3 mmol), HOBt (175 mg, 1.3 mmol), Intermediate A (240 mg, 0.87 mmol) and it was stirred at rt overnight. The mixture was diluted with DCM (20 mL), washed with water (50 mL x 2) and brine (50 mL x 1), dried over anhydrous Na₂SO₄, concentrated, and purified by prep-HPLC to give Compound **21** (20 mg, yield 5%) as a white solid. LC-MS (m/z): 491 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.15 (br, 4H), 2.61 (m, 2H), 2.91 (m, 5H), 3.38 (br, 1H), 3.54 (br, 1H), 3.88 (s, 2H), 4.20 (m, 4H), 4.44 (s, 1H), 5.20 (s, 1H), 6.83 (m, 4H), 6.90 (m, 1H), 7.05 (m, 1H), 7.39 (m, 1H), 11.42 (s, 1H).

Example 22



[000384] To a solution of ethyl 2-(diethoxyphosphoryl)acetate (7.2 g, 32 mmol) in THF (150 mL) was added NaH (1.3 g, 32 mmol) at 0 °C under N₂ and it was stirred at this temperature for 30 min, followed by the addition of Compound **22A** (5 g, 32 mmol) in THF (15 mL). Stirred at 40 °C for 1 h, the mixture was first cooled down to rt, and then added water, extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂S₂O₄, concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to give Compound **22B** (7 g, yield 97%). LC-MS (m/z): 227 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.36 (t, *J* = 6.8 Hz, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 6.54 (d, *J* = 16 Hz, 1H), 7.5 (m, 2H), 7.65 (d, *J* = 10 Hz, 1H), 7.82 (m, 4H), 7.91 (s, 1H).

[000385] To a solution of Compound **22B** (7 g, 31 mmol) in methanol (50 mL) and THF (30 mL) was added Pd/C (700 mg) and it was stirred at 25 °C for 4 h under H₂. The mixture was filtered, and the filtrate was concentrated to render Compound **22C** (7 g, crude), which was used for the next step without further purification. LC-MS (m/z): 229 [M+1]⁺.

[000386] To a solution of AlLiH₄ (1.16 g, 31 mmol) in THF (100 mL) was added Compound **22C** (7 g, 31 mmol) in THF (20 mL) at -60 °C under N₂ and the mixture was stirred for 2 h, and then allowed the temperature raised to rt. Sodium sulfate was added to the mixture. After filtration, the filtrate was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to yield the Compound **22D** (5.6 g, yield 98%) as a white solid. LC-MS (m/z): 169 [M-18]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic

peaks: δ (ppm) 1.06 (s, 1H), 1.97 (m, 2H), 2.87 (d, $J = 7.6$ Hz, 2H), 3.70 (d, $J = 6.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.43 (m, 2H), 7.63 (s, 1H), 7.78 (m, 3H).

[000387] To a solution of Compound **22D** (3 g, 16 mmol) in DCM (100 mL) was added DMP (8.2 g, 19 mmol) and the mixture was stirred at rt for 2 h, and then filtered. The filtrate was washed with aq sat. NaHCO_3 (2 x 50 mL), extracted with DCM (2 x 50 mL), washed with brine (1 x 50 mL), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **22E** (2.6 g, yield 88%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.87 (d, $J = 7.2$ Hz, 2H), 3.12 (d, $J = 7.6$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.44 (m, 2H), 7.63 (s, 1H), 7.79 (m, 3H), 9.86 (s, 1H).

[000388] Compound **22E** (2.6 g, 14 mmol) was added to a solution of sodium metabisulfate (2.7 g, 14 mmol) in water (100 mL). The mixture was vigorously stirred for 2 h at rt, and after the addition of NaCN (1.4 mg, 28 mmol) it was stirred overnight. The mixture was added water (30 mL) and THF (10 mL), extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na_2SO_4 , concentrated to yield Compound **22F** (2 g, 66% yield). LC-MS (m/z): 212 [$\text{M}+1$]⁺; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 2.25 (m, 2H), 2.99 (m, 2H), 4.43 (t, $J = 6.8$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.44 (m, 2H), 7.65 (s, 1H), 7.81 (m, 3H).

[000389] To a solution of Compound **22F** (2.0 g, 9.5 mmol) in EtOH (30 mL) at 0 °C was bubbled with a gentle stream of HCl (gas) (dried over $\text{con.H}_2\text{SO}_4$) for 5 h. The mixture was added water (20 mL), stirred at rt for 2 h, and adjusted pH to 7 with diluted NaOH (2 M). It was extracted with DCM (100 mL x 2), washed with brine (50 mL x 1), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 33% v/v) to render Compound **22G** (1.56 g, yield 64%) as a yellow oil. LC-MS (m/z): 259 [$\text{M}+1$]⁺; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.27 (t, $J = 7.6$ Hz, 1H), 2.03 (m, 1H), 2.22 (m, 1H), 2.92 (m, 2H), 4.20 (m, 3H), 7.35 (d, $J = 9.2$ Hz, 1H), 7.44 (m, 2H), 7.65 (s, 1H), 7.79 (m, 3H).

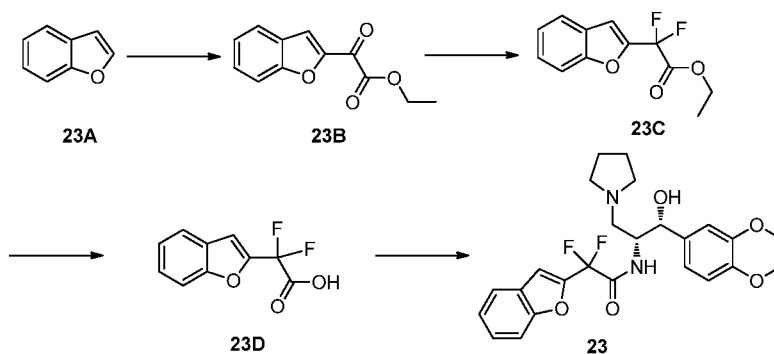
[000390] To a solution of Compound **22G** (500 mg, 1.94 mmol) in DCM (20 mL) was added DMP (986 mg, 2.3 mmol) and the mixture was stirred at rt for 2 h and then filtered. The filtrate was washed with aq sat. NaHCO_3 (50 mL x 2) and aq sat. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL x 2), extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na_2SO_4 , and concentrated to yield Compound **22H** (450 mg, yield 91%) as a yellow oil. LC-MS (m/z): 239 [$\text{M}-18$]⁺.

[000391] To a solution of Compound **22H** (450 mg, 1.76 mmol) in DCM (20 mL) was added DAST (1.4 g, 8.8 mmol) at 0 °C and the mixture was stirred at rt overnight. The reaction mixture was poured into ice-water, extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂S₂O₄, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to yield Compound **22I** (450 mg, yield 92%) as a colorless oil. LC-MS (m/z): 279 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.31 (t, *J* = 7.2 Hz, 1H), 2.47 (m, 2H), 2.98 (m, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.45 (m, 2H), 7.63 (s, 1H), 7.77 (m, 3H).

[000392] To a solution of Compound **22I** (450 mg, 1.6 mmol) in EtOH (5 mL) was added LiOH (136 mg, 3.2 mmol) in water (5 mL) and the mixture was stirred at rt overnight. After concentration by evaporation, the mixture was adjusted to pH 2 with diluted HCl, extracted with DCM (20 mL x 2), washed with brine (20 mL x 1), dried over Na₂S₂O₄, and concentrated to give Compound **22J** (250 mg, yield 62%), which was used for the next step without further purification. LC-MS (m/z): 251 [M+]⁺.

[000393] A mixture of Compound **22J** (100 mg, 0.4 mmol), EDCI (115 mg, 0.6 mmol), HOBt (82 mg, 0.6 mmol), Intermediate A (110 mg, 0.4 mmol) in DCM (20 mL) was stirred at rt overnight. The reaction mixture was diluted with water, extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂S₂O₄, and concentrated. The crude product was purified first by prep-HPLC, followed by chiral-prep-HPLC to give Compound **22K** (24 mg, yield 12%) as a white solid and Compound **22** (22 mg, yield 11%) as a white solid. For Compound **22K**: LC-MS (m/z): 511 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.81 (s, 4H), 2.46 (m, 3H), 2.70 (m, 5H), 2.98 (d, *J* = 3.6 Hz, 2H), 3.94 (m, 4H), 4.20 (s, 1H), 5.07 (s, 1H), 6.82 (m, 4H), 7.22 (m, 1H), 7.45 (m, 2H), 7.54 (s, 1H), 7.77 (m, 3H). For Compound **22**: LC-MS (m/z): 511 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.89 (s, 4H), 2.36 (m, 2H), 2.88 (m, 4H), 2.99 (m, 3H), 3.19 (s, 1H), 4.04 (m, 4H), 4.25 (s, 1H), 4.77 (d, *J* = 5.6 Hz, 1H), 6.86 (m, 3H), 7.28 (m, 1H), 7.44 (m, 2H), 7.59 (s, 1H), 7.78 (m, 3H).

Example 23



[000394] To a solution of Compound **23A** (2.36 g, 20.0 mmol) in tetrahydrofuran (30 mL) stirring at -70°C (CO_2 , acetone bath) was added n-BuLi (8.0 mL, 20.0 mmol, 1.6 M in hexanes). The reaction was stirred for 30 min (yellow color) and added dropwise via a cannulated needle into a solution of diethyl oxalate (2.92 g, 20.0 mmol) in tetrahydrofuran (20 mL) stirring at -70°C . The reaction mixture was stirred for 1 h and then quenched with saturated aqueous ammonium chloride solution. The mixture was warmed to rt, diluted with dichloromethane, and washed with 0.1 N HCl. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to provide Compound **23B** (1.10 g, yield 25%). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.46 (t, $J=7.2$ Hz, 3H), 4.87 (q, $J=7.2$ Hz, 2H), 7.35-7.37 (m, 1H), 7.55-7.57 (m, 1H), 7.61-7.64 (m, 1H), 7.77-7.78 (m, 1H), 8.09-8.10 (m, 1H).

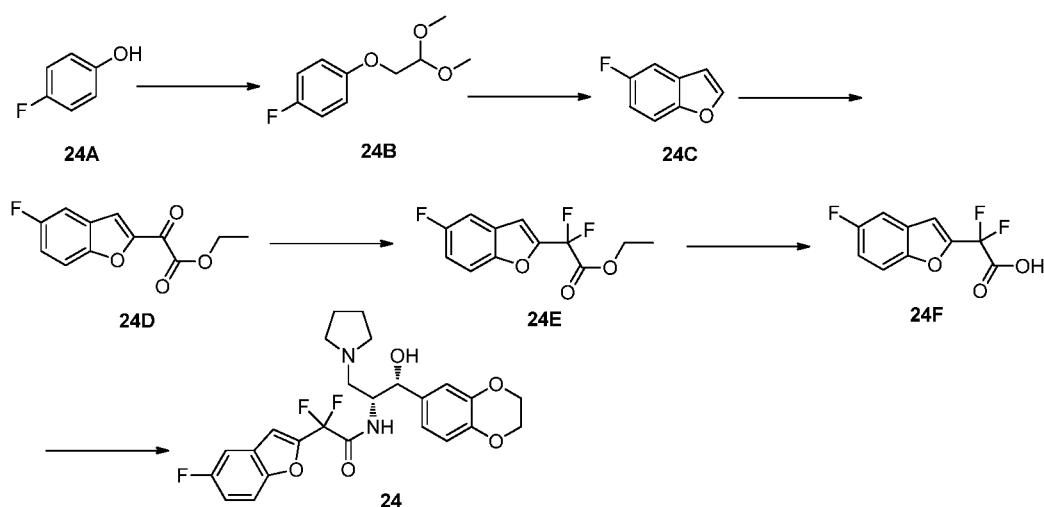
[000395] To a solution of Compound **23B** (800 mg, 3.67 mmol) in CH_2Cl_2 (10 mL) was added DAST (1.77 g, 11.01 mmol). The reaction mixture was stirred for 10 h and then poured into ice-water, extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered, evaporated to give desired product Compound **23C** (860 mg, yield 97%). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.35-1.40 (m, 3H), 4.33-4.43 (m, 2H), 7.14-7.15 (m, 1H), 7.31-7.33 (m, 1H), 7.38-7.42 (m, 1H), 7.54-7.56 (m, 1H), 7.64-7.66 (m, 1H).

[000396] To a solution of Compound **23C** (480 mg, 2 mmol) in THF (2 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (3 mmol, 126 mg), H_2O (2 mL) and MeOH (2 mL). The reaction mixture was stirred for 3 h at 25°C , neutralized with 1 N HCl, and evaporated to dryness. The residue was dissolved in H_2O and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, evaporated to give Compound **23D** (290 mg, yield 68%). LCMS (m/z): 213 [$\text{M}+1$].

[000397] To a solution of Compound **23D** (88 mg, 0.41 mmol) in DCM (10 mL) was added Intermediate **A** (114 mg, 0.41 mmol), HOBt (82 mg, 0.61 mmol) and EDCI (116 mg,

0.61mmol). The mixture was stirred for 3 h at 25 °C, washed with brine, dried over Na_2SO_4 , filtered, evaporated, and purified by prep-HPLC to give Compound **23** (30 mg, yield 15%) as a white solid. LC-MS (m/z): 473 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (MeOO-d_4 , 400 MHz) major characteristic peaks: δ (ppm) 1.77-1.78 (m, 4H), 2.55-2.64 (m, 4H), 2.74-2.75 (m, 2H), 4.08-4.14 (m, 4H), 4.35-4.36 (m, 1H), 4.79 (d, $J=4.0$ Hz, 1H), 6.66-6.68 (m, 1H), 6.76-6.78 (m, 1H), 6.83-6.84 (m, 1H), 7.00 (s, 1H), 7.30-7.34 (m, 1H), 7.41-7.45 (m, 1H), 7.55-7.57 (m, 1H), 7.66-7.68 (m, 1H), 7.81-7.83 (m, 1H).

Example 24



[000398] A mixture of Compound **24A** (10 g, 89 mmol), 2-bromo-1,1-dimethoxyethane (15 g, 89 mmol), K_2CO_3 (18.4 g, 134 mmol), KI (100 mg) in DMF (100 mL) was stirred at reflux for 3 h, then cooled to rt, and filtered. The filtrate was added water (200 mL), extracted with ethyl acetate (100 mL x 2), washed with water (100 mL x 3), brine (100 mL x 1), dried over Na_2SO_4 , concentrated, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to render Compound **24B** (15 g, yield 85%) as a colorless liquid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.46 (s, 6H), 3.96 (d, $J = 5.2$ Hz, 2H), 4.71 (t, $J = 5.6$ Hz, 1H), 6.90 (m, 2H), 7.26 (m, 2H).

[000399] A solution of polyphosphoric acid (90 g) in toluene was stirred to 90 °C, then to the solution was added Compound **24B** (15 g, 75 mmol) in toluene (20 mL) and the mixture was stirred at 90 °C for 3 h, then poured into ice, and stirred for 30 min. It was extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na_2SO_4 , concentrated, and purified by column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **24C** (4.5 g, yield 44%) as a red liquid. $^1\text{H-NMR}$ (CDCl_3 , 400

MHz) major characteristic peaks: δ (ppm) 6.742-6.746 (m, 1H), 6.994-7.035 (m, 1H), 7.24-7.26 (m, 1H), 7.41-7.44 (m, 1H), 7.651-7.655 (d, $J = 1.6$ Hz, 1H).

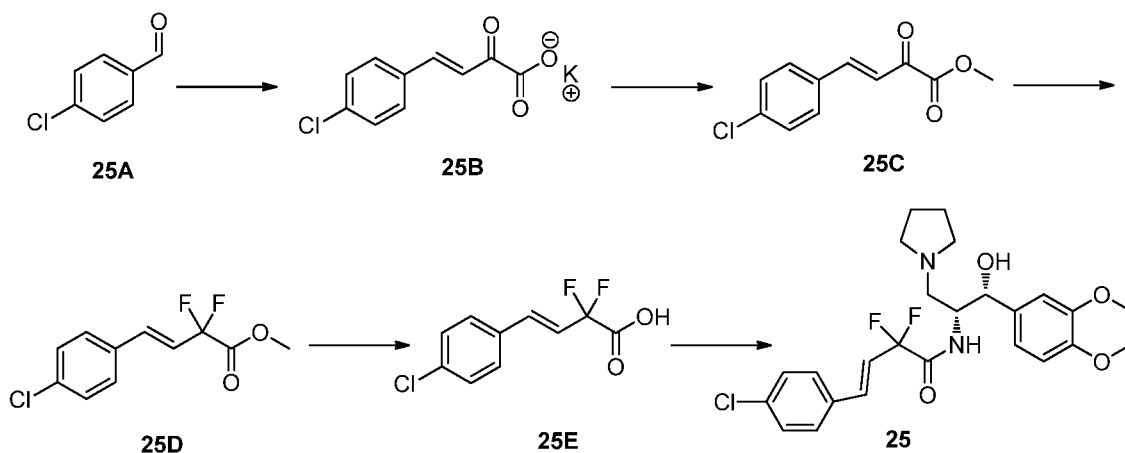
[000400] To a solution of Compound **24C** (4.5 g, 33 mmol) in THF (20 mL) was added *n*-BuLi (15 mL) at -78 °C under N₂ and the mixture was stirred for 30 min, before the addition of diethyl oxalate (10.8 g, 74 mmol). The mixture was stirred at -78 °C for 1 h, and quenched with addition of aq sat. NH₄Cl. It was extracted with ethyl acetate (2 x 50 mL), washed with sat. NaHCO₃ (50 mL x 2), brine (50 mL), dried over Na₂SO₄, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to give Compound **24D** (2.5 g, yield 32%) as a yellow solid.

[000401] To a solution of Compound **24D** (1 g, 4.2 mmol) in DCM (50 mL) was added DAST (3.18 g, 18 mmol) at 0 °C and the mixture was stirred at rt overnight, poured into ice-water, and added sat. aq NaHCO₃ (20 mL). The mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **24E** (600 mg, yield 55%) as a yellow liquid.

[000402] To a solution of Compound **24E** (120 mg, 0.46 mmol) in EtOH (5 mL) was added LiOH (46 mg, 1.09 mmol) in water (5 mL) and the mixture was stirred at rt overnight, concentrated to remove EtOH, and adjusted to pH 7 with diluted HCl. Lyophilization of the solution provided Compound **24F** (60 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 229 [M-1]⁻.

[000403] A mixture of Compound **24F** (60 mg, 0.26 mmol), EDCI (75 mg, 0.39 mmol), HOBt (53 mg, 0.39 mmol), Intermediate **A** (72 mg, 0.41 mmol) in DCM (10 mL) was stirred at rt overnight. After quenched with sat. NaHCO₃, the mixture was extracted with DCM (2 x 50 mL), washed with brine (1 x 50 mL), dried over Na₂SO₄, concentrated. The crude product was purified by prep-HPLC to give Compound **24** (2 mg, yield 2%) as a white solid. LC-MS (m/z): 491 [M+1]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.85 (m, 4H), 3.07 (m, 2H), 3.43 (m, 4H), 4.15 (s, 4H), 4.45 (s, 1H), 4.70 (s, 1H), 5.90 (s, 1H), 6.67 (m, 2H), 6.79 (s, 1H), 7.02 (s, 1H), 7.36 (s, 1H), 7.56 (s, 1H), 7.73 (s, 1H), 8.85 (s, 1H), 9.49 (s, 1H).

Example 25



[000404] Compound **25A** (5.64 g, 40 mmol) and 2-oxopropanoic acid (3.52 g, 40 mmol) were dissolved in MeOH (4 mL). To this solution, KOH (3.95 g, 60 mmol) in MeOH (10 mL) was added. The mixture was stirred at rt for 5 h. The precipitate was isolated by filtration. Compound **25B** (8.5g, yield 85%) was obtained as a yellow solid. LCMS (m/z): 211 [M+]⁺.

[000405] Acetyl chloride (3.84 mL) was added dropwise to MeOH (23 mL) at 0 °C. Then Compound **25B** (3.98 mg, 16 mmol) was added to the mixture. The mixture was heated to reflux overnight. After evaporation, the mixture was diluted with water, extracted by ethyl acetate and dried over anhydrous Na₂SO₄. After evaporation to dryness, the residue was recrystallized from EtOH. Compound **25C** (1.34 g, yield 37%) was obtained as a yellow solid. LCMS (m/z): 247 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.94 (s, 3H), 7.36 (d, *J* = 16 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 16.4 Hz, 1H).

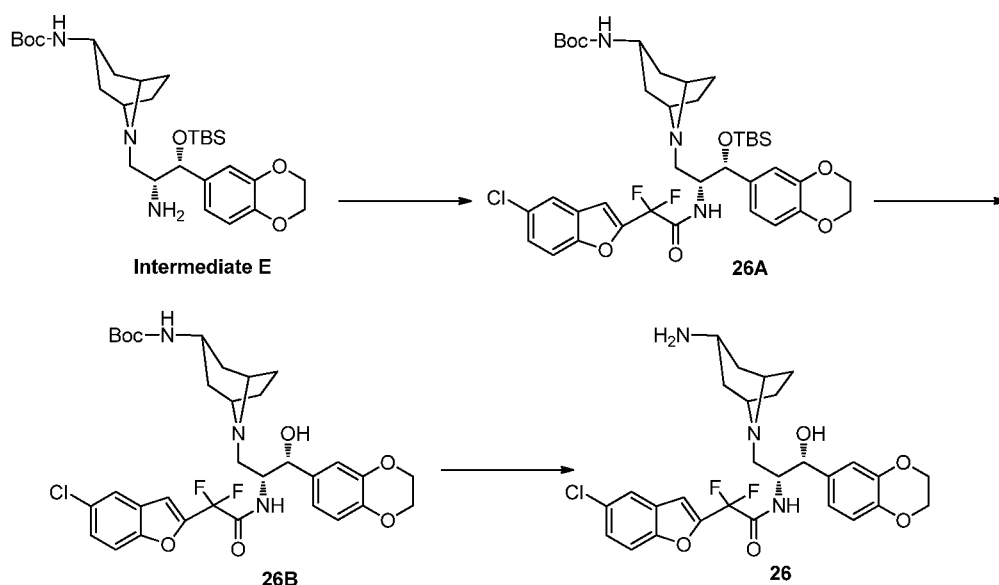
[000406] To the solution of Compound **25C** (225 mg, 1 mmol) in CH₂Cl₂ (5 mL) was added DAST (483.6 mg, 3 mmol) at 0 °C. The mixture was stirred at rt overnight. After evaporation, the residue was purified by silica gel column chromatography (ethyl acetate in petroleum, 5% v/v). Compound **25D** was obtained as a yellow solid (150 mg, 60%). LCMS (m/z): 227 [M-19]⁺.

[000407] To the solution of compound **25D** (86 mg, 0.35 mmol) in MeOH (5 mL) and H₂O (1.5 mL) was added LiOH·H₂O (74 mg, 1.75 mmol) at 0 °C. The mixture was stirred for an hour at rt. After evaporation of the solvent, the residue was diluted with water and the mixture was adjusted to pH 4 with 1 M HCl. The resulted mixture was extracted with ethyl acetate and dried over anhydrous Na₂SO₄. After evaporation, Compound **25E** was obtained as a yellow solid (63 mg, yield 77%). LCMS (m/z): 231 [M-1]⁻; ¹H-NMR (CDCl₃, 400 MHz)

major characteristic peaks: δ (ppm) 6.27-6.31 (m, 1H), 7.08 (d, $J = 16.4$ Hz, 1H), 7.34-7.40 (m, 4H).

[000408] To the solution of Compound **25E** (63 mg, 0.27 mmol), Intermediate **A** (75 mg, 0.27 mmol) in DCM (4 mL) was added EDCI (52 mg, 0.27 mmol). The mixture was stirred at rt overnight. After evaporation, the crude was purified by prep-HPLC to give Compound **25** (11 mg, yield 6.7%) as a white solid. LCMS (m/z): 493 $[M+1]^+$; 1H -NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.02 (m, 4H), 2.71-2.85 (m, 2H), 3.09 (m, 2H), 3.60-3.89 (m, 3H), 4.15 (s, 4H), 4.34 (s, 1H), 4.91 (s, 1H), 6.19-6.23 (m, 1H), 6.78-7.00 (m, 4H), 7.30-7.35 (m, 4H), 8.72 (s, 1H), 11.7 (s, 1H).

Example 26



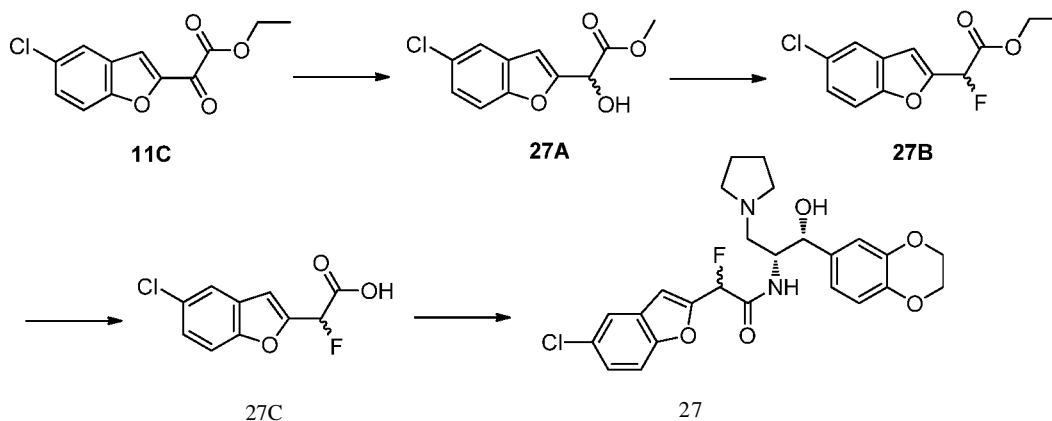
[000409] A solution of Compound **HE** (100 mg, 0.41 mmol), Intermediate **C** (222 mg, 0.41 mmol), EDCI (118 mg, 0.62 mmol) and HOBT (84 mg, 0.62 mmol) in DCM (20 mL) was stirred at rt overnight. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, dried over anhydrous Na₂S₄, and evaporated to render Compound **26A** (200 mg, yield 63%) as a yellow oil, which was used for next step directly. LCMS (m/z): 776 $[M+1]^+$.

[000410] A mixture of Compound **26A** (200 mg, 0.23 mmol) and Bu₄NF (20 mg) in THF (10 mL) was stirred at 25 °C overnight. It was then diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂S₄, evaporated, and purified by prep-HPLC to yield Compound **26B** (103 mg, yield 68%) as colorless oil. LCMS (m/z): 662 $[M+1]^+$.

[000411] A solution of Compound **26B** (103 mg, 0.16 mmol) and TFA (0.5 mL) in DCM (5 mL) was stirred at rt for 2 h. The reaction was quenched with saturated aqueous

NaHCO₃, diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂SO₄, evaporated, and purified by prep-HPLC to afford Compound **26** (30 mg, yield 33%) as a white solid. LCMS (m/z): 562 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 1.92-2.16 (m, 7H), 3.26-3.60 (m, 6H), 4.05-4.20 (m, 5H), 4.51 (s, 1H), 6.00-6.13 (m, 1H), 6.68-6.84 (m, 3H), 7.51-7.54 (m, 1H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 17.6 Hz, 1H), 8.15 (br s, 2H).

Example 27



[000412] To a solution of Compound **11C** (564 mg, 2.24 mmol) in dichloromethane, under an atmosphere of nitrogen at -76 °C was added diisobutylaluminium hydride (2.95 ml, 2.95 mmol). The solution was stirred at -76 °C for 45 min, and then allowed to warm to rt. A mixture of water/methanol (10 mL, 1/1 v/v) was added dropwise. The two layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried, evaporated and purified on silica gel column (ethyl acetate/PE) to give Compound **27A** (153 mg, yield 27%) as a yellow solid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.25-1.29 (m, 3H), 4.27-4.35 (m, 2H), 5.29 (s, 1H), 6.72 (s, 1H), 7.242-7.248 (d, *J* = 2.4 Hz, 1H), 7.261-7.269 (d, *J* = 3.2 Hz, 1H), 7.38-7.40 (d, *J* = 8.4 Hz, 1H), 7.534-7.538 (d, *J* = 2.4 Hz, 1H).

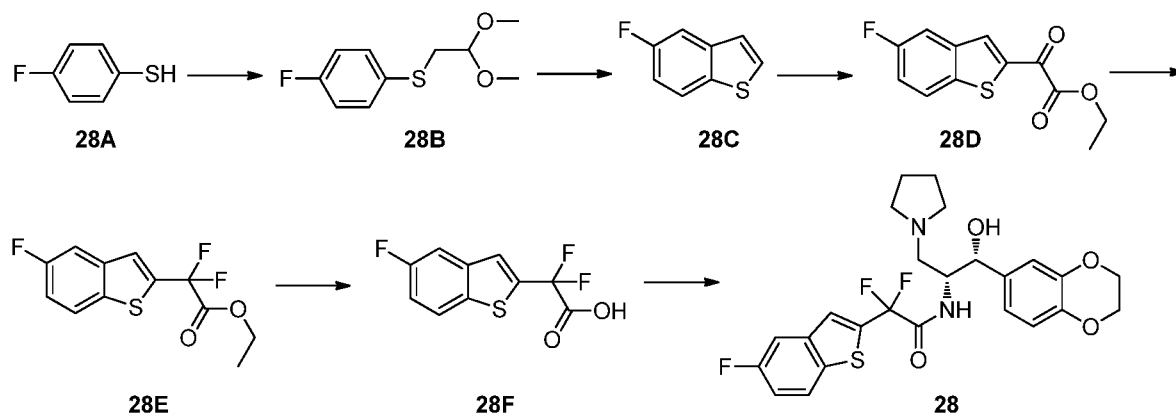
[000413] To a solution of Compound **27A** (184 mg, 0.72 mmol) in DCM (8 mL) was added DAST (380 mg, 2.36 mmol) at 0 °C and the mixture was stirred at rt overnight. It was poured into ice-water, extracted with DCM (2 x 50 mL), washed with brine (1 x 50 mL), dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **27B** (70 mg, yield 37.9%) as a yellow liquid. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.30-1.34 (m, 3H), 4.33-4.37 (m, 2H), 5.85-5.97 (d, *J* = 47.6 Hz, 1H), 6.89-6.90 (d, *J*

= 4.0 Hz, 1H), 7.30-7.33 (d, J = 8.8 Hz, 1H), 7.43-7.45 (d, J = 8.8 Hz, 1H), 7.583-7.588 (d, J = 2.0 Hz, 1H).

[000414] To a solution of Compound **27B** (70 mg, 0.273 mmol) in THF (5 mL) was added LiOH (22 mg, 0.52 mmol) in water (2.5 mL) and the mixture was stirred at rt for 4 h. It was concentrated and adjusted to pH 6 with diluted HCl. Lyophilization of the solution led to Compound **27C** (210 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 227 [M-1]⁻.

[000415] A mixture of Compound **27C** (66 mg, 0.29 mmol), EDCI (80.8 mg, 0.42 mmol), HOBT (56 mg, 0.42 mmol), Intermediate **A** (77.8 mg, 0.28 mmol) in DCM (12 mL) was stirred at rt overnight. It was diluted with sat. aq NaHCO₃, extracted with DCM (2 x 50 mL), washed with brine (1 x 50 mL), dried over Na₂S₄O₆, and concentrated. The crude product was purified by prep-HPLC to give Compound **27** (15 mg, yield 10.6%) as a white solid. LC-MS (m/z): 489.1 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.03-2.08 (m, 4H), 2.48 (s, 6H), 2.73-3.50 (m, 3H), 3.83-3.90 (m, 2H), 4.16-4.22 (m, 3H), 4.45-4.64 (m, 1H), 4.88-5.08 (m, 1H), 5.72-5.96 (m, 1H), 6.76-6.95 (m, 3H), 7.28-7.38 (m, 1H), 7.49-7.56 (m, 1H), 7.75-8.70 (m, 1H), 11.11-11.80 (m, 1H).

Example 28



[000416] To 4-fluorothiophenol **28A** (1.28 g, 10 mmol) in anhydrous acetone (40 mL), under nitrogen at rt was added potassium carbonate (1.38 g, 10 mmol). To the mixture was slowly added bromoacetaldehyde diethyl acetal (1.69 g, 10 mmol). The reaction mixture was stirred at rt overnight. The potassium carbonate was filtered off and washed thoroughly with acetone. The filtrate was then concentrated and the oily residue diluted with H₂O and extracted with ethyl acetate. The ethyl acetate extracts were washed with 0.5 M KOH, H₂O and brine, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) afforded Compound **28B** (1.54 g, yield 71%). ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks:

δ (ppm) 3.05 (d, $J = 6.4$ Hz, 2H), 3.32 (s, 6H), 4.49 (t, $J = 6.4$ Hz, 1H), 6.97-7.01 (m, 2H), 7.38-7.42 (m, 2H).

[000417] To a 3-neck 100 mL flask was introduced polyphosphoric acid (5 g) and anhydrous chlorobenzene (30 ml). The mixture was stirred under nitrogen at reflux. Compound **28B** (1.54 g, 7.1 mmol) was then added over 5 min period in 2 mL of chlorobenzene. Within 30 min the reaction mixture turned relatively dark and it was kept under reflux for 3 h. The mixture was cooled down to rt and the chlorobenzene layer decanted. The black tar was suspended in H₂O (50 mL) and stirred for about 30 min. The aqueous layer was extracted with CH₂Cl₂. The organic extracts were pooled with the chlorobenzene layer, treated with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (petroleum ether, 100% v/v) afforded Compound **28C** (470 mg, yield 43%). ¹H-NMR (MeOD-*d*₄, 400 MHz) major characteristic peaks: δ (ppm) 7.11-7.16 (m, 1H), 7.34-7.35 (m, 1H), 7.53-7.56 (m, 1H), 7.66-7.67 (m, 1H), 7.86-7.89 (m, 1H).

[000418] Compound **28C** (470 mg, 3.1 mmol) was added to THF (10 mL) followed by addition of n-BuLi (1.24 mL, 3.1 mmol) at rt. The reaction mixture was stirred at rt for 60 min. Diethyl oxalate (905 mg, 6.2 mmol) was added to THF (30 mL) -78 °C. To this solution, 5-fluorobenzo[3,4]thiophene anion solution was added dropwise and the reaction was stirred at -78 °C for 20 min. It was quenched with saturated aqueous NH₄Cl (30 mL) and extracted with ethyl acetate (30 mL x 3). The organic extracts were concentrated in vacuum and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give the Compound **28D** (450 mg, yield 57%) as an orange oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.36 (t, $J = 7.2$ Hz, 3H), 4.36 (q, $J = 7.2$ Hz, 2H), 7.25-7.30 (m, 1H), 7.65-7.68 (m, 1H), 7.87-7.91 (m, 1H), 7.77-7.78 (m, 1H), 8.35 (s, 1H).

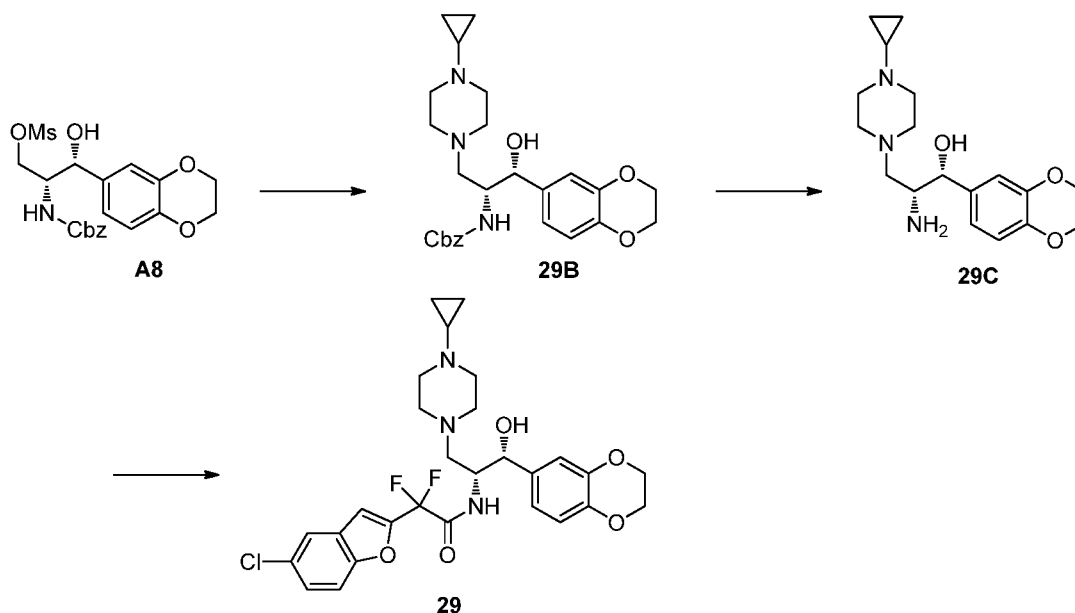
[000419] To a solution of Compound **28D** (450 mg, 1.78 mmol) in CH₂Cl₂ (10 mL) was added DAST (2.86 g, 17.8 mmol). The reaction mixture was stirred for 10 h before poured into ice-water and extracted with CH₂Cl₂ (50 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to give Compound **28E** (88 mg, yield 18%). ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.34 (t, $J = 7.2$ Hz, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 7.26-7.31 (m, 1H), 7.64-7.67 (m, 1H), 7.72 (s, 1H), 7.94-7.98 (m, 1H).

[000420] To a solution of Compound **28E** (88 mg, 0.32 mmol) in THF (2 mL) was added LiOH·H₂O (20 mg, 0.48 mmol), H₂O (2 mL) and MeOH (2 mL). The reaction mixture was stirred for 3 hours at 25 °C, and then neutralized with 1 N HCl, It was evaporated to dryness, the resulted residue was dissolved in H₂O and extracted with ethyl acetate. The

organic layer was dried over Na_2SO_4 , filtered, and evaporated to give Compound **28F** (80 mg, yield 100%). LCMS (m/z): 245 $[\text{M}-1]^-$.

[000421] To a solution of Compound **28F** (80 mg, 0.32 mmol) in DCM (10 mL) was added Intermediate **A** (88 mg, 0.32 mmol), HOBt (65 mg, 0.48 mmol) and EDCI (92 mg, 0.48 mmol). The mixture was stirred overnight at 25 °C, then washed with brine, dried over Na_2SO_4 , filtered, evaporated, and purified by prep-HPLC to give Compound **28** (31 mg, yield 19%) as a white solid. LC-MS (m/z): 507 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.11-2.17 (m, 4H), 2.89-3.01 (m, 2H), 3.494-3.51 (m, 2H), 3.79-3.81 (m, 2H), 4.03-4.13 (m, 4H), 4.45-4.47 (m, 1H), 5.08 (s, 1H), 6.72-6.74 (m, 1H), 6.82 (s, 1H), 7.17-7.19 (m, 2H), 7.43-7.46 (m, 1H), 7.73-7.77 (m, 1H), 7.85-7.87 (m, 1H), 7.66-7.68 (m, 1H), 11.94 (br, 1H).

Example 29

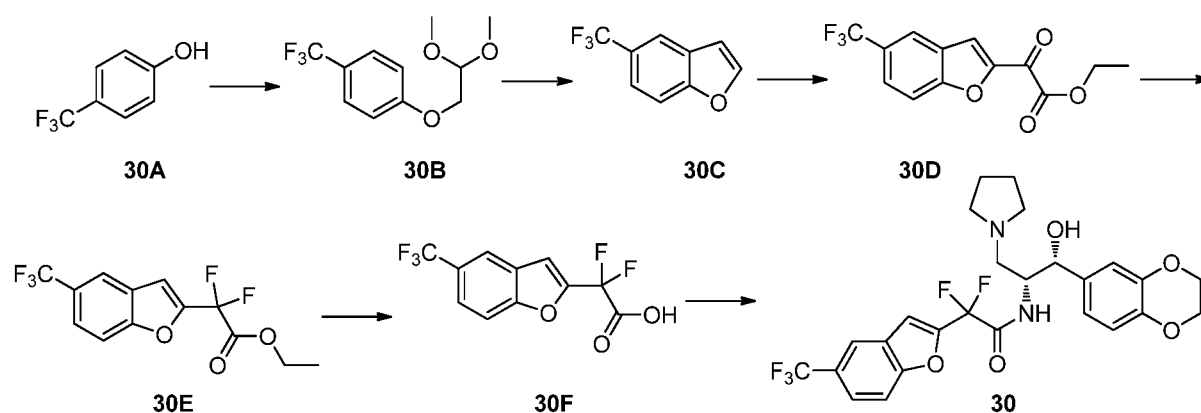


[000422] To a solution of Compound **A8** (406 mg, 0.93 mmol) in CH_3CN (15 mL) was added 1-cyclopropylpiperazine (350 mg, 2.80 mmol), K_2CO_3 (387 mg, 2.80 mmol) and NaI (100 mg). The mixture was heated at 82 °C for 2 h. It was cooled to rt and filtered. The filtrate was concentrated in vacuum to give a crude product Compound **29B** (450 mg, crude) as a yellow oil. LCMS (m/z): 468 $[\text{M}+1]^+$.

[000423] To a solution of Compound **29B** (450 mg, 0.96 mmol) in EtOH/water (10 mL, 9:1, v/v) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (126 mg, 2.88 mmol). After refluxed overnight, water (20 mL) was added to the mixture. It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a crude product Compound **29C** (350 mg, crude) as a yellow oil. LCMS (m/z): 334 $[\text{M}+1]^+$.

[000424] To a mixture of Compound **29C** (100 mg, 0.30 mmol) in DCM (10 mL) was added EDCI (86 mg, 0.45 mmol), HOBT (61 mg, 0.45 mmol) and Intermediate **A** (88 mg, 0.30 mmol) and stirred at 25 °C for 2 h. Water (10 mL) was added to the mixture, which was then extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to yield a trifluoroacetic acid salt of Compound **29** (33 mg, yield 20%) as a white solid. LCMS (m/z): 562 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.87 (d, $J = 8$ Hz, 2H), 1.17(s, 2H), 2.45(s, 1H), 3.28 (d, $J = 16$ Hz, 1H), 3.49-3.63 (m, 10H), 4.12-4.16(m, 4H), 4.54 (s, 1H), 4.84 (s, 1H), 6.78-6.86 (m, 4H), 7.35(d, $J = 8$ Hz, 1H), 7.44 (d, $J = 8$ Hz, 1H), 7.59 (s, 1H), 8.23 (d, $J = 8$ Hz, 1H).

Example 30



[000425] A mixture of Compound **30A** (10 g, 62 mmol), 2-bromo-1,1-dimethoxyethane (18.2 g, 108 mmol), Cs_2CO_3 (28 g, 86 mmol), NaI (100 mg) in DMF (10 mL) was stirred at 65 °C overnight. It was then cooled to rt and filtered. The filtrate was added water (200 mL), and extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with water (100 mL x 3), brine (100 mL x 1), and dried over Na_2SO_4 . Filtration and concentration of the mixture gave rise to Compound **30B** (10 g, yield 67%>) as a yellow liquid. ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.46 (s, 6H), 4.03-4.05 (d, $J = 5.2$ Hz, 2H), 4.72-4.74 (t, $J = 4.8$ Hz, 1H), 6.98-6.99 (d, $J = 8.8$ Hz, 2H), 7.53-7.55 (d, $J = 8.8$ Hz, 2H).

[000426] A solution of polyphosphoric acid (8.1 g, 24 mmol) in toluene (10 mL) was added compound **30B** (5 g, 20 mmol) in toluene (10 mL) and the mixture was stirred at 80 °C for 2 h. It was then poured into ice, stirred for 30 min, and extracted with DCM (50 mL x 3). The combined extracts were washed with brine (50 mL x 1), dried over Na_2SO_4 , concentrated, and purified by column chromatography on silica gel (petroleum, 100%, v/v) to afford Compound **30C** (690 mg, yield 19%) as a yellow solution in petroleum. ¹H-NMR (CDCl_3 ,

400 MHz) major characteristic peaks: δ (ppm) 6.79 (s, 1H), 7.54 (m, 2H), 7.67 (s, 1H), 7.87 (s, 1H).

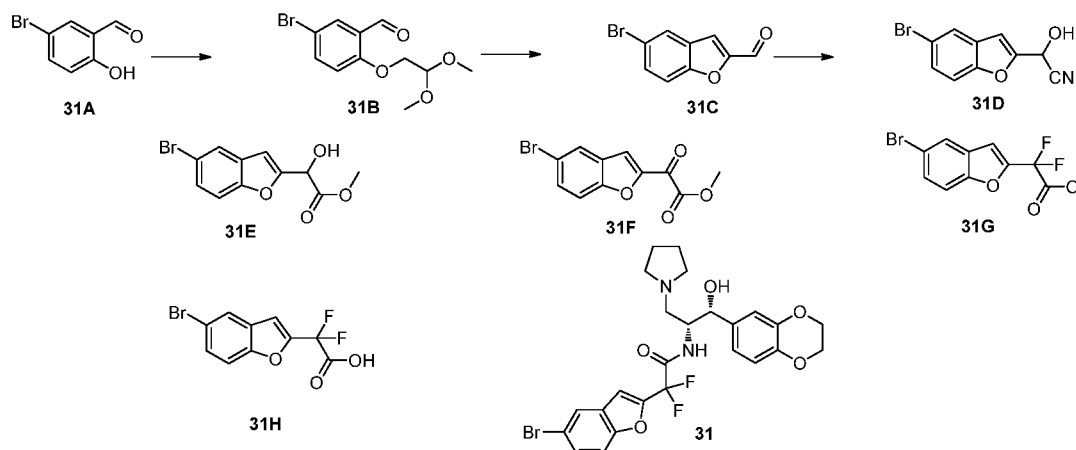
[000427] To a solution of Compound **30C** (690 mg, 3.71 mmol) in petroleum ether from last step and anhydrous THF (10 mL) was added n-BuLi (2.5 M in hexane, 1.78 mL) at -78 °C under N₂. After stirred for 30 min, to the mixture was added diethyl oxalate (2.7 g, 18.5 mmol). Stirred at -78 °C for 1 h, it was quenched with sat. aq NH₄Cl, and extracted with ethyl acetate (50 mL x 2). The combined extracts were washed with brine (50 mL x 1), dried over Na₂SO₄, concentrated and recrystallized from MeOH (3 mL) to afford Compound **30D** (500 g, yield 47%) as a yellow solid. 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.35-1.38 (t, $J = 7.2$ Hz, 3H), 4.37-4.43 (q, $J = 7.6$ Hz, 2H), 7.93-8.03 (m, 2H), 8.34 (s, 1H), 8.42-8.44 (m, 1H).

[000428] To a solution of Compound **30D** (500 mg, 1.75 mmol) in DCM (10 mL) was added DAST (1.41 g, 8.76 mmol) at 0 °C and the mixture was stirred at rt for 1 h. It was poured into ice-water, added sat. NaHCO₃ (20 mL), and extracted with DCM (50 mL x 2). The combined extracts were washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 4% v/v) to render Compound **30E** (200 mg, yield 62%) as a yellow liquid. 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.36-1.39 (t, $J = 7.2$ Hz, 3H), 4.39-4.45 (q, $J = 7.2$ Hz, 2H), 7.23 (s, 1H), 7.63-7.68 (m, 2H), 7.96 (s, 1H).

[000429] To a solution of Compound **30E** (170 mg, 0.55 mmol) in EtOH (2 mL) was added LiOH·H₂O (28 mg, 0.66 mmol) in water (0.5 mL) and the mixture was stirred at rt overnight. It was then adjusted pH to 4-5 with 1 N HCl, and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, and concentrated to give Compound **30F** (150 mg, yield 100%) as a yellow solid. LC-MS (m/z): 279 [M-1]⁻.

[000430] A mixture of Compound **30F** (60 mg, 0.21 mmol), EDCI (61 mg, 0.31 mmol), HOBT (48 mg, 0.31 mmol), Intermediate **A** (59 mg, 0.21 mmol) in DCM (5 mL) was stirred at 28 °C overnight before quenched with sat. aq NaHCO₃. The mixture was extracted with DCM (50 mL x 2). The combined extracts were washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **30** (5 mg, yield 4%) as a white solid. LC-MS (m/z): 541 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (m, 4H), 2.70-3.02 (m, 2H), 3.49-3.54 (m, 2H), 3.83 (m, 2H), 4.13-4.18 (m, 4H), 4.50 (m, 1H), 5.10 (s, 1H), 6.75-6.84 (m, 4H), 7.60-7.67 (m, 2H), 7.88-7.92 (m, 2H), 11.96 (s, 1H).

Example 31



[000431] A mixture of Compound **31A** (3.00 g, 14.93 mmol), 2-bromo-1,1-dimethoxyethane (2.77 g, 16.42 mmol) and K_2CO_3 (4.12 g, 29.86 mmol) in DMF (26 mL) was stirred at 150 °C for 2 h. It was evaporated to remove DMF. The residue was diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to render Compound **31B** (3.80 g, yield 88%) as a white solid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 4.10 (d, $J = 5.2$ Hz, 2H), 4.75 (t, $J = 5.2$ Hz, 1H), 6.89 (d, $J = 9.2$ Hz, 1H), 7.61-7.64 (m, 1H), 7.93 (s, 1H), 10.42 (s, 1H).

[000432] A mixture of Compound **31B** (2.00 g, 6.90 mmol) in Acetic acid (50 mL) was stirred at 120 °C overnight. The mixture was evaporated to remove Acetic acid, diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to yield Compound **31C** (1.26 g, yield 81%) as a white solid. 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks : δ (ppm) 7.49-7.52 (m, 2H), 7.60-7.64 (m, 1H), 7.90 (s, 1H), 9.89 (s, 1H).

[000433] To a solution of Compound **31C** (2.00 g, 8.93 mmol) and NaCN (1.31 g, 26.78 mmol) in MeOH (100 mL) was added Acetic acid (1.61 g, 26.78 mmol). The mixture was stirred at rt overnight. It was then quenched with sat. aq $NaHCO_3$ solution, diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel column chromatography (ethyl acetate in petroleum, 30 % v/v) to provide Compound **31D** (1.60 g, yield 71 %) as a colorless oil. LCMS: 252 [M+] $^+$; 1H -NMR ($DMSO-d_6$, 400 MHz) major characteristic peaks : δ (ppm) 6.10 (d, $J = 6.8$ Hz, 1H), 7.06 (s, 1H), 7.48-7.54 (m, 2H), 7.65 (d, $J = 8.8$ Hz, 1H), 7.93 (s, 1H).

[000434] A solution of Compound **31D** (1.00 g, 3.98 mmol) in MeOH (20 mL) was stirred at rt overnight with bubbling of HCl gas. The reaction was quenched with H_2O (100 mL) and stirred at rt for 2 h. It was evaporated to remove MeOH, diluted with ethyl acetate

(150 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to render Compound **31E** (900 mg, yield 82%) as a white solid. LCMS: 285 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 3.69 (s, 3H), 5.41 (d, *J* = 6.4 Hz, 1H), 6.52 (t, *J* = 6.4 Hz, 1H), 6.90 (s, 1H), 7.43-7.47 (m, 1H), 7.55-7.58 (m, 1H), 7.86 (s, 1H).

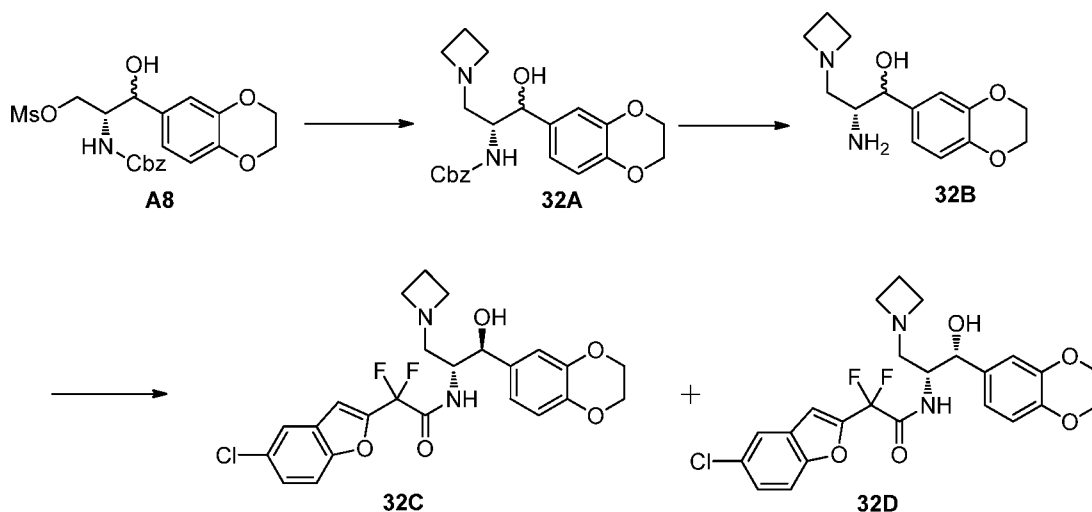
[000435] A suspension of Compound **31E** (400 mg, 1.40 mmol) and DMP (712 mg, 1.68 mmol) in DCM (20 mL) was stirred at rt overnight. It was quenched with saturated aq $\text{Na}_2\text{S}_2\text{O}_3$, diluted with ethyl acetate (150 mL), washed with water and brine, and purified by silica gel column chromatography eluted with ethyl acetate in petroleum (from 10% to 20%, v/v) to give Compound **31F** (180 mg, yield 46%) as a white solid. LCMS: 283 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks : δ (ppm) 3.92 (s, 3H), 7.77 (m, 2H), 8.19 (d, *J* = 7.6 Hz, 2H).

[000436] To a solution of Compound **31F** (500 mg, 1.77 mmol) in DCM (5 mL) was added DAST (1.42 g, 8.85 mmol). The mixture was stirred at rt overnight. The mixture was purified by column chromatography on silica gel eluted with ethyl acetate in petroleum (10%, v/v) to yield Compound **31G** (300 mg, yield 55%) as a white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 3.95 (s, 3H), 7.55 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 9.6 Hz, 1H), 8.01 (s, 1H).

[000437] A mixture of Compound **31G** (300 mg, 0.98 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (123 mg, 2.94 mmol) in MeOH/ H_2O (10 mL/2 mL) was stirred at rt for 2 h. The mixture was evaporated to remove MeOH. The residue was adjusted to pH 3 with 1 N HCl and filtered to afford Compound **31H** (200 mg, yield 70%) as a white solid. LCMS: 289 [M-]⁻.

[000438] A solution of Intermediate **A** (95 mg, 0.34 mmol), Compound **31H** (100 mg, 0.34 mmol), EDCI (98 mg, 0.51 mmol) and HOBt (67 mg, 0.51 mmol) in DCM (5 mL) was stirred at rt overnight. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and purified by prep-HPLC to afford Compound **31** (100 mg, yield 53%) as a white solid. LCMS: 551 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.12 (br s, 4H), 2.89-3.02 (m, 2H), 3.48 (s, 2H), 3.81 (br s, 3H), 4.07-4.19 (m, 4H), 4.45-4.52 (m, 1H), 5.09 (s, 1H), 6.73-6.76 (m, 3H), 6.83 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.39-7.50 (m, 1H), 7.74 (s, 1H), 7.83 (s, 1H).

Example 32



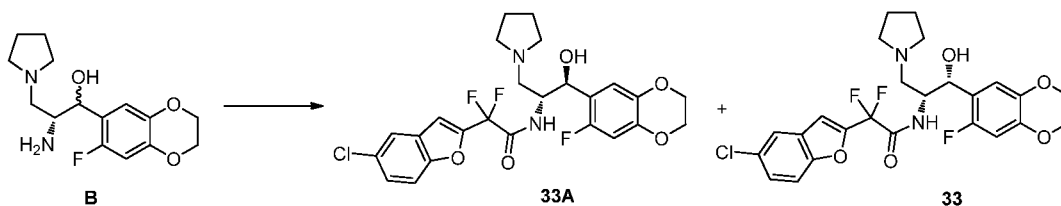
[000439] To a solution of Compound **A8** (437 mg, 1mmol) in ACN (20 mL) was added azetidine (171 mg, 3 mmol), K_2CO_3 (414 mg, 3 mmol) and Nal (449 mg, 3 mmol). The mixture was heated at 82 °C overnight. It was cooled to rt and filtered. The filtration was concentrated in vacuum to give crude product Compound **32A** (330 mg, crude) as a yellow oil. LCMS (m/z): 399 [M+1]⁺.

[000440] To a solution of Compound **32A** (330 mg, 0.83 mmol) in EtOH/water (10 mL, 9:1, v/v) was added $LiOH \cdot H_2O$ (104 mg, 2.48 mmol). The mixture was refluxed overnight. After reaction, water (20 mL) was added. It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a crude product Compound **32B** (170 mg, crude) as a yellow oil. LCMS (m/z): 265 [M+1]⁺.

[000441] To a mixture of Compound **32B** (150 mg, 0.57 mmol) in DCM (20 mL) was added EDCI (164 mg, 0.85 mmol), HOBT (115 mg, 0.85 mmol) and Compound **HE** (140 mg, 0.57 mmol) and stirred at 25 °C overnight. It was added water (10 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC and followed by prep-chiral-HPLC to render trifluoroacetic acid salts of Compound **32C** (10 mg, yield 3.6%) as a white solid and Compound **32D** (5 mg, yield 1.8%) as a white solid. For Compound **32C**, LCMS (m/z): 493 [M+1]⁺; ¹H-NMR ($CDCl_3$, 400 MHz) major characteristic peaks : δ (ppm) 2.42 (s, 1H), 2.66(s, 2H), 3.50-3.61(m, 2H), 4.06-4.14 (m, 6H), 4.23-4.30 (m, 3H), 4.12-4.16 (m, 4H), 4.63 (d, $J = 8$ Hz, 1H), 6.56 (s, 1H), 6.73 (d, $J = 8$ Hz, 1H), 6.80-6.85 (m, 3H), 7.37 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 7.61 (s, 1H); For Compound **32D**, LCMS (m/z): 493 [M+1]⁺; ¹H-NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 2.40 (s, 1H), 2.70 (s, 1H), 3.38 (s, 1H), 3.47 (d, $J = 8$ Hz, 2H), 4.10-4.17 (m, 5H), 4.20-4.30 (m, 3H), 4.89-

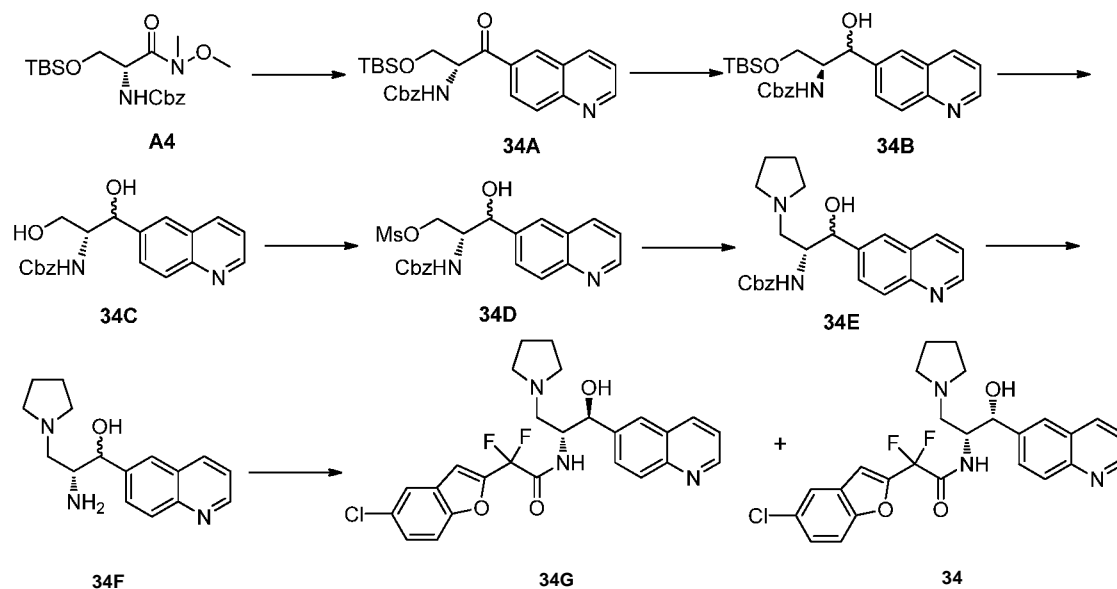
4.90 (d, $J = 4$ Hz, 1H), 6.75 (s, 3H), 6.82 (s, 1H), 7.36 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 7.60 (s, 1H).

Example 33



[000442] To a solution of Intermediate **B** (300 mg, 1 mmol) in DCM (15 mL) was added EDCI (288 mg, 1.5 mmol), HOBt (200 mg, 1.5 mmol), and Compound **HE** (247 mg, 1 mmol). It was stirred at rt overnight. The mixture was added DCM (20 mL), washed with water (50 mL x 2), brine (50 mL x 1), and dried over anhydrous Na_2SO_4 . The residue was purified by prep-HPLC, followed by prep-chiral-HPLC to give Compound **33A** (70 mg, yield 13%) as a white foam and Compound **33** (65 mg, yield 12%) as a white foam. For Compound **33A**, LC-MS (m/z): 525 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.09 (s, 4H), 2.87 (d, $J = 39.6$ Hz, 2H), 3.34 (s, 1H), 3.81 (s, 3H), 4.11 (m, 4H), 4.60 (s, 1H), 5.12 (s, 1H), 6.45 (d, $J = 10.8$ Hz, 1H), 6.91 (m, 2H), 7.32 (m, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.57 (d, $J = 2.4$ Hz, 1H), 8.49 (d, $J = 6.8$ Hz, 1H), 10.65 (s, 1H). For Compound **33**, LC-MS (m/z): 525 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.09 (s, 4H), 2.84 (d, $J = 44$ Hz, 2H), 3.29 (d, $J = 10.8$ Hz, 1H), 3.73 (m, 3H), 4.12 (m, 4H), 4.58 (s, 1H), 5.14 (d, $J = 5.2$ Hz, 1H), 6.47 (d, $J = 10.8$ Hz, 1H), 6.94 (m, 2H), 7.32 (m, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 1.6$ Hz, 1H), 8.60 (d, $J = 8$ Hz, 1H), 11.06 (s, 1H).

Example 34



[000443] To a solution of 6-bromoquinoline (7.9 g, 38 mmol) in THF (200 mL) was added n-BuLi (15 mL) at -60 °C under N₂ and after stirred for 0.5 h, Compound **A4** (5 g, 13 mmol) in THF (10 mL) was added slowly. The reaction mixture was maintained at this temperature with stirring for 1 h, and then added saturate aq NH₄Cl, extracted with ethyl acetate (100 mL x 2), brine (100 mL), and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to give Compound **34A** (4.4 g, yield 75%) as a colorless liquid. LC-MS (m/z): 465 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.00(s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 4.22 (m, 2H), 5.33 (s, 2H), 5.40 (s, 1H), 7.55 (m, 5H), 8.37 (m, 4H), 8.66 (s, 1H), 9.20 (m, 1H).

[000444] Compound **34A** (4.4 g, 9.5 mmol) was dissolved in THF (60 mL) and cooled down -80 °C under nitrogen atmosphere. L-Selectride (20 mL of 1M solution in THF, 18.9 mmol) was added dropwise while keeping the temperature at -80 °C. After an hour, the reaction was quenched with saturate aq NH₄Cl solution and the mixture was extracted with ethyl acetate (50mL x 2), washed with brine (100 mL), and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to render Compound **34B** (3 g, yield 68%) as a colorless liquid. LC-MS (m/z): 466 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.03 (m, 6H), 0.92(m, 9H), 4.10 (m, 3H), 4.96(m, 1H), 5.12 (s, 1H), 7.20 (s, 1H), 7.35 (m, 2H), 7.41 (m, 1H), 7.62 (m, 1H), 7.88 (m, 1H), 8.18 (m, 2H), 8.91 (s, 1H).

[000445] Compound **34B** (3 g, 6.4 mmol) was dissolved in THF (50 mL) at 0 °C, to this solution was added TBAF (839 mg, 3.2 mmol) at 0 °C. The mixture was stirred at rt overnight. It was condensed by evaporation of solvent, added water (50 mL), and extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL), dried over Na₂SO₄, and concentrated. The residue was suspended in a mixture of ethyl acetate in petroleum (10% v/v). Filtration gave Compound **34C** (1.7 g, yield 75%) as a white solid. LC-MS (m/z): 466 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.72 (m, 3H), 4.89 (m, 4H), 5.63 (m, 1H), 6.80 (m, 1H), 7.15 (m, 5H), 7.52 (m, 1H), 7.74 (m, 1H), 7.89 (s, 1H), 7.93 (m, 1H), 8.32 (m, 1H), 8.87 (s, 1H).

[000446] Compound **34C** (1 g, 2.8 mmol) was dissolved in THF (20 mL), to the mixture was added TEA (860 mg, 8.5 mmol). The mixture was cooled to -15 °C, to the mixture was added MsCl (360 mg, 3.1 mmol) slowly. Stirred at this temperature for 30 min, the mixture was diluted with water, extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL),

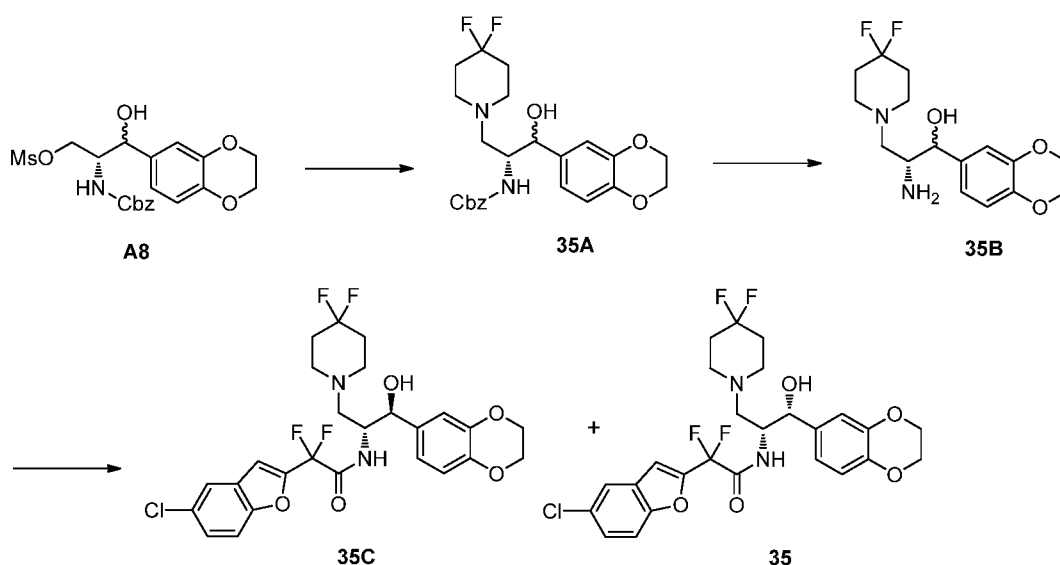
dried over Na₂S₀₄, and concentrated to yield Compound **34D** (1.2 g, crude), which was used for the next step without further purification. LC-MS (m/z): 431 [M+]⁺.

[000447] To a solution of Compound **34D** (1.2 g, 2.8 mmol) in THF (20 mL) was added pyrrolidine (2 g, 28mmol). The reaction mixture was allowed to warm up to rt and then heated at 50 °C overnight. The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give **34E** (1 g, yield 91%). LC-MS (m/z): 406 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 4H), 2.77 (s, 2H), 2.86 (m, 4H), 3.63 (m, 1H), 4.15 (m, 1H), 4.94 (s, 1H), 5.04 (s, 1H), 7.15 (s, 1H), 7.24 (m, 4H), 7.39 (m, 1H), 7.68 (m, 1H), 7.85 (m, 1H), 8.08 (m, 2H), 8.90 (m, 1H).

[000448] To a solution of Compound **34E** (1 g, 2.5 mmol) in methanol (20 mL) was added Pd(OH)₂ (100 mg) and the mixture was stirred at rt under H₂ overnight. Filtration and evaporation of the mixture gave Compound **34F** (400 mg, yield 60%). LC-MS (m/z): 272 [M+]⁺.

[000449] A mixture of Compound **HE** (182 mg, 0.74 mmol), EDCI (212 mg, 1.1 mmol), HOBT (150 mg, 1.1 mmol), Compound **34F** (200 mg, 0.74 mmol) in DCM (20 mL) was stirred at rt overnight. After added water, the mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂S₀₄, and concentrated. The crude product was purified by prep-HPLC and followed by chiral-prep-HPLC to give Compound **34G** (46 mg, yield 13%) as a white solid and Compound **34** (58 mg, yield 16%) as a white solid. For Compound **34G**, LC-MS (m/z): 500 [M+]⁺. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.08 (s, 4H), 2.90 (m, 2H), 3.52 (m, 1H), 3.64 (m, 2H), 3.94 (t, *J* = 16.8 Hz, 1H), 4.71 (m, 2H), 5.14 (d, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 7.20 (m, 1H), 7.23 (s, 1H), 7.38 (s, 1H), 7.66 (m, 1H), 8.06 (m, 2H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.88 (d, *J* = 4.0 Hz, 1H), 9.43 (d, *J* = 8.4 Hz, 1H), 1.56 (s, 1H); For Compound **34**, LC-MS (m/z): 500 [M+]⁺. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.16 (s, 2H), 3.05 (s, 2H), 3.74 (s, 3H), 4.32 (s, 4H), 4.81 (s, 1H), 5.43 (s, 1H), 6.70 (s, 1H), 7.17 (m, 1H), 7.24 (m, 1H), 7.34 (m, 1H), 7.66 (m, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 8.05 (s, 1H), 8.23 (m, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.96 (d, *J* = 4.4 Hz, 1H), 11.80 (s, 1H).

Example 35



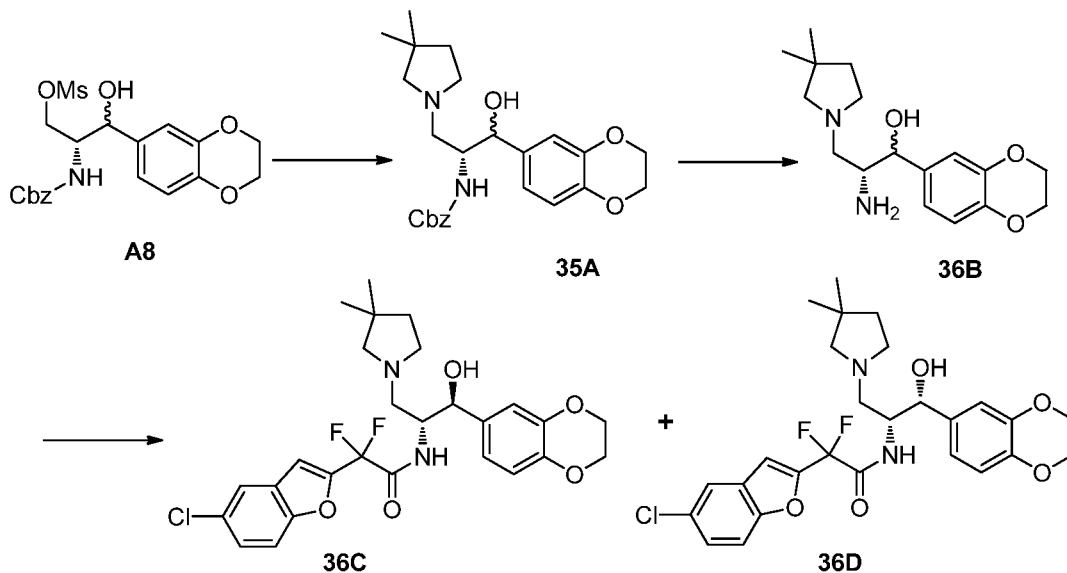
[000450] To a solution of Compound **A8** (847 mg, 2 mmol) in ACN (20 mL) was added 4,4-difluoropiperidine (628 mg, 4 mmol), K_2CO_3 (414 mg, 3 mmol) and NaI (449 mg, 3 mmol). The mixture was heated at 82 °C overnight. It was cooled to rt, filtered and added ethyl acetate (30 mL). It was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a crude product Compound **35A** (900 mg, crude) as a colorless solid. LCMS (m/z): 463 [M+]⁺.

[000451] To a solution of Compound **35A** (100 mg, 0.22 mmol) in EtOH/water (10 mL, 9:1, v/v) was added $LiOH \cdot H_2O$ (28 mg, 0.66 mmol). The mixture was refluxed overnight, cooled down to rt, and added water (20 mL). It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give crude product Compound **35B** (70 mg, crude) as a yellow oil. LCMS (m/z): 329 [M+]⁺.

[000452] To a mixture of Compound **35B** (70 mg, 0.20 mmol) in DCM (10 mL) was added EDCI (57 mg, 0.30 mmol), HOBt (40 mg, 0.30 mmol) and Compound **HE** (49 mg, 0.2 mmol) and stirred at 25 °C overnight. It was diluted with water (10 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by chiral-prep-HPLC to give Compound **35C** (6.5 mg, yield 4.5%) as a white solid and Compound **35** (16.5 mg, yield 11.5%) as a white solid. For Compound **35C**, LCMS (m/z): 557 [M+]⁺; ¹H-NMR ($CDCl_3$, 400 MHz) major characteristic peaks : δ (ppm) 2.32 (s, 4H), 3.16 (dd, $J = 4, 12$ Hz, 2H), 3.81 (t, $J = 12$ Hz, 1H), 4.14-4.20 (m, 5H), 4.55 (s, 1H), 4.89 (d, $J = 4$ Hz, 1H), 6.77-6.84 (m, 2H), 6.89 (d, $J = 8$ Hz, 2H), 7.32-7.37 (m, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.60 (s, 1H), 8.93 (d, $J = 8$ Hz, 1H); For Compound **35**, LCMS (m/z): 557 [M+]⁺; ¹H NMR ($CDCl_3$, 400 MHz) major

characteristic peaks: δ (ppm) 2.38 (s, 4H), 3.33 (dd, $J = 4, 12$ Hz, 2H), 3.52-3.58 (m, 2H), 4.07-4.21 (m, 5H), 4.56 (s, 1H), 4.98 (s, 1H), 6.75 (s, 2H), 6.82 (s, 2H), 7.35 (d, $J = 8$ Hz, 1H), 7.43 (d, $J = 8$ Hz, 1H), 7.59 (s, 1H), 7.94 (d, $J = 8$ Hz, 1H).

Example 36



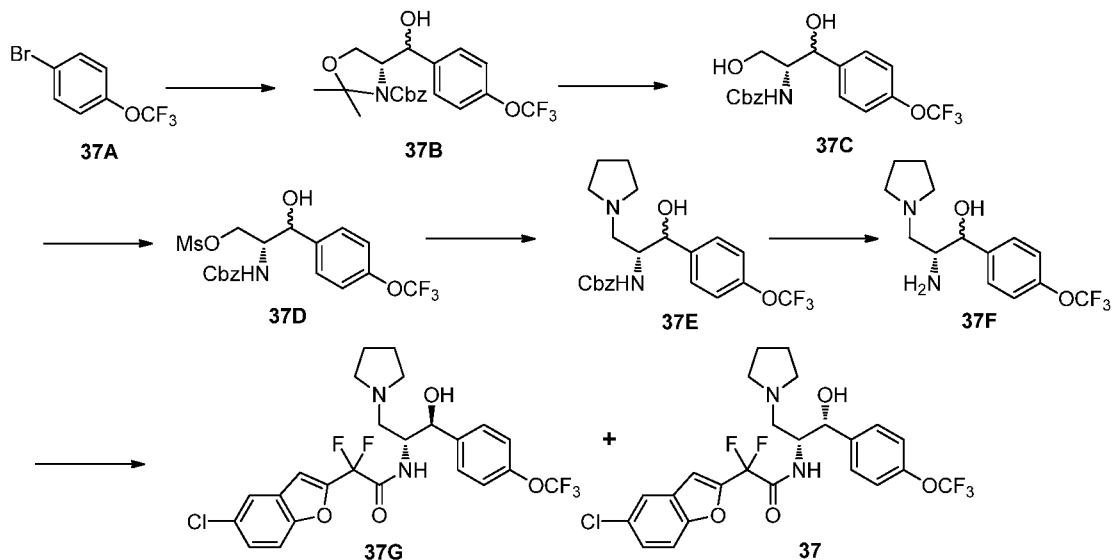
[000453] To a solution of 3,3-dimethylpyrrolidine (645 mg, 4.79 mmol) in THF (15 mL) was added Compound **A8** (520 mg, 1.19 mmol) and TEA (1 mL). The reaction mixture was stirred at 85 °C overnight. The solvents were removed and the residue was purified by prep-HPLC to afford the Compound **36A** (110 mg, yield 21%). LCMS: 441 [M+]⁺.

[000454] To a solution of Compound **36A** (110 mg, 0.25 mmol) in MeOH (5 mL) was added Pd(OH)₂ (15 mg). The reaction mixture was stirred at rt overnight, then filtered and evaporated to give Compound **36B** (80 mg, yield 100 %). LCMS: 307 [M+]⁺.

[000455] A solution of Compound **36B** (80 mg, 0.26 mmol), Compound **HE** (64.5 mg, 0.26 mmol), HOBT (53 mg, 0.39 mmol), EDCI (75 mg, 0.39 mmol) in DCM (10 mL) was stirred at rt overnight. After added water (50 mL), the mixture was extracted with DCM (50 mL x 2). The combined organic phases were dried over Na₂SO₄, filtered, evaporated, and purified by chiral-prep-HPLC to give Compound **36C** (13.8 mg, yield 10%) as a white solid and Compound **36D** (10.4 mg, yield 7.5%) as a white solid. For Compound **36C**, LCMS (m/z): 535 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.09-1.31 (m, 6H), 1.84-1.94 (d, $J = 20$ Hz, 2H), 2.46-2.52 (m, 1H), 2.90-3.01 (m, 1H), 3.13-3.27 (m, 2H), 3.55-3.96 (m, 2H), 4.16-4.19 (m, 4H), 4.43 (s, 1H), 4.90 (s, 1H), 6.76-6.78 (m, 1H), 6.82-6.91 (m, 3H), 7.31-7.34 (m, 1H), 7.42-7.44 (m, 1H), 7.58-7.59 (m, 1H), 9.07-9.38 (m, 1H), 11.85 (s, 1H); For Compound **36D**, LCMS (m/z): 535 [M+]⁺; ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.19-1.24 (m, 6H), 1.90-2.00 (d, $J = 20$ Hz, 2H),

2.65-2.83 (m, 1H), 3.07-3.09 (m, 1H), 3.42 (s, 1H), 3.54 (s, 2H), 3.88 (s, 1H), 4.06-4.20 (m, 4H), 4.44 (s, 1H), 5.08-5.12(m, 1H), 6.72-6.75 (m, 3H), 6.83 (s, 1H), 7.32-7.35 (m, 1H), 7.40-7.43 (m, 1H), 7.57-7.58 (m, 1H), 7.70-7.988 (m, 1H), 11.78-12.01 (m, 1H).

Example 37



[000456] To a solution of Compound **37A** (2 g, 8.3 mmol) in THF (30 mL) was added *n*-BuLi (4 mL, 2.5 M) under N₂ at -60 °C. The mixture was stirred for 1 h, Compound **8C** (2.2 g, 8.3 mmol) in THF (10 mL) was added. Stirred at rt for 15 min, the mixture was diluted with aq NH₄Cl (40 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and evaporated to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **37B** (1.4 g, yield 40%) as colorless oil. LC-MS (m/z): 426 [M+1]⁺.

[000457] A solution of Compound **37B** (1 g, 2.4 mmol) in THF (10 mL) and 1 N aq HCl (5 mL) was stirred at rt for 5 h. The mixture was quenched with water (10 mL), extracted with ethyl acetate (20 mL x 2), washed with brine (30 mL x 2), and evaporated to dryness. The crude product was purified by column chromatography silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **37C** (693 mg, yield 75%) as colorless oil. LC-MS (m/z): 386 [M+1]⁺.

[000458] To a solution of Compound **37C** (0.5 g, 1.3 mmol) in THF (10 mL) was added triethylamine (0.26 g, 2.6 mmol) and MsCl (164 mg, 1.4 mmol) under N₂ at -40 °C. The mixture was stirred at this temperature for 3 h, quenched with water (20 mL), extracted with ethyl acetate (30 mL x 2), washed with brine (50 mL x 2), and evaporated to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate in

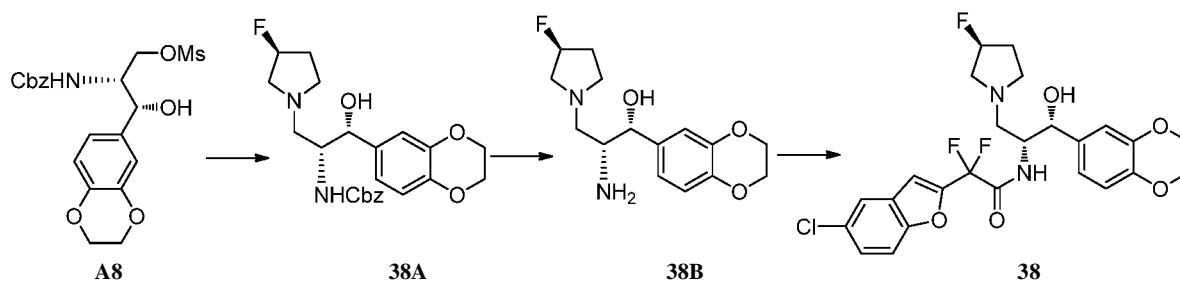
petroleum ether, 50% v/v) to yield Compound **37D** (0.42 g, yield 70%>) as colorless oil. LC-MS (m/z): 464 [M-17]⁺.

[000459] To a solution of Compound **37D** (0.4 g, 0.86 mmol) in THF (10 mL) was added pyrrolidine (0.61 g, 8.6 mmol). The mixture was stirred at 60 °C overnight, quenched with water (20 mL), extracted with ethyl acetate (30 mL x 3), washed with brine (100 mL x 2), and evaporated to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 50%> v/v) to give Compound **37E** (0.2 g, yield 53%) as a colorless oil. LC-MS (m/z): 439 [M+1]⁺.

[000460] A solution of Compound **37E** (0.2 g, 0.46 mmol) and LiOH·H₂O (57 mg, 1.4 mmol) in ethanol (10 mL) was heated to reflux overnight. The mixture was quenched with water (10 mL), extracted with ethyl acetate (20 mL x 3), washed with brine (50 mL x 2), and evaporated to dryness to give Compound **37F** (126 mg, yield 90%>) as a colorless oil. LC-MS (m/z): 305 [M+1]⁺.

[000461] To a solution of Compound **37F** (0.1 g, 0.33 mmol) in dichloromethane (10 mL) was added Compound **HE** (81 mg, 0.33 mmol), EDCI (95 mg, 0.5 mmol), HOBt (68 mg, 0.5 mmol). The mixture was stirred at rt overnight, quenched with water (20 mL), extracted with dichloromethane (20 mL x 2), washed with brine (50 mL x 2), and evaporated to dryness. The crude product was purified by prep-HPLC and followed Chiral-HPLC to give two isomers Compound **37G** (11 mg) as a white solid and Compound **37** (6 mg) as a white solid. For Compound **37G**, LC-MS (m/z): 533 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 4H), 3.11 (m, 2H), 3.52 (m, 4H), 4.31 (m, 1H), 4.60 (m, 1H), 6.22 (s, 1H), 6.84 (s, 1H), 7.12 (m, 2H), 7.38 (m, 2H), 7.52 (m, 1H), 7.67 (m, 1H), 7.78 (m, 1H), 9.28 (m, 1H), 9.82 (s, 1H). For Compound **37**, LC-MS (m/z): 533 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.87 (m, 4H), 3.10 (m, 2H), 3.50 (m, 4H), 4.51 (m, 1H), 4.89 (m, 1H), 6.11 (s, 1H), 7.05 (m, 3H), 7.39 (m, 2H), 7.54 (m, 1H), 7.73 (m, 1H), 7.82 (m, 1H), 8.94 (m, 1H), 9.63 (s, 1H).

Example 38

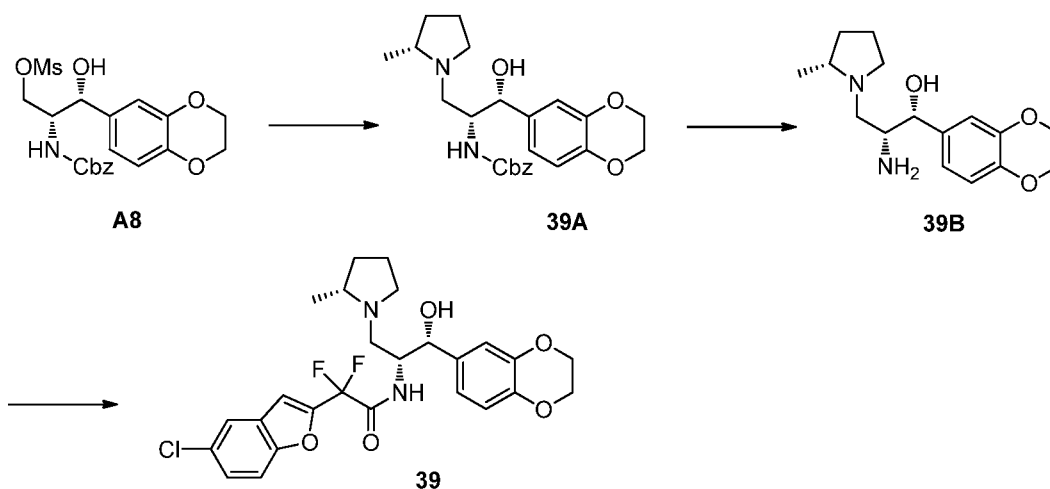


[000462] To a solution of (5)-3-fluoropyrrolidine (650 mg, 5.2 mmol) in CH₃CN (50 mL) was added Na₂CO₃ (717 mg, 5.2 mmol) and it was stirred at rt for 30 min. Compound **A6** (756 mg, 1.73 mmol) was added and the reaction mixture was heated to reflux overnight. It was poured into ice-water, extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by prep-HPLC to afford the Compound **38A** (270 mg, yield 36%) as a yellow liquid. LCMS: 431 [M+]⁺.

[000463] To a solution of Compound **38A** (170 mg, 0.55 mmol) in EtOH (2 mL) was added LiOH·H₂O (79 mg, 1.89 mmol) in water (1 mL) and the mixture was stirred at reflux overnight. It was quenched with H₂O (50 mL), extracted by ethyl acetate (50 mL x 3), washed with brine (20 mL), dried over Na₂SO₄, and evaporated to dryness to give Compound **38B** (200 mg, 100%) as a yellow oil. LC-MS (m/z): 297 [M+]⁻.

[000464] A mixture of Compound **HE** (165 mg, 0.67 mmol), EDCI·HCl (192 mg, 0.99 mmol), HOBT (135 mg, 0.99 mmol), Compound **38B** (200 mg, 0.67 mmol) in DCM (10 mL) was stirred at 28 °C overnight. The reaction was quenched with sat. aq NaHCO₃ (100 mL). The mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by prep-HPLC to give Compound **38** (100 mg, yield 28%) as a white solid. LC-MS (m/z): 525 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.04-2.49 (m, 2H), 3.21-3.97 (m, 6H), 4.06-4.20 (m, 4H), 4.52 (s, 1H), 5.04 (s, 1H), 5.32-5.45 (d, *J* = 52.4 Hz, 1H), 6.70-6.83 (m, 4H), 7.33-7.44 (m, 2H), 7.58 (s, 1H), 7.74-7.76 (d, *J* = 7.6 Hz, 1H).

Example 39



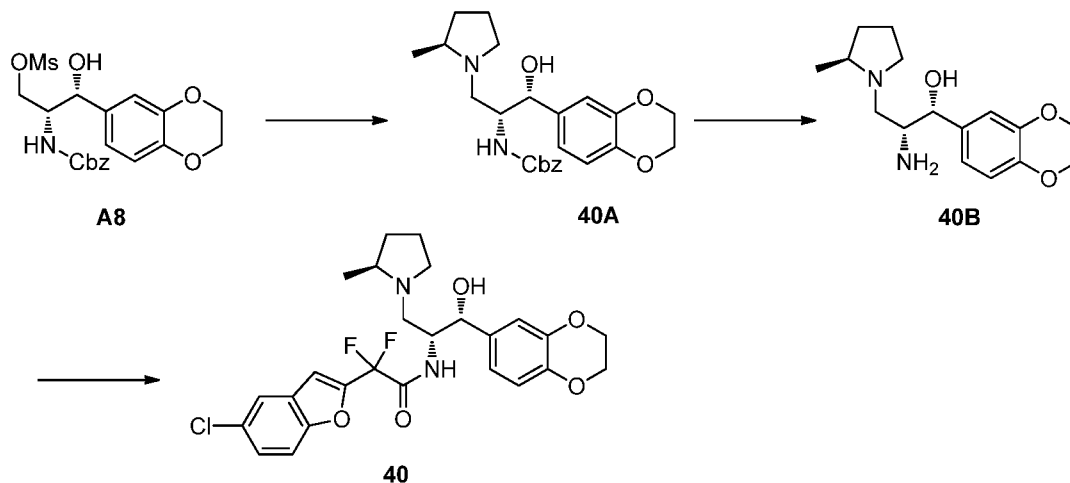
[000465] To a solution of Compound **A8** (514 mg, 1.16 mmol) in THF (15 mL) was added (*i*)-2-methylpyrrolidine (400 mg, 4.7 mmol) and Et₃N (0.5 mL). The reaction mixture

was stirred at 85 °C overnight. After the removal of solvents, the residue was purified by prep-HPLC to afford the Compound **39A** (150 mg, yield 30%) as a white solid. LCMS: 427 [M+]⁺.

[000466] To a solution of Compound **39A** (150 mg, 0.35 mmol) in MeOH (5 mL) was added Pd(OH)₂ (15 mg). The reaction mixture was stirred in the presence of H₂ at rt overnight. Filtration and evaporation of the solution led to Compound **39B** (102 mg, yield 100%) as the colorless oil. LCMS: 293 [M+]⁺.

[000467] A solution of Compound **39B** (102 mg, 0.35 mmol), Compound **HE** (86.3 mg, 0.35 mmol), HOBt (71.4 mg, 0.52 mmol), EDCI (100 mg, 0.52 mmol) in DCM (10 mL) was stirred at rt overnight. It was added water (50 mL), extracted with DCM (50 mL x 2), dried over Na₂S₄, filtered, and evaporated to dryness. The residue was purified by prep-HPLC to give desired product Compound **39** (8.7 mg, yield 5%) as the colorless oil. LCMS (m/z): 521 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.25-1.49 (m, 3H), 1.97-2.11 (m, 2H), 2.25-2.26 (m, 2H), 2.96-3.19 (m, 3H), 3.75-3.80 (m, 1H), 4.01 (s, 1H), 4.04-4.19 (m, 4H), 4.46 (s, 1H), 5.23 (s, 1H), 6.64 (s, 1H), 6.69-6.79 (m, 2H), 6.84 (s, 1H), 7.31-7.35 (m, 1H), 7.40-7.43 (m, 1H), 7.53-7.57 (m, 2H), 11.48 (s, 1H).

Example 40

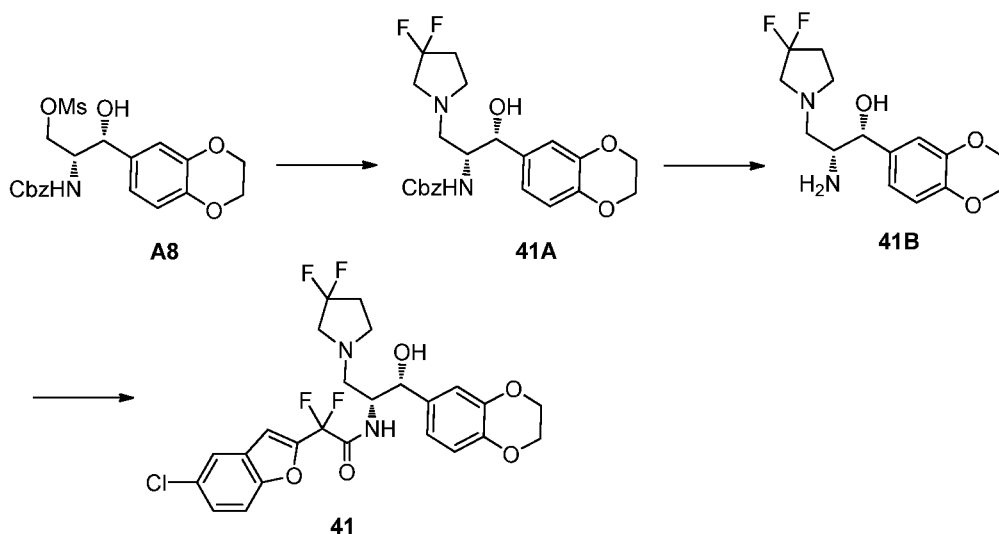


[000468] To a solution of (5)-2-methylpyrrolidine hydrochloride (540 mg, 4.4 mmol) in CH₃CN (10 mL) was added Na₂CO₃ (600 mg, 4.4 mmol). Stirred at rt for 30 min, Compound **A8** (437 mg, 1 mmol) was added. The reaction mixture was stirred at reflux overnight. It was poured into ice-water, extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na₂S₄, and concentrated to afford the mixture of Compound **40A** (300 mg) as a yellow oil. LCMS: 427 [M+]⁺.

[000469] To a solution of Compound **40A** (300 mg) in EtOH (10 mL) was added LiOH·H₂O (197 mg, 4.7 mmol) in water (5 mL) and the mixture was stirred reflux overnight. It was quenched in H₂O (50 mL) and the mixture was extracted by ethyl acetate (50 mL x 3), washed with brine (20 mL), dried over Na₂SO₄, and concentrated to render Compound **40B** (326 mg, yield 100%) as a yellow oil. LC-MS (m/z): 293 [M+1]⁺.

[000470] A mixture of Compound **40B** (326 mg, 1.12 mmol), EDCI·HCl (233 mg, 1.66 mmol), HOBT (164 mg, 1.66 mmol), Compound **HE** (200 mg, 1.12 mmol) in DCM (10 mL) was stirred at 28 °C overnight. After quenched with sat. aq NaHCO₃ (100 mL), the mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **40** (126 mg, yield 18%) as a white solid. LC-MS (m/z): 525 [M+1]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 1.31-1.33 (d, *J* = 6.4 Hz, 3H), 1.59-1.65 (m, 1H), 1.90-2.00 (m, 2H), 2.16-2.21 (m, 1H), 3.21-3.26 (m, 1H), 3.42-3.61 (m, 4H), 4.06-4.16 (m, 4H), 4.45-4.47 (m, 1H), 4.66-4.67 (m, 1H), 5.91 (s, 1H), 6.62-6.77 (m, 3H), 7.01 (s, 1H), 7.52-7.55 (m, 1H), 7.75-7.77 (d, *J* = 8.8 Hz, 1H), 7.83-7.85 (m, 1H), 8.92-8.99 (m, 2H).

Example 41



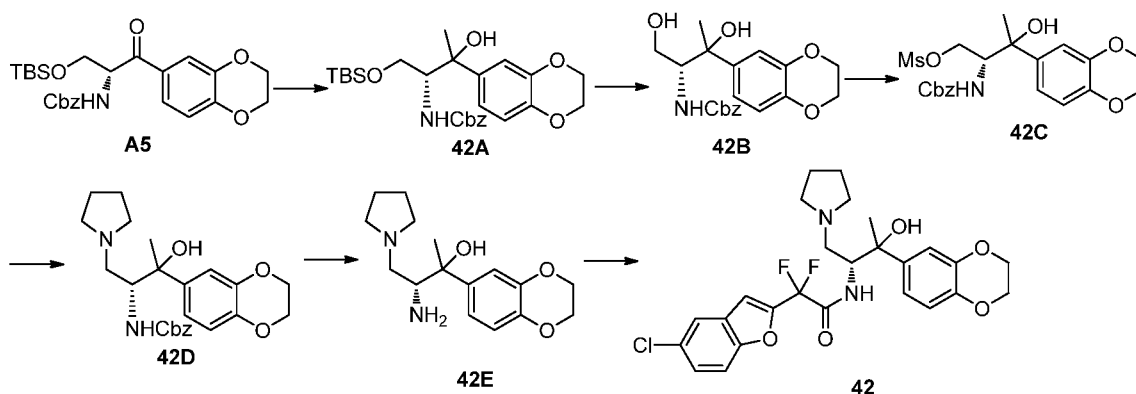
[000471] To a solution of 3,3-difluoropyrrolidine (384 mg, 3 mmol) in CH₃CN (20 mL) was added Compound **A8** (437 mg, 1 mmol), K₂CO₃ (414 mg, 3 mmol) and NaI (449 mg, 3 mmol). The mixture was heated at 82 °C overnight. It was cooled to rt, filtered and concentrated in vacuum to give a crude product Compound **41A** (250 mg, crude) as a yellow oil. LCMS (m/z): 449 [M+1]⁺.

[000472] To a solution of Compound **41A** (200 mg, 0.45 mmol) in EtOH/water (10 mL, 9:1, v/v) was added LiOH·H₂O (93.6 mg, 2.23 mmol). The mixture was refluxed overnight.

The mixture was diluted with water (20 mL) and then extracted with ethyl acetate (20 mL x 3), dried over anhydrous Na_2SO_4 , and concentrated in vacuum to give a crude Compound **41B** (170 mg, crude) as a yellow oil. LCMS (m/z): 315 [M+]⁺.

[000473] To a mixture of Compound **41B** (150 mg, 0.47 mmol) in DCM (20 mL) was added EDCI (164 mg, 0.85 mmol), HOBT (115 mg, 0.85 mmol) and Compound **HE** (140 mg, 0.57 mmol) and stirred at 25 °C overnight. After the addition of water (10 mL), the mixture was extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford Compound **41** (40 mg) as a white solid. LCMS (m/z): 543 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.59 (s, 2H), 3.44 (s, 1H), 3.60-3.74 (m, 4H), 4.07-4.15 (m, 4H), 4.46 (s, 1H), 4.99 (s, 1H), 6.73-6.80 (m, 4H), 7.32-7.35 (m, 1H), 7.40-7.43 (d, 1H), 7.57 (d, 1H), 7.78 (s, 1H).

Example 42



[000474] Compound **A5** (4.64 g, 9.85 mmol) was dissolved in anhydrous THF (100 mL) and cooled down -30 °C under nitrogen atmosphere. CH_3MgBr (9.85 mL, 3M solution in ether, 29.55 mmol) was added dropwise while keeping the temperature at -30 °C. Then the reaction was warmed to rt and stirred for 3 hrs. The reaction was quenched with saturate aq NH_4Cl solution and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed water, brine, and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to give Compound **42A** (3.76g, yield 78%) as a white solid. LC-MS (m/z): 193 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) -0.09 (s, 3H), -0.05 (s, 3H), 0.84 (s, 9H), 1.42 (s, 3H), 3.51 (dd, $J = 2.0, 10.4$ Hz, 1H), 3.53 (dd, $J = 2.0, 10.4$ Hz, 1H), 3.91 (d, $J = 7.2$ Hz, 1H), 3.71 (m, 1H), 4.26 (s, 4H), 4.45 (m, 1H), 5.16 (s, 2H), 5.72 (d, $J = 7.2$ Hz, 1H), 6.85 (m, 2H), 6.95 (s, 1H), 7.38 (m, 5H).

[000475] To a solution of Compound **42A** (5.9 g, 12.11 mmol) in THF (120 mL) was added a solution of TBAF (1.58 g, 6.06 mmol) in THF (10 mL) at 0 °C and the mixture was

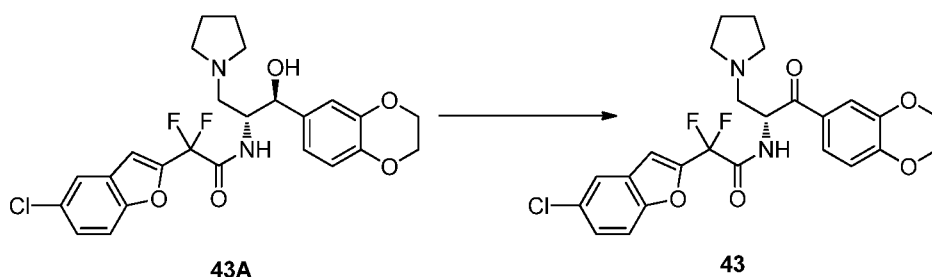
stirred at 25 °C overnight. The mixture was condensed by removal of solvent and added water (50 mL). It was extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 1), dried over Na₂S₄. The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 3% v/v) to give Compound **42B** (3.2 g, yield 71%) as a yellow oil. LC-MS (m/z): 356 [M-17]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.49 (s, 3H), 3.34 (s, 1H), 3.58 (m, 2H), 3.91 (d, *J* = 8.8 Hz, 1H), 4.25 (s, 4H), 5.15 (s, 2H), 5.79 (d, *J* = 8.8 Hz, 1H), 6.85 (m, 2H), 6.96 (s, 1H), 7.38 (m, 5H).

[000476] To a solution of Compound **42B** (3.2 g, 8.58 mmol) in THF (80 mL) was added Et₃N (2.6 g, 25.7 mmol) and the mixture was cooled to -40 °C, MsCl (0.7 mL, 9.01 mmol) was added slowly and kept with stirring at -40 °C about 0.5 h. Pyrrolidine (5.48 g, 77.2 mmol) was added to -40 °C. The reaction mixture was allowed to warm up to rt and then heated to 50 °C overnight. The mixture was added water (50 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 1), and dried over Na₂S₄. The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 3% v/v) to give Compound **42C** (2.52 g, yield 77%) as a white syrup. LC-MS (m/z): 356 [M-17]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.40 (s, 3H), 1.69 (m, 4H), 2.35 (m, 1H), 2.57 (m, 1H), 4.16 (m, 1H), 4.27 (s, 4H), 5.15 (s, 2H), 5.59 (d, *J* = 10.2 Hz, 1H), 6.86 (m, 2H), 6.98 (s, 1H), 7.38 (m, 5H).

[000477] To a solution of Compound **42C** (2.52 g, 5.92 mmol) in methanol (60 mL) was added Pd(OH)₂ (250 mg) and then the mixture was stirred at 25 °C under H₂ overnight. It was filtered and evaporated to render Compound **42D** (1.82 g, crude). LC-MS (m/z): 356 [M-17]⁺.

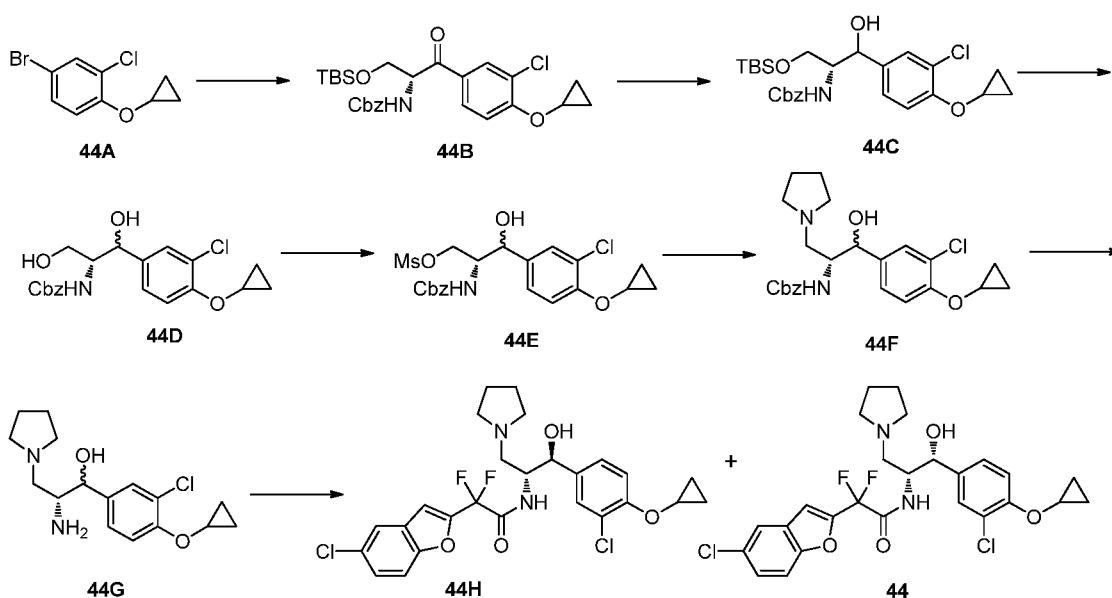
[000478] To a solution of compound **42D** (200 mg, 0.68 mmol) and Compound **HE** (168 mg, 0.68 mmol) in DCM (210 mL) was added EDCI (197 mg, 1.03 mmol) and HOBT (139 mg, 1.03 mmol) under N₂. The mixture was stirred at 25 °C overnight. When TLC showed the starting material was consumed, water was added to the mixture. It was then extracted with DCM (50 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to give a crude product. The crude product was purified by prep-HPLC to give Compound **42** (145 mg, yield 41%) as a white solid. LC-MS (m/z): 521 (M+)⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.52 (s, 3H), 1.99-2.06 (m, 4H), 2.60-2.74 (m, 4H), 3.60-3.69 (m, 2H), 3.88 (t, *J* = 7.2 Hz, 1H), 4.03 (m, 2H), 4.27 (s, 4H), 4.61 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 7.15 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 9.19 (d, *J* = 8.4 Hz, 1H), 11.20 (s, 1H).

Example 43



[000479] To a stirred solution of Compound **43A** (100 mg, 0.2 mmol), NaHCO_3 (33 mg, 0.4 mmol) and NMP (126 mg, 0.3 mmol) in DCM (5 mL) was stirred at rt for 2h. The mixture was diluted with saturation aq NaHSO_3 (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with saturate aq NaHSO_3 (15 mL), brine (15 mL), dried over Na_2SO_4 , and concentrated to give a crude product. The crude product was purified by prep-HPLC to afford Compound **43** (17 mg, yield 14%) as a white solid. LC-MS (m/z): 505 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 2.95-2.96 (m, 2H), 3.58-3.61 (m, 2H), 3.89-3.99 (m, 2H), 4.06-4.23 (m, 4H), 5.47 (s, 1H), 6.70-6.72 (d, $J = 9$ Hz, 2H), 6.86 (s, 1H), 7.30-7.33 (m, 4H), 7.54 (s, 1H), 9.66-9.68 (d, $J = 8$ Hz, 1H).

Example 44



[000480] To a solution of Compound **44A** (3.73 g, 15.1 mmol) in THF (200 mL) was added n-BuLi (6.1 mL) at -60 °C under N_2 and it was stirred for 0.5 h, and then added slowly Compound **A4** (2 g, 5.06 mmol) in THF (10 mL). The mixture was stirred at -60 °C for 1 h. After the addition of saturate aq NH_4Cl solution, the mixture was extracted with ethyl acetate

(100 mL x 2), brine (100 mL), and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to yield Compound **44B** (1.2 g, yield 47%) as a colorless oil. LC-MS (m/z): 504.2 [M+]⁺.

[000481] Compound **44B** (714 mg, 1.42 mmol) was dissolved in THF (9 mL) and cooled down -80 °C under nitrogen atmosphere. L-Selectride (3 mL of 1M solution in THF, 18.9 mmol) was added dropwise while keeping the temperature at -80 °C. After an hour, the reaction was quenched with saturate aq NH_4Cl solution and extracted with ethyl acetate (50mL x 2), washed with brine (100 mL), and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (10% ethyl acetate in petroleum) to give Compound **44C** (350 g, yield 49%) as a colorless oil. LC-MS (m/z): 488.2 [M-17]⁺.

[000482] A solution of Compound **44C** (2.08 g, 4.11 mmol) in THF (40 mL) was added TBAF (537 mg, 2.06 mmol) at 0 °C and the mixture was stirred at rt overnight. The mixture was condensed and then added water (50 mL). It was extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL), dried over Na_2SO_4 , and concentrated. The residue was suspended in a mixture solution of ethyl acetate in petroleum (10% v/v). Filtration gave Compound **44D** (1 g, yield 65%) as a white solid. LC-MS (m/z): 374.1 [M+]⁺.

[000483] A solution of Compound **44D** (0.9 g, 2.3 mmol) in THF (60 mL) was added Et_3N (700 mg, 6.9 mmol) and the mixture was cooled to -15 °C, to the mixture was added MsCl (467 mg, 4.1 mmol) slowly. The mixture was stirred at -15 °C about half an hour, and then diluted water. It was extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , and concentrated to give Compound **44E** (1.12 g, crude), which was used for the next step without further purification. LC-MS (m/z): 452.1 [M+]⁺.

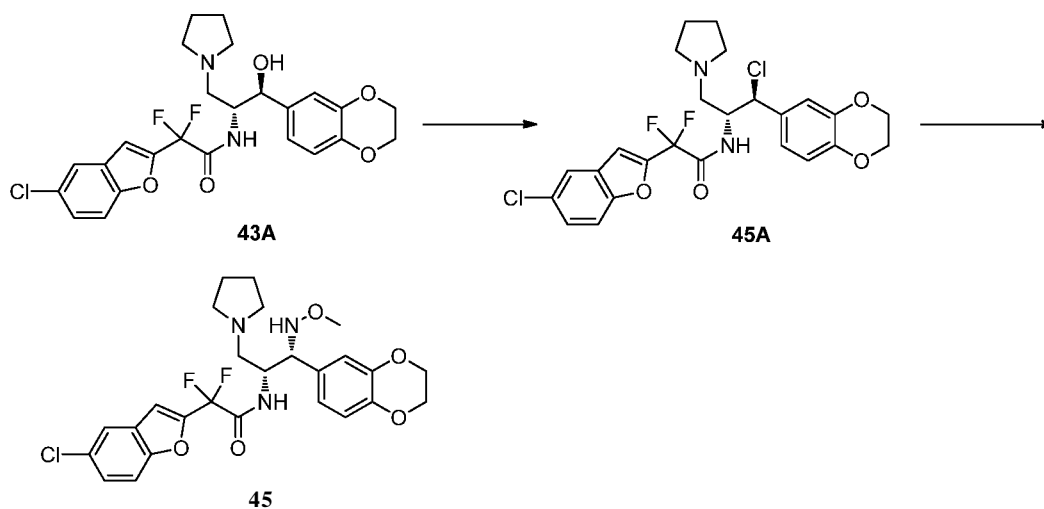
[000484] To a solution of Compound **44E** (1.12 g, 2.83mmol) in THF (60 mL) was added pyrrolidine (2 g, 28mmol). The reaction mixture was allowed to warm up to rt and then heated at 50 °C overnight. The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to render Compound **44F** (0.5 g, yield 50%). LC-MS (m/z): 445 [M+]⁺.

[000485] To a solution of Compound **44F** (520 mg, 1.17 mmol) in ethanol (12 mL) and water (2 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (197 mg, 4.68 mmol). The mixture was stirred at 80 °C overnight, diluted water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , and concentrated to give Compound **44G** (360 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 311.1 [M+]⁺.

[000486] A mixture of Compound **44E** (149 mg, 0.60mmol), EDCI (175 mg, 0.9 mmol), HOBT (150 mg, 1.1 mmol), Compound **44G** (188 mg, 0.60 mmol) in DCM (10 mL)

was stirred at rt overnight. The mixture was added water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC and followed by chiral-prep-HPLC to give Compound **44H** (23 mg, yield 7%) as a white solid and Compound **44** (22 mg, yield 7%) as a white solid. For Compound **44H**, LC-MS (m/z): 539.1 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.72-0.79 (m, 4H), 2.06 (s, 4H), 2.78-3.20 (m, 6H), 3.60-3.93 (m, 4H), 4.50 (s, 1H), 4.93-4.95 (d, $J = 5.6$ Hz, 1H), 6.83 (s, 1H), 7.10-7.12 (d, $J = 8.4$ Hz, 1H), 7.20-7.22 (d, $J = 8.0$ Hz, 1H), 7.30-7.33 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.40-7.42 (m, 2H), 7.56-7.57 (d, $J = 2.0$ Hz, 1H), 9.07-9.09 (d, $J = 8.0$ Hz, 1H). For Compound **44**, LC-MS (m/z): 539.1 [M+]⁺; ¹H NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.72-0.77 (m, 4H), 2.08-2.14 (d, $J = 24.4$ Hz, 4H), 2.94-3.02 (d, $J = 34.4$ Hz, 5H), 3.53-3.58 (m, 3H), 3.81-3.82 (d, $J = 2.4$ Hz, 2H), 4.48-4.50 (d, $J = 9.6$ Hz, 1H), 5.14 (s, 1H), 6.71(s,1H), 7.04-7.06 (d, $J = 8.4$ Hz, 1H), 7.12-7.14 (d, $J = 8.4$ Hz, 1H), 7.32-7.41 (m, 3H), 7.56 (s, 1H), 7.88-7.90 (d, $J = 7.2$ Hz, 1H).

Example 45

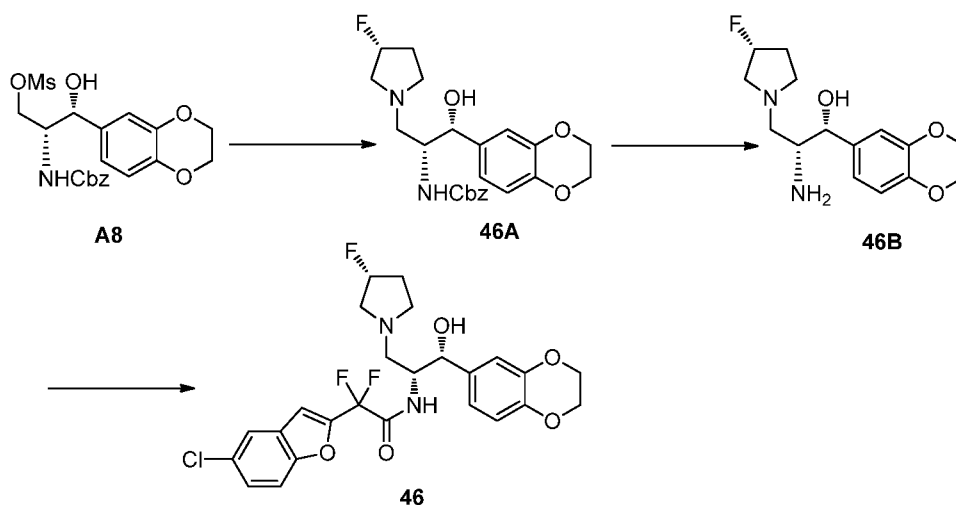


[000487] To a solution of Compound **43A** (100 mg, 0.2 mmol) in DCM (10 mL) was added SOCl_2 (0.1 mL). The mixture was stirred at 25 °C for 3 h, and concentrated to afford the Compound **45A** (105 mg) as a yellow liquid. LCMS (m/z): 525 [M+]⁺.

[000488] A solution of NH_2OCH_3 in MeOH (30%, m/v, 1 mL) was added to the Compound **45A** (105 mg, 0.2 mmol). The mixture was stirred at 25 °C for 3 h. After reaction, the mixture was concentrated. The crude product was purified by prep-HPLC to give Compound **45** (15 mg, yield 15%) as a white solid. LC-MS (m/z): 536 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.82 (m, 4H), 2.72 (m, 5H), 2.91-2.96 (m, 1H), 3.76 (s, 3H), 4.06-4.07 (m, 1H), 4.23-4.27 (m, 4H), 4.94 (d, $J = 2.4$ Hz, 1H), 5.26-

5.28 (d, $J = 10.8$ Hz, 1H), 6.72 (s, 1H), 6.75-6.81 (m, 2H), 6.86 (s, 1H), 7.31-7.34 (m, 1H), 7.43-7.45 (m, 1H), 7.55-7.56 (m, 1H).

Example 46

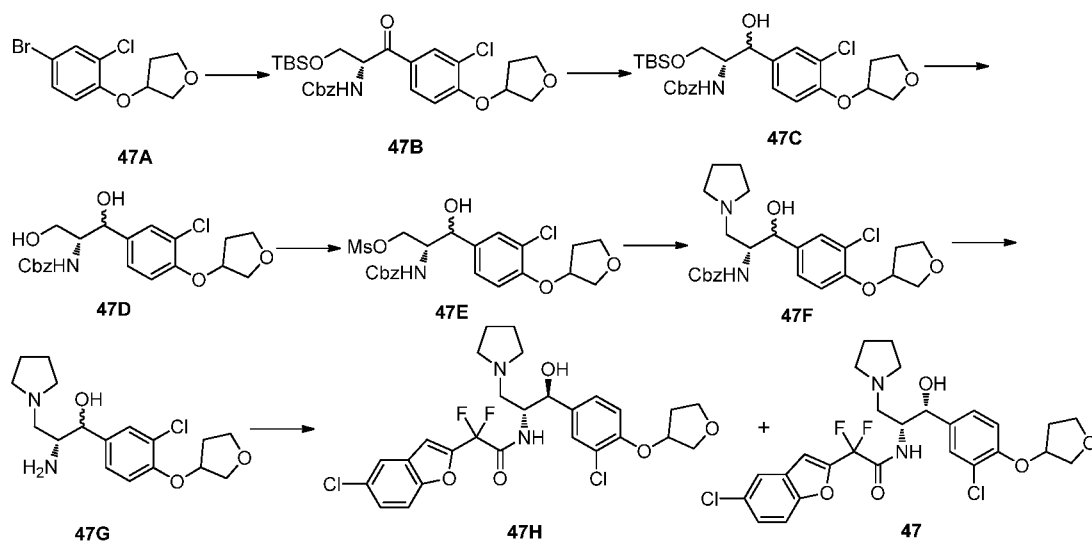


[000489] To a solution of (*R*)-3-fluoropyrrolidine (174 mg, 1.38 mmol) in CH_3CN (10 mL) was added K_2CO_3 (190 mg, 1.38 mmol). Stirred at rt for 30 min, Compound **A8** (200 mg, 0.46 mmol) was added. The reaction mixture was stirred at reflux overnight. It was poured into ice-water, extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL x 1), dried over Na_2SO_4 , and concentrated to give a crude Compound **46A** (200 mg, 100%), which was used for the next step without further purification. LC-MS (m/z): 431 $[\text{M}+1]^+$.

[000490] To a solution of Compound **46A** (200 mg, 0.62 mmol) in EtOH (10 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (130 mg, 3.1 mmol) in water (10 mL) and the mixture was stirred at reflux overnight. It was poured into H_2O (50 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (20 mL), dried over Na_2SO_4 , and concentrated to yield a crude Compound **46B** (170 mg, yield 100%) as a yellow oil. LC-MS (m/z): 297 $[\text{M}+1]^+$.

[000491] A mixture of Compound **HE** (140 mg, 0.57 mmol), EDCI (160 mg, 0.84 mmol), HOBT (113 mg, 0.84 mmol) and Compound **46B** (170 mg, 0.57 mmol) in DCM (20 mL) was stirred at 28 °C overnight. The mixture was added sat. NaHCO_3 (100 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC to give Compound **46** (60 mg, 20%) as a white solid. LC-MS (m/z): 525 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.08-2.39 (m, 2H), 3.19-3.86 (m, 6H), 4.03-4.14 (m, 4H), 4.49 (s, 1H), 4.71 (s, 1H), 5.38-5.54 (d, $J = 48.4$ Hz, 1H), 5.91 (s, 1H), 6.64-6.72 (m, 3H), 6.96-6.99 (m, 1H), 7.52-7.55 (m, 1H), 7.71-7.83 (m, 2H), 8.82-8.89 (m, 1H), 10.33 (s, 1H).

Example 47



[000492] To a solution of Compound **47A** (12.6 g, 45.5 mmol) in THF (300 mL) was added n-BuLi (18.3 mL) at $-60\text{ }^{\circ}\text{C}$ under N_2 and it was stirred for 0.5 h, and then slowly added **A4** (6 g, 15.2 mmol) in THF (40 mL). The mixture was stirred at $-60\text{ }^{\circ}\text{C}$ for 1 h, and followed by the addition of saturate aq NH_4Cl solution. It was extracted with ethyl acetate (300 mL x 2), brine (200 mL), dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10 v/v) to give Compound **47B** (4 g, yield 50%) as a colorless oil. LC-MS (m/z): 534.2 $[\text{M}+1]^+$.

[000493] Compound **47B** (4.05 g, 7.6 mmol) was dissolved in THF (48 mL) and cooled down to $-80\text{ }^{\circ}\text{C}$ under nitrogen atmosphere. L-Selectride (16 mL of 1M solution in THF, 15 mmol) was added dropwise while keeping the temperature at $-80\text{ }^{\circ}\text{C}$. After an hour, the reaction was quenched with saturate aq NH_4Cl solution and then extracted with ethyl acetate (200 mL x 2), washed with brine (200 mL), and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to give Compound **47C** (3.2 g, 79%) as a colorless oil. LC-MS (m/z): 518.2 $[\text{M}-17]^+$.

[000494] A solution of Compound **47C** (3.2 g, 5.98 mmol) in THF (40 mL) was added TBAF (780 mg, 3 mmol) at $0\text{ }^{\circ}\text{C}$. The mixture was stirred at rt overnight, condensed by removal of solvents, and added water (150 mL). It was extracted with ethyl acetate (250 mL x 2), washed with brine (100 mL), dried over Na_2SO_4 , concentrated. The residue was suspended in a solution of ethyl acetate in petroleum (10% v/v). filtration of the suspension gave Compound **47D** (2.25 g, yield 89%) as a white solid. LC-MS (m/z): 422.1 $[\text{M}+1]^+$.

[000495] A solution of Compound **47D** (2.25 g, 5.34 mmol) in THF (120 mL) was added Et_3N (1.63 g, 16 mmol) and MsCl (1.08 g, 9.43 mmol) slowly at $-15\text{ }^{\circ}\text{C}$. The mixture

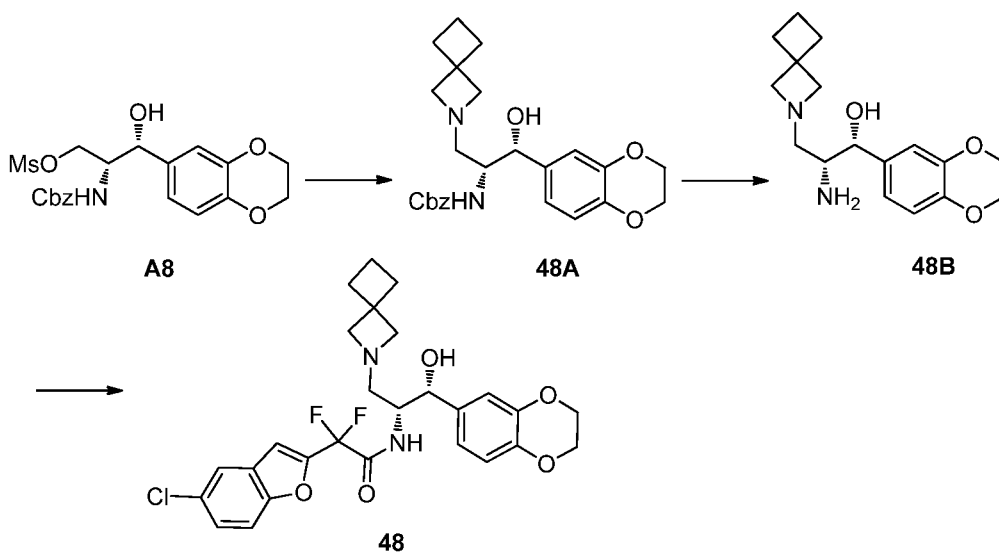
was stirred about half an hour, and then diluted water, extracted with ethyl acetate (200 mL x 2), washed with brine (150 mL), dried over Na₂S₀₄, and concentrated to render Compound **47E** (2.3 g, crude), which was used for the next step without further purification. LC-MS (m/z): 482 [M-17]⁺.

[000496] To a solution of Compound **47E** (2.3 g, 4.61 mmol) in THF (60 mL) was added pyrrolidine (3.5 g, 49 mmol). The reaction mixture was allowed to warm up to rt and then heated at 50 °C overnight. The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **47F** (0.52 g, yield 23.8%). LC-MS (m/z): 475 [M+1]⁺.

[000497] To a solution of Compound **47F** (520 mg, 1.1 mmol) in ethanol (12 mL) and water (2 mL) was added LiOH·H₂O (197 mg, 4.68 mmol). The mixture was stirred at 80 °C overnight, and then diluted water, extracted with DCM (150 mL x 2), washed with brine (150 mL), dried over Na₂S₀₄, and concentrated to afford Compound **47G** (360 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 341.2 [M+1]⁺.

[000498] A mixture of Compound **HE** (149 mg, 0.60 mmol), EDCI (175 mg, 0.9 mmol), HOBt (150 mg, 1.1 mmol), Compound **47G** (206 mg, 0.60 mmol) in DCM (10 mL) was stirred at rt overnight. The mixture was added water, extracted with DCM (150 mL x 2), washed with brine (100 mL), dried over Na₂S₀₄, and concentrated. The crude product was purified by prep-HPLC and followed by chiral-prep-HPLC to give Compound **47H** (13 mg, yield 4%) as a white solid and Compound **47** (31 mg, 10.5%) as a white solid. For Compound **47H**, LC-MS (m/z): 569.2 [M+1]⁺; ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.05-2.81 (m, 6H), 2.78-2.89 (m, 5H), 3.21-3.22 (d, J = 4.0 Hz, 1H), 3.62 (s, 1H), 3.75 (s, 1H), 3.90-4.02 (m, 5H), 4.50 (s, 1H), 4.77 (s, 1H), 4.90 (s, 1H), 6.63-6.66 (dd, J₁ = 5.2 Hz, J₂ = 8.0 Hz, 1H), 6.80-6.81 (d, J = 4.8 Hz, 1H), 7.17-7.19 (d, J = 8.0 Hz, 1H), 7.30-7.32 (m, 1H), 7.38-7.41 (dd, J₁ = 3.2 Hz, J₂ = 8.0 Hz, 1H), 7.44-7.46 (d, J = 6.4 Hz, 1H), 7.55-7.56 (m, 1H), 9.14 (s, 1H), 11.57 (s, 1H). For Compound **47**, LC-MS (m/z): 569.2 [M+1]⁺; ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.02-2.11 (m, 6H), 2.97-3.02 (m, 2H), 3.50 (s, 1H), 3.69-4.12 (m, 9H), 4.56 (m, 1H), 4.71 (s, 1H), 5.10 (s, 1H), 6.55-6.57 (d, J = 8.0 Hz, 1H), 6.63-6.65 (d, J = 7.6 Hz, 1H), 7.09-7.11 (d, J = 7.2 Hz, 1H), 7.31-7.40 (m, 3H), 7.55 (s, 1H), 8.06 (s, 1H), 11.48 (s, 1H).

Example 48

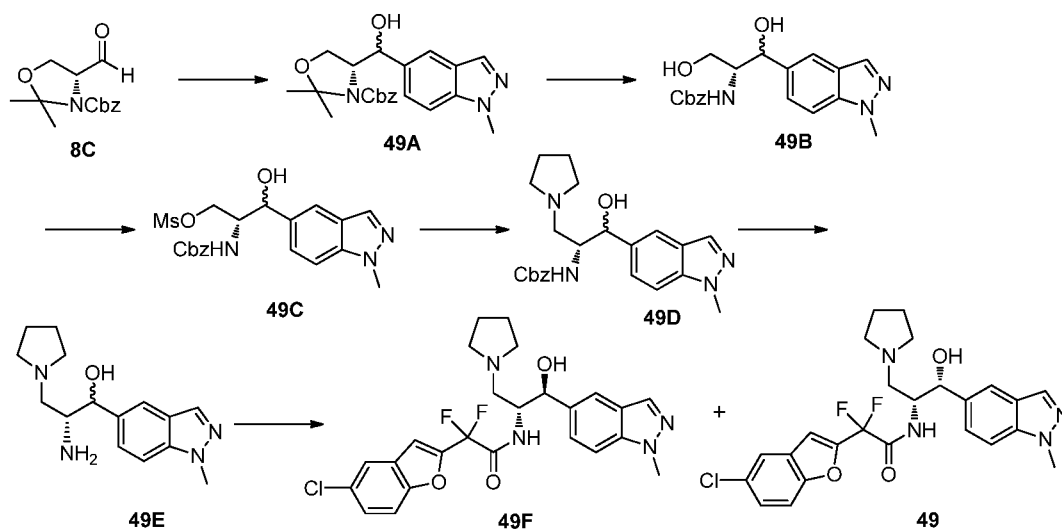


[000499] To a solution of 2-azaspiro [3.3] heptane (100 mg, 1.0 mmol) in CH_3CN (10 mL) was added K_2CO_3 (414 mg, 3.0 mmol) and Compound **A6** (437 mg, 1.0 mmol). The reaction mixture was stirred at reflux overnight. It was poured into ice-water, extracted with ethyl acetate (20 mL x 2), washed with brine (20 mL x 1), dried over Na_2SO_4 , and concentrated to afford the Compound **48A** (180 mg, yield 40%) as a yellow liquid. LC-MS (m/z): 439 [M+]⁺.

[000500] To a solution of Compound **48A** (180 mg, 0.4 mmol) in EtOH (3 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (84 mg, 2.0 mmol) in water (1 mL) and the mixture was stirred at reflux overnight. The mixture was diluted with H_2O (30 mL), extracted by ethyl acetate (30 mL x 3), washed with brine (20 mL), dried by Na_2SO_4 , and concentrated to render Compound **48B** (100 mg, yield 80%) as a yellow oil. LC-MS (m/z): 305 [M+]⁺.

[000501] A mixture of Compound **HE** (81 mg, 0.3 mmol), EDCI (76 mg, 0.4 mmol), HOBt (54 mg, 0.4 mmol), Compound **48B** (100 mg, 0.3 mmol) in DCM (5 mL) was stirred at 28 °C overnight. After the addition of sat. aq NaHCO_3 (100 mL), the mixture was extracted with DCM (30 mL x 2), washed with brine (30 mL x 1), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC to give Compound **48** (14 mg, yield 8%) as a white solid. LC-MS (m/z): 533 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.83-1.88 (m, 2H), 2.15 (s, 2H), 2.34 (s, 2H), 3.34 (s, 2H), 3.78-3.84 (m, 2H), 4.06-4.19 (m, 4H), 4.28-4.38 (m, 3H), 5.01 (s, 1H), 6.74-6.81 (m, 4H), 7.34-7.7.36 (m, 1H), 7.42-7.44 (m, 1H), 7.58-7.58 (m, 1H), 7.84-7.86 (m, 1H), 12.29-12.30 (m, 1H).

Example 49



[000502] To a solution of 5-bromo-1-methyl-1H-indazole (3.2 g, 15 mmol) in THF (50 mL) was added n-BuLi (7.2 mL, 2.5 M) under N₂ at -60 °C. The mixture was stirred for 1 h, Compound **8C** (1.3 g, 5 mmol) in THF (10 mL) was added. After stirred at rt for 3 h, the mixture was diluted with aq NH₄Cl (40 mL) solution, extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and evaporated. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **49A** (1.0 g, yield 51%) as a colorless oil. LC-MS (m/z): 396 [M+]⁺.

[000503] A solution of Compound **49A** (0.5 g, 1.3 mmol) in THF (20 mL) and 1 N aq HCl (4 mL) was stirred at rt for 5 h. The mixture was quenched with water (10 mL), extracted with ethyl acetate (20 mL x 2), washed with brine (30 mL x 2), and evaporated to remove the solvents. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **49B** (374 mg, yield 81%) as a colorless oil. LC-MS (m/z): 356 [M+]⁺.

[000504] To a solution of Compound **49B** (1 g, 2.8 mmol) in THF (25 mL) was added triethylamine (0.44 g, 4.4 mmol) and MsCl (0.4 g, 3.5 mmol) under N₂ at -40 °C. The mixture was stirred at this temperature for 3 h, quenched with water (40 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), NS evaporated to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **49C** (0.87 g, yield 72%) as a colorless oil. LC-MS (m/z): 416 [M-17]⁺.

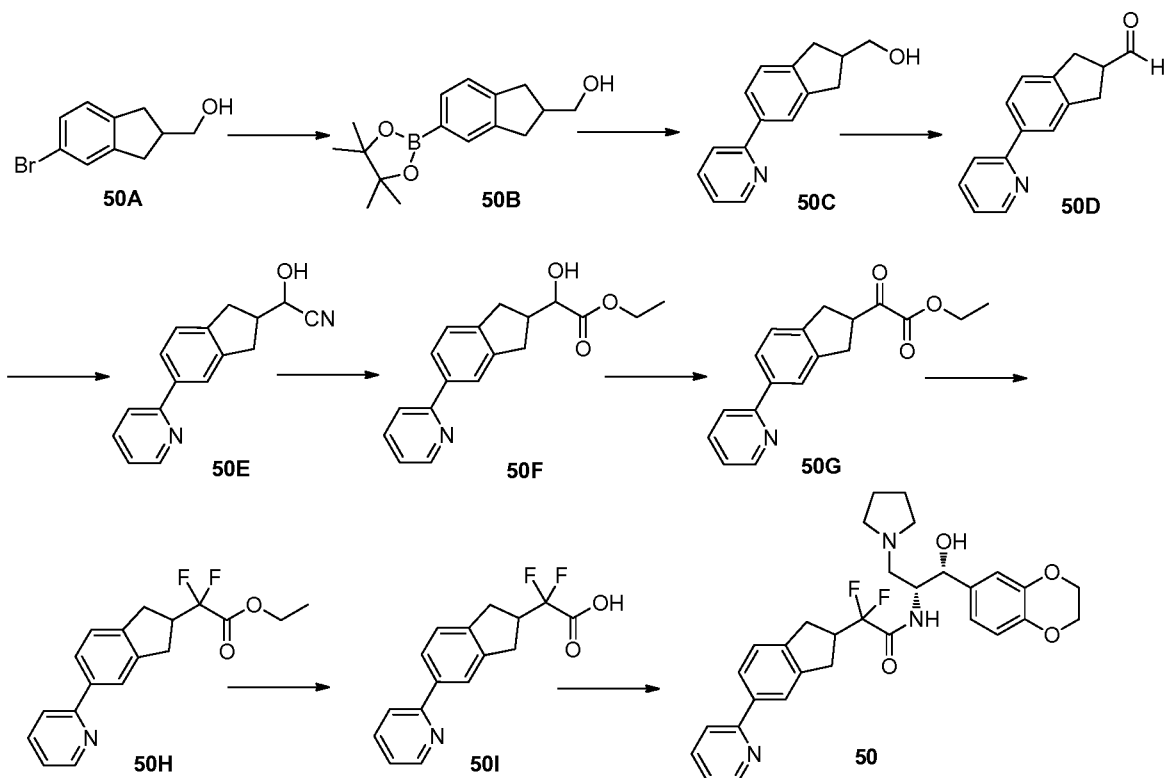
[000505] To a solution of Compound **49C** (0.8 g, 1.8 mmol) in THF (25 mL) was added pyrrolidine (1.3 g, 18 mmol). The mixture was stirred at 60 °C overnight, quenched with water (40 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2),

and evaporated to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **49D** (0.4 g, yield 55%) as colorless oil. LC-MS (m/z): 409 [M+]⁺.

[000506] A solution of Compound **49D** (0.4 g, 1 mmol) and LiOH·H₂O (157 mg, 3.6 mmol) in ethanol (20 mL) was heated to reflux overnight. After the addition of water (40 mL), the mixture was extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL x 2), evaporated to give Compound **49E** (247 mg, yield 90%>) as a colorless oil. LC-MS (m/z): 275 [M+]⁺.

[000507] To a solution of Compound **49E** (0.2 g, 0.73 mmol) in dichloromethane (15 mL) was added Compound **HE** (222 mg, 0.9 mmol), EDCI (216 mg, 1.13 mmol), HOBt (152 mg, 1.13 mmol). The mixture was stirred at rt overnight, quenched with water (20 mL), extracted with dichloromethane (20 mL x 2), washed with brine (50 mL x 2), and evaporated to dryness. The crude product was purified by prep-HPLC and followed by chira-prepl-HPLC to give two isomers Compound **49F** (5 mg) as white solid and Compound **49** (5 mg) as white solid. For Compound **49F**, LC-MS (m/z): 503 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 4H), 3.14 (m, 2H), 3.58 (m, 2H), 3.68 (m, 1H), 3.92 (s, 3H), 4.44 (m, 1H), 4.66 (m, 1H), 6.12 (s, 2H), 7.47 (m, 5H), 7.63 (s, 1H), 7.92 (s, 1H), 9.27 (s, 1H), 9.70 (s, 1H); For Compound **49**, LC-MS (m/z): 503 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 2.0 (m, 6H), 3.17 (m, 3H), 3.50 (m, 3H), 3.98 (m, 4H), 4.60 (s, 1H), 4.96 (s, 1H), 6.05 (s, 1H), 6.69 (s, 1H), 7.57 (m, 9H), 7.88 (s, 1H), 8.92 (s, 1H), 9.65 (s, 1H).

Example 50



[000508] To a stirred solution of Compound **50A** (500 mg, 2.21 mmol) in dioxane (10 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (618 mg, 2.43 mmol), KOAc (694 mg, 7.08 mmol) and Pd(PPh₃)₂C₁₂ (90 mg, 0.11 mmol) under N₂. The mixture was stirred at 90 °C overnight. The reaction mixture was evaporated to remove the solvent. The residue was diluted with ethyl acetate (100 mL), washed with water, brine, and dried over anhydrous Na₂SO₄. Filtration and evaporation of the solvents gave Compound **50B** (606 mg, yield 100%) as a brown oil which was used for the next step without purification. LCMS: (m/z) 275 [M+]⁺;

[000509] To a stirred solution of Compound **50B** (606 mg, 2.21 mmol) in dioxane (10 mL) was added Pd(PPh₃)₄ (127 mg, 0.11 mmol), 2-bromopyridine (384 mg, 2.43 mmol) and 3 mL of 30% aq NaOH under N₂. The mixture was stirred at 90 °C overnight. The mixture was evaporated to remove the solvents. The residue was diluted with ethyl acetate (100 mL), washed with water, brine, and dried over anhydrous Na₂SO₄. The crude was purified by column chromatography on silica gel (methanol in DCM, 5% v/v) to render Compound **50C** (230 mg, yield 46%, two steps) as a yellow oil. LCMS: (m/z) 226 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.58 (brs, 1H), 2.76-2.85 (m, 3H), 3.10-3.18 (m, 2H), 3.69 (d, *J* = 6.0 Hz, 2H), 7.20 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.71-7.75 (m, 3H), 7.86 (s, 1H), 8.67 (d, *J* = 4.8 Hz, 1H).

[000510] To a stirred solution of Compound **50C** (230 mg, 1.02 mmol) in DCM (10 mL) was added DMP (520 mg, 1.23 mmol). The mixture was stirred at rt for 3 h. The reaction mixture was quenched with sat. aq Na_2S_3 solution. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 . The crude was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 34% v/v) to give Compound **50D** (200 mg, yield 88%) as colorless oil. LCMS: (m/z) 224 [M+]⁺.

[000511] To a stirred solution of Compound **50D** (200 mg, 0.90 mmol) in H_2O (10 mL) was added NaS_2O_5 (170 mg, 0.90 mmol). The mixture was stirred at rt for 3 h, and NaCN (88 mg, 1.79 mmol) was added to the mixture. After stirred at rt overnight, the mixture was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 . Filtration and evaporation of the solvents gave Compound **50E** (180 mg, yield 80%) as a white solid. LCMS: (m/z) 251 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.86-3.03 (m, 3H), 3.15-3.18 (m, 3H), 4.28 (d, $J = 4.2$ Hz, 1H), 7.30 (m, 2H), 7.65-7.69 (m, 2H), 7.77-7.80 (m, 2H), 8.70 (d, $J = 2.8$ Hz, 1H).

[000512] A solution of Compound **50E** (1.88 g, 7.52 mmol) in ethanol (80 mL) was bubbled with a gentle stream of HCl gas (dried over cone H_2SO_4) for 6 h and left to stand overnight at 4 °C. The mixture was added water (30 mL) and stirred at 80 °C for 2 h. After cooled down to rt, the mixture was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica gel (methanol in dichloromethane, 3% v/v) to yield Compound **50F** (1.17 g, yield 52%) as a yellow solid. LCMS: (m/z) 298 [M+]⁺.

[000513] To a stirred solution of Compound **50F** (210 mg, 0.71 mmol) in DCM (11 mL) was added NaHCO_3 (119 mg, 1.41 mmol), and DMP (360 mg, 0.85 mmol) at 0 °C. The mixture was stirred at 0 °C for one hour. The reaction mixture was quenched with sat. aq Na_2S_3 solution. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 . The crude was purified by column chromatography on silica gel (methanol in dichloromethane, 3% v/v) to afford Compound **50G** (180 mg, yield 86%) as yellow oil. LCMS: (m/z) 224 [M+]⁺.

[000514] To a stirred solution of Compound **50G** (233 mg, 0.79 mmol) in DCM (10 mL) was added DAST (720 mg, 4.47 mmol). The mixture was stirred at rt overnight. After cooled down to rt, the mixture was poured into water and then extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with water, brine, and dried over

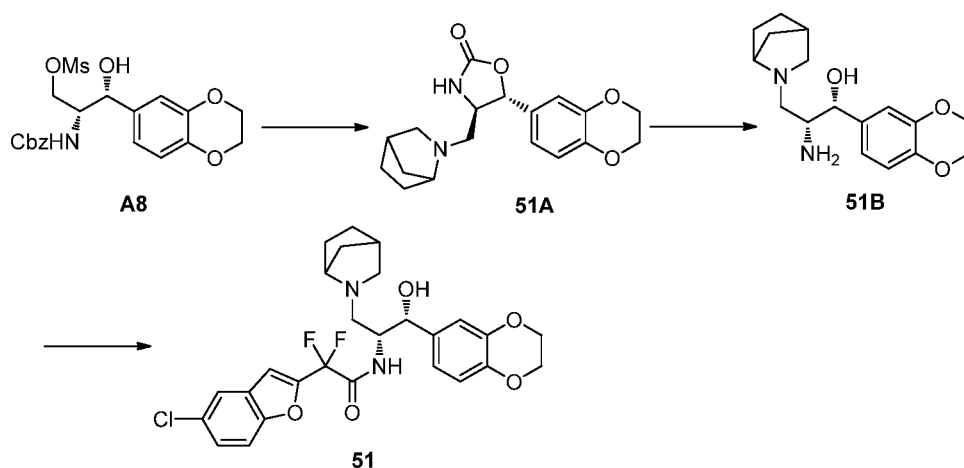
anhydrous Na_2SO_4 , purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **50H** (140 mg, yield 56%) as a yellow oil.

LCMS: (m/z) 318 [M+]⁺.

[000515] To a stirred solution of Compound **50H** (140 mg, 0.44 mmol) in THF (10 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (37 mg, 0.88 mmol) and water (2 mL). The mixture was stirred at rt for 3 h. The mixture was acidified to pH 1 with 1M HCl and evaporated. The aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 , concentrated to give Compound **50I** (110 mg, yield 86%) as a yellow oil. LCMS: (m/z) 290 [M+]⁺.

[000516] To a solution of Compound **50I** (110 mg, 0.38 mmol) in DCM (10 mL) was added EDCI (110 mg, 0.57 mmol), HOBT (77 mg, 0.57 mmol), Intermediate A (106 mg, 0.38 mmol). Then it was stirred at rt overnight. The mixture was added DCM (20 mL), washed with water (50 mL x 2) and brine (50 mL x 1), dried over anhydrous Na_2SO_4 , concentrated, and purified by prep-HPLC twice to give Compound **50** (1.6 mg, yield 1%) as a colorless oil. LC-MS (m/z): 550 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.95 (m, 4H), 2.68-2.96 (m, 5H), 3.29-3.38 (m, 2H), 3.76 (s, 2H), 4.11 (s, 4H), 4.37 (s, 1H), 5.08 (m, 1H), 5.28 (s, 1H), 6.79-6.85 (m, 3H), 7.30 (s, 1H), 7.47 (m, 1H), 7.65 (m, 3H), 7.92 (m, 1H), 8.24 (m, 1H), 8.96 (m, 1H), 11.79 (s, 1H).

Example 51

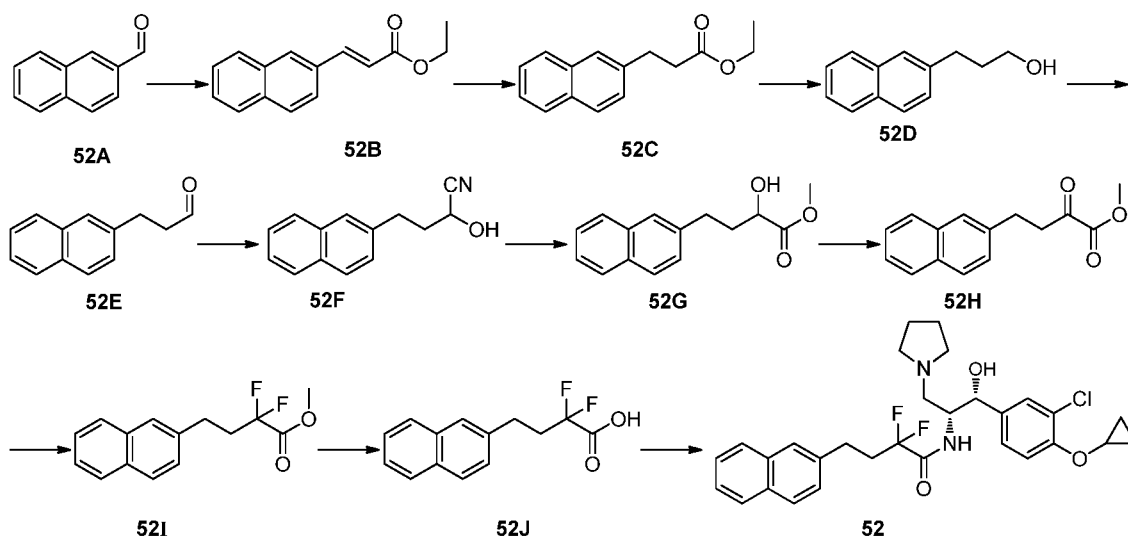


[000517] To a solution of 2-azabicyclo [2.2.1] heptane (132 mg, 1 mmol) in MeCN (10 mL) was added K_2CO_3 (69 mg, 0.5 mmol) and Compound **A8** (219 mg, 0.5 mmol). The mixture was stirred at 70 °C for 48 h. After evaporation to remove solvents, the residue was dissolved in H_2O , extracted with ethyl acetate; the combined organic layers were dried over anhydrous Na_2SO_4 . After filtration and evaporation, a crude Compound **51A** (210 mg) was obtained as an oil, which was used for the next step directly. LCMS (m/z): 331 [M+]⁺.

[000518] To a solution of Compound **51A** (210 mg, 0.64 mmol) in EtOH (9 mL) and H₂O (9 mL) was added LiOH·H₂O (267 mg, 6.4 mmol). The reaction mixture was refluxed for 24 h. After removal of the solvents, the residue was dissolved in H₂O, extracted with ethyl acetate, and dried over Na₂SO₄ to give Compound **51B** (190 mg), which was used for the next step without purification. LCMS (m/z): 305 [M+]⁺.

[000519] To a solution of Compound **51B** (91 mg, 0.3 mmol) in DCM (12 mL) was added Compound **HE** (111 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol) and EDCI (86 mg, 0.45 mmol). The mixture was stirred for 12 h at 25 °C. The mixture was washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the residue was purified by prep-HPLC to give Compound **51** (38 mg, yield 19%) as a white solid. LC-MS (m/z): 507 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.52-1.90 (m, 4H), 2.04-2.24 (m, 1H), 2.57-2.98 (m, 2H), 3.30-3.72 (m, 3H), 4.07-4.50 (m, 8H), 5.01-5.16 (m, 1H), 6.68-6.83 (m, 4H), 7.33-7.35 (m, 1H), 7.42-7.44 (m, 1H), 7.57 (d, *J* = 1.2 Hz, 1H), 8.02-8.17 (m, 1H), 10.21-10.33 (m, 1H).

Example 52



[000520] To a solution of ethyl 2-(diethoxyphosphoryl) acetate (10.77 g, 48.08 mmol) in THF (50 mL) was added *t*-BuOK (5.38 g, 48.08 mmol) at room temperature. After stirred for 30 min, Compound **52A** (5.00 g, 32.05 mmol) was added. The mixture was stirred at room temperature overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, and purified with silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to render Compound **52B** (6.60 g, yield 91%>) as a colorless oil. LC-MS (m/z): 227 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.36 (t,

$J = 7.2$ Hz, 3H), 4.26-4.32 (m, 2H), 6.55 (d, $J = 15.6$ Hz, 1H), 7.5-7.53 (m, 2H), 7.65-7.69 (m, 1H), 7.83-7.87 (m, 4H).

[000521] A suspension of Pd/C (1.00 g, 10%) and Compound **52B** (7.30 g, 32.0 mmol) in MeOH (100 mL) was stirred at room temperature overnight under H_2 . The mixture was filtered to remove Pd/C. The filtrate was evaporated to yield Compound **52C** (7.30 g, yield 100%) as a colorless oil. LC-MS (m/z): 229 [M+]⁺; ¹H-NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.23 (t, $J = 7.2$ Hz, 3H), 2.71 (t, $J = 7.6$ Hz, 2H), 3.12 (t, $J = 8.4$, 2H), 4.10-4.16 (m, 2H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.40-7.47 (m, 2H), 7.64 (s, 1H), 7.76-7.81 (m, 3H).

[000522] To a solution of Compound **52C** (7.30 g, 32.02 mmol) in dry THF (80 mL) was added $LiAlH_4$ (1.20 g, 32.0 mmol) at 0 °C. Then it was warmed to room temperature and stirred for 2 h. It was added with $Na_2SO_4 \cdot 10H_2O$ and filtered to remove the solid. The filtrate was evaporated to give Compound **52D** (6.10 g, yield 100 %) as a colorless oil. LC-MS (m/z): 187 [M+]⁺; ¹H-NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.95-2.02 (m, 2H), 2.88 (t, $J = 8.0$ Hz, 2H), 3.72 (t, $J = 6.8$ Hz, 2H), 7.33 (d, $J = 7.2$ Hz, 1H), 7.39-7.47 (m, 2H), 7.63 (s, 1H), 7.76-7.81 (m, 3H).

[000523] A mixture of Compound **52D** (16 g, 86 mmol) in DCM (300 mL) was added DMP (43 g, 103 mmol) at room temperature. Then it was stirred at room temperature for 1 h. The mixture was diluted with EA (400 mL), filtered to remove solid, washed with water and brine, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **52E** (14 g, yield 88%) as a colorless oil. LC-MS (m/z): 185 [M+]⁺.

[000524] A mixture of Compound **52E** (8.00 g, 43.4 mmol) and $2NaO_5S_2$ (8.3 g, 43.4 mmol) in water/dioxane (100/20 mL) was stirred at room temperature for 2 h. Then NaCN (4 g, 86.95 mmol) was added. The mixture was stirred at room temperature overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 50% v/v) to give Compound **52F** (6.6 g, yield 72%) as a colorless oil. LC-MS (m/z): 212 [M+]⁺; ¹H-NMR ($DMSO-d_6$, 400 MHz) major characteristic peaks: δ (ppm) 2.07-2.13 (m, 2H), 2.87-2.91 (m, 2H), 4.50-4.55 (m, 1H), 6.48-6.49 (d, $J = 4$ Hz, 1H), 7.40-7.51 (m, 3H), 7.73 (s, 1H), 7.85-7.89 (m, 3H).

[000525] A solution of Compound **52F** (6.6 g, 31.27 mmol) in MeOH (150 mL) was bubbled with a gentle stream of HCl gas at room temperature for 6 h. Then it was quenched with H_2O (30 mL) and stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate (300 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to

give Compound **52G** (6.7 g, yield 87%) as colorless oil. LC-MS (m/z): 245 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.91-2.03 (m, 2H), 2.81-2.85 (t, *J* = 8 Hz, 2H), 3.64 (s, 3H), 5.54-5.55 (m, 1H), 7.37-7.39 (m, 1H), 7.42-7.50 (m, 2H), 7.69 (s, 1H), 7.83-7.87 (t, *J* = 8 Hz, 3H).

[000526] To a solution of Compound **52G** (6.7 g, 27.46 mmol) in DCM (50 mL) was added DMP (14 g, 33 mmol). The mixture was stirred at room temperature for 2 h. Then it was diluted with ethyl acetate (150 mL), filtered to remove the solid, washed with water and brine, dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 30% v/v) to yield Compound **52H** (5 g, yield 75%) as a colorless oil. LC-MS (m/z): 243 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.98-3.02 (t, *J* = 8 Hz, 2H), 3.24-3.28 (t, *J* = 8 Hz, 2H), 3.77 (s, 3H), 7.39-7.48 (m, 3H), 7.71 (s, 1H), 7.82-7.87 (m, 3H).

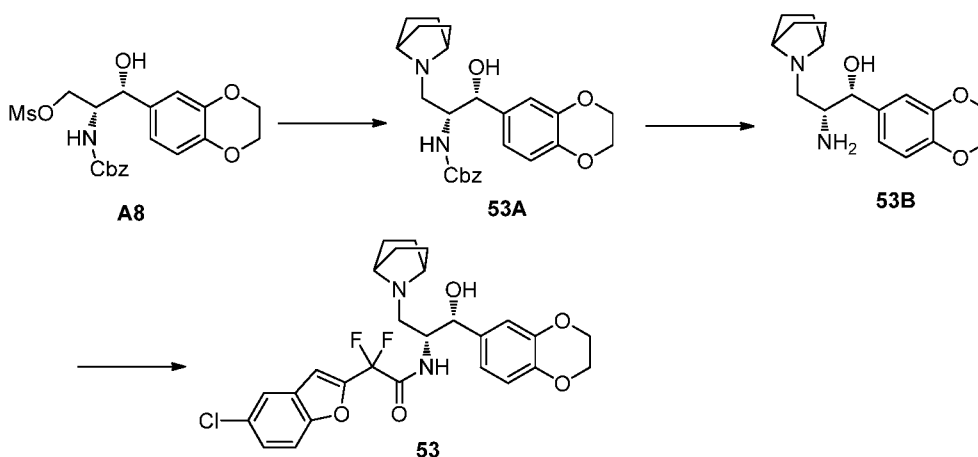
[000527] To a solution of Compound **52H** (2.0 g, 8.26 mmol) in DCM (50 mL) was added DAST (3 mL, 41.3 mmol) at room temperature. The mixture was stirred at room temperature overnight. Then it was diluted with ethyl acetate (150 mL), washed with saturated NaHCO₃, water and brine, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 40% v/v) to afford Compound **52I** (2.0 g, yield 91%) as a white solid. LC-MS (m/z): 265 [M+]⁺.

[000528] A mixture of Compound **52I** (2.5 g, 4.47 mmol) and LiOH.H₂O (1.2 g, 28.4 mmol) in THF/MeOH/H₂O (10/10/4 mL) was stirred at room temperature for 2 h. Then it was adjusted to pH 6 with 1 M HCl aq solution. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, dried with anhydrous Na₂SO₄, and purified by silica gel column chromatography (ethyl acetate in petroleum ether, 30% v/v) to give Compound **52J** (1.8 g, yield 75%) as a white solid. LC-MS (m/z): 251 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.45-2.49 (m, 2H), 2.88-2.92 (m, 2H), 7.42-7.50 (m, 3H), 7.76 (s, 1H), 7.84-7.88 (m, 3H).

[000529] A solution of Compound **HE** (200 mg, 0.64 mmol), Compound **52J** (241 mg, 0.96 mmol), EDCI (183 mg, 0.96 mmol) and HOBt (130 mg, 0.96 mmol) in DCM (15 mL) was stirred at room temperature overnight. Then it was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to afford Compound **52** (108 mg, yield 30%) as a white solid. LC-MS (m/z): 543 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 0.41-0.44 (m, 2H), 0.54-0.59 (m, 2H), 1.87-1.88 (m, 2H), 2.01 (s, 2H), 2.16-2.27 (m, 2H), 2.49-2.71 (m, 2H), 3.10-3.15 (m, 2H), 3.46-3.61 (m, 5H),

4.47-4.48 (m, 1H), 4.82 (s, 1H), 6.01-6.02 (m, 1H), 7.24-7.34 (m, 3H), 7.38 (s, 1H), 7.45-7.51 (m, 2H), 7.65 (s, 1H), 7.83-7.89 (m, 3H), 8.41-8.44 (m, 1H), 9.52 (s, 1H).

Example 53

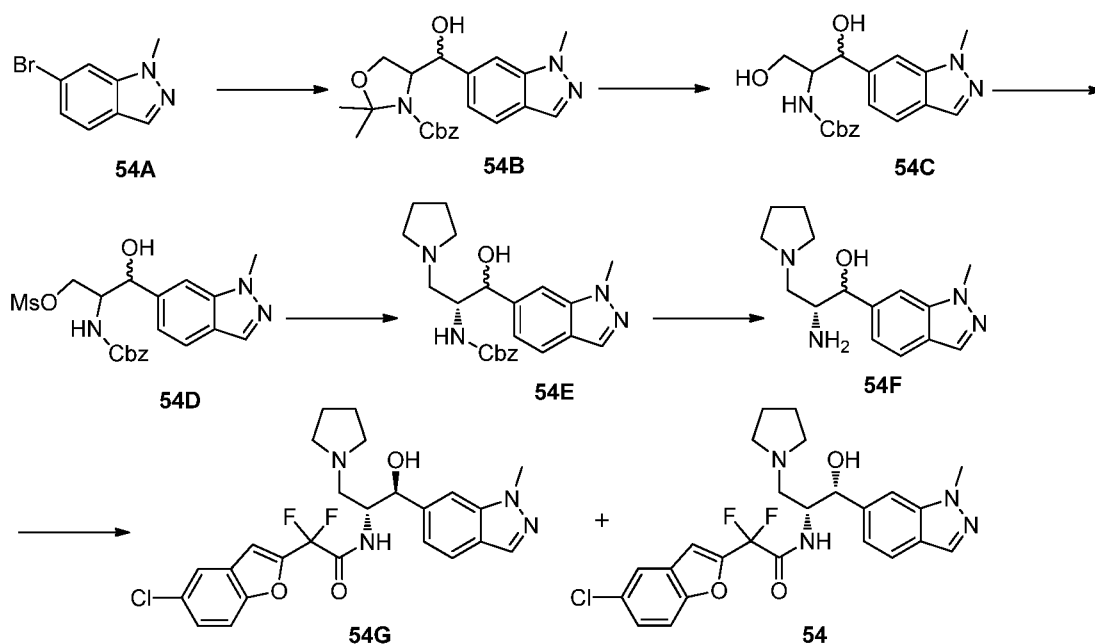


[000530] To a solution of Compound **A8** (500 mg, 1.1 mmol) in THF (20 mL) was added 7-azabicyclo [2.2.1] heptane (1.1 g, 11 mmol) and stirred at 50 °C for 16 h. The mixture was added water (50 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was washed with water (50 mL x 3), brine (50 mL x 1), dried over anhydrous Na₂S₄, and concentrated to give Compound **53A** (600 mg, crude) as a colorless oil. LCMS: 439 [M+]⁺.

[000531] A mixture of Compound **53A** (660 mg, crude), LiOH·H₂O (150 mg) in EtOH (30 mL) and H₂O (5 mL) was stirred at 100 °C for 16 h. The mixture was concentrated and added water (50 mL), and then extracted with DCM (30 mL x 3), dried over anhydrous Na₂S₄, and concentrated to give Compound **53B** (400 mg, crude) as a colorless oil. LCMS: 305 [M+]⁺.

[000532] To a solution of Compound **HE** (250 mg), EDCI (290 mg), HOBt (200 mg, 0.75 mmol) in DCM (10 mL) was added Compound **53B** (400 mg, crude). The mixture was stirred at 25 °C for 24 h, added water (50 mL), extracted with DCM (30 mL x 3), dried over anhydrous Na₂S₄, and purified by prep-HPLC to give Compound **53** (15 mg, yield 2%) as a colorless oil. LCMS: 533 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.69 (m, 4H), 2.14 (m, 4H), 3.35 (br, 1H), 3.47 (br, 1H), 4.11 (m, 5H), 4.49 (br, 2H), 5.06 (s, 1H), 6.78 (m, 4H), 7.33 (m, 1H), 7.41 (m, 1H), 7.58 (m, 1H), 8.10 (br, 1H), 10.58 (br, 1H).

Example 54



[000533] To a solution of Compound **54A** (14.1 g, 19.4 mmol) in THF (15 mL) was added n-BuLi (8.1 mL, 19.4 mmol) carefully at $-68\text{ }^{\circ}\text{C}$. The mixture was stirred at $-68\text{ }^{\circ}\text{C}$ for 15 min, and then Compound **8C** (1.70 g, 6.48 mmol) in THF (10 mL) was added. The mixture was stirred at $-68\text{ }^{\circ}\text{C}$ for 15 min before quenched with saturated aq NH_4Cl . It was diluted with ethyl acetate (100 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to give Compound **54B** (1.90 g, yield 79%) as a light yellow oil. LC-MS (m/z): 396 [M+]⁺.

[000534] A mixture of Compound **54B** (1.90 g, 4.81 mmol) in THF (5 mL) and hydrochloric acid (6 M, 5 mL) was stirred at $20\text{ }^{\circ}\text{C}$ overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, purified by silica gel chromatography eluted with MeOH in DCM (from 0% to 5%, v/v) to render Compound **54C** (500 mg, yield 48%) as a colorless oil. LC-MS (m/z): 356 [M+]⁺.

[000535] To a solution of Compound **54C** (520 mg, 1.46 mmol) in THF (50 mL) was added dropwise MsCl (184 mg, 161 mmol) at $-40\text{ }^{\circ}\text{C}$. The mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 2 h. It was quenched with ice-water, diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to give Compound **54D** (500 mg, yield 79%) as a colorless oil. LC-MS (m/z): 434 [M+]⁺.

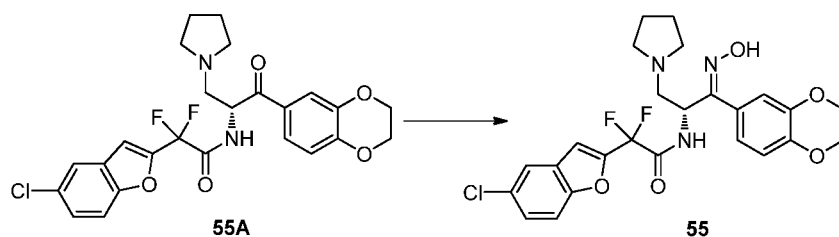
[000536] A mixture of Compound **54D** (500 mg, 1.15 mmol) and pyrrolidine (3 mL) in THF (20 mL) was stirred at $50\text{ }^{\circ}\text{C}$ overnight. It was evaporated to remove THF. The residue was diluted with ethyl acetate (150 mL), washed with water and brine, purified by silica gel

chromatography (methanol in dichloromethane, from 0% to 8% v/v) to yield Compound **54E** (120 mg) as a colorless oil. LC-MS (m/z): 409 [M+]⁺.

[000537] A mixture of Compound **54E** (120 mg, 0.29 mmol) in EtOH/H₂O (10/2 mL) was stirred at 85 °C overnight. It was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by silica gel chromatography (methanol in dichloromethane, from 0% to 10% v/v) to give Compound **54F** (90 mg, yield 100%) as a colorless oil. LC-MS (m/z): 275 [M+]⁺.

[000538] The mixture of Compound **54F** (90 mg, 0.33 mmol), EDCI (95 mg, 0.50 mmol), HOBT (68 mg, 0.50 mmol) and Compound **HE** (81 mg, 0.33 mmol) in DCM (5 mL) was stirred at 20 °C overnight. It was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to afford Compound **54G** (20 mg) as a white solid and Compound **54** (15 mg) as a white solid. For Compound **54G**, LC-MS (m/z): 503 [M+]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 2.07 (s, 2H), 2.21 (s, 2H), 3.13-3.26 (m, 2H), 3.52-3.58 (m, 1H), 3.77-3.89 (m, 3H), 3.91 (s, 3H), 4.61-4.67 (m, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 6.34 (s, 1H), 7.21-7.27 (m, 2H), 7.35-7.38 (m, 2H), 7.47 (s, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.87 (s, 1H). For Compound **54**, LC-MS (m/z): 503 [M+]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 2.05 (s, 2H), 2.20 (s, 2H), 3.17-3.26 (m, 2H), 3.64-3.82 (m, 4H), 3.85 (s, 3H), 4.80 (d, *J* = 5.2 Hz, 1H), 5.16 (s, 1H), 6.34 (s, 1H), 7.18-7.21 (m, 1H), 7.32-7.34 (m, 1H), 7.38-7.40 (m, 2H), 7.55-7.60 (m, 2H), 7.91 (s, 1H).

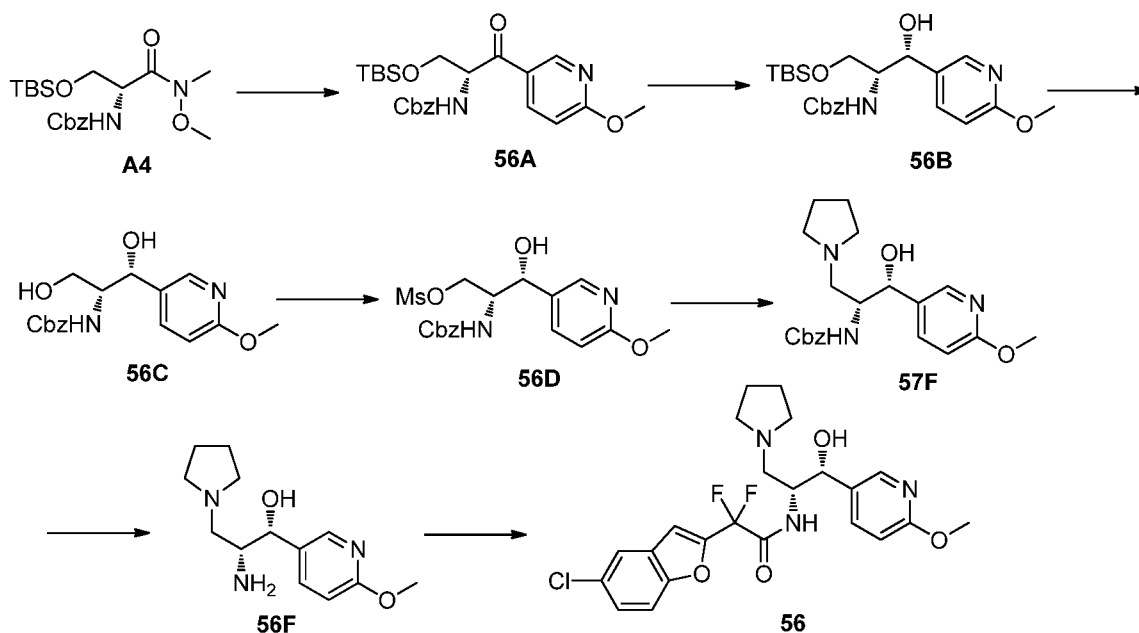
Example 55



[000539] A solution of Compound **55A** (100 mg, 0.2 mmol), hydroxylamine hydrochloride (41 mg, 0.6 mmol) in MeOH (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with saturation aq NaHCO₃ (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, and concentrated to give a crude product. The crude product was purified by prep-HPLC to give a trifluoroacetic acid salt of Compound **55** (1.6 mg, yield 1.3%) as a white solid. LC-MS (m/z): 520 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.82 (s, 4H), 2.00-2.22 (m, 2H), 2.65-2.75 (m, 3H), 2.92-2.97 (m, 1H), 4.18-4.24 (m, 4H), 5.33-5.47 (m,

2H), 6.82-6.84 (m, 1H), 6.95 (s, 1H), 7.13-7.14 (m, 2H), 7.33-7.34 (m, 1H), 7.40-7.43 (m, 1H), 7.54-7.55 (m, 1H).

Example 56



[000540] To a solution of 5-bromo-2-methoxypyridine (10 g, 53.2 mmol) in THF (200 mL) was added n-BuLi (2.5 M, 22 mL) at -60 °C under N₂. It was stirred for 0.5 h, and then a solution of Compound **A4** (7.02 g, 17.7 mmol) in THF (50 mL) was added. The reaction mixture was stirred at -60 °C for an additional 1 h, before quenched with saturate aq NH₄Cl solution. It was extracted with ethyl acetate (100 mL x 2), brine (100 mL), and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to give Compound **56A** (7.5 g, yield 95%) as a colorless liquid. LC-MS (m/z): 445[M+]⁺; 1H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) -0.13 (s, 3H), -0.11 (s, 3H), 0.75 (s, 9H), 3.88-3.92 (m, 1H), 3.99-4.00 (m, 1H), 4.02 (s, 3H), 5.14 (s, 2H), 5.29 (t, *J* = 3.6 Hz, 1H), 5.93 (d, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 7.37-7.38 (m, 5H), 8.13 (dd, *J* = 2.0, 8.8 Hz, 1H), 8.80 (d, *J* = 2.0 Hz, 1H).

[000541] Compound **56A** (7.5 g, 16.9 mmol) was dissolved in anhydrous THF (500 mL) and cooled down -80 °C under nitrogen atmosphere. L-Selectride (33.8 mL, 1M solution in THF, 33.8 mmol) was added dropwise to the solution while keeping the temperature at -80 °C. The reaction was stirred at -80 °C for 0.5 h before quenched with saturate aq NH₄Cl solution. It was extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed water and brine, and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to give Compound **56B** (5.1g, yield 68%) as a colorless oil. LC-MS (m/z): 447 [M+]⁺; 1H-NMR (CDCl₃, 400 MHz)

major characteristic peaks: δ (ppm) -0.08 (s, 6H), 0.92 (s, 9H), 3.68 (m, 1H), 3.84 (m, 3H), 3.94 (s, 3H), 5.05 (m, 3H), 5.46 (d, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 7.32-7.34 (m, 5H), 7.59 (d, $J = 8.4$ Hz, 1H), 8.14 (s, 1H).

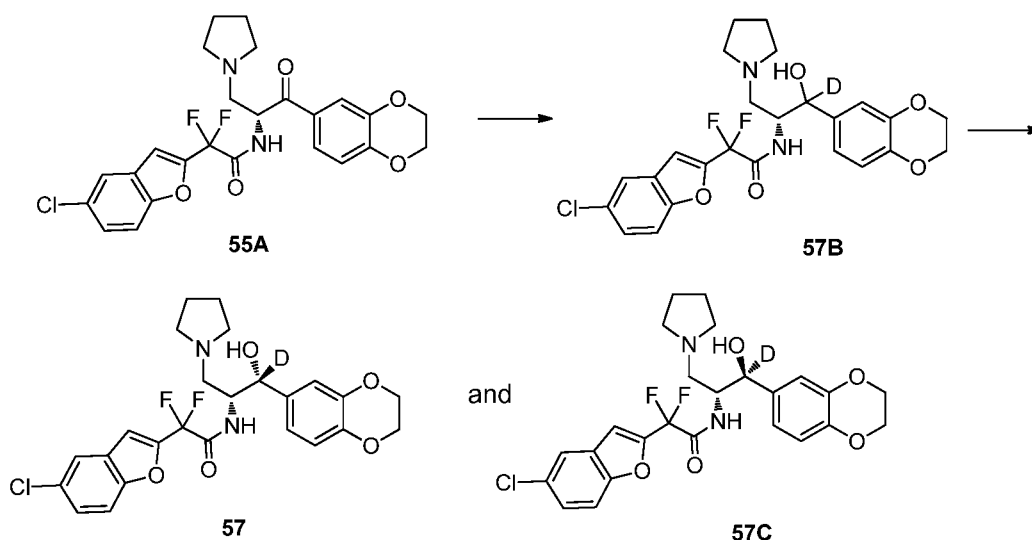
[000542] To a solution of Compound **56B** (5.1 g, 11.4 mmol) in THF (120 mL) was added a solution of TBAF (1.49 g, 5.7 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 25 °C overnight, and then evaporated to reduce the volume, added water (50 mL), extracted with ethyl acetate (100 mL x 3), washed with brine, and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **56C** (3.42 g, yield 52 %) as a colorless oil. LC-MS (m/z): 333 [M+]⁺.

[000543] To a solution of Compound **56C** (3.42 g, 8.58 mmol) in THF (100 mL) was added Et_3N (3.12 g, 30.9 mmol). The mixture was cooled to -40 °C, and then MsCl (1.30 g, 11.3 mmol) was added slowly. It was stirred at -40 °C about half an hour before added pyrrolidine (3.78 g, 53.2 mmol). The reaction mixture was allowed to warm up to rt and then heated to 50 °C. Stirred overnight, the mixture was added water (50 mL), extracted with ethyl acetate (50 mL x 3), washed with brine (100 mL), and dried over Na_2SO_4 . The crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 3% v/v) and flash column (reverse-phase, 0.05 % $\text{NH}_4\text{OH}/\text{MeOH}$, v/v) to give Compound **56D** (800 mg, yield 39%) as white syrup. LC-MS (m/z): 386 [M+]⁺.

[000544] To a solution of Compound **56D** (400 mg, 1.04 mmol) in methanol (10 mL) was added $\text{Pd}(\text{OH})_2$ (40 mg). The mixture was stirred at 25 °C under H_2 overnight. It was filtered and evaporated to give Compound **56E** (260 mg, crude). LC-MS (m/z): 252 [M+]⁺.

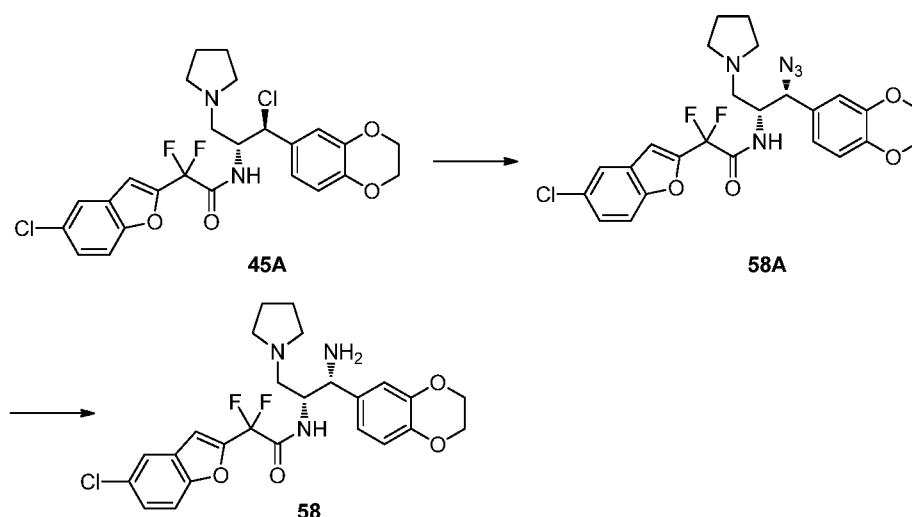
[000545] To a solution of Compound **56E** (260 mg, 1.04 mmol) and Compound **HE** (255 mg, 1.04 mmol) in DCM (10 mL) was added EDCI (298 mg, 1.55 mmol) and HOBt (210 mg, 1.55 mmol) under N_2 . The mixture was stirred at 25 °C overnight. TLC showed the starting material was consumed completely; water was added to the mixture and then extracted with DCM (50 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to give a crude product. The crude product was purified by prep-HPLC to give Compound **56** (98.6 mg, yield 19%) as a white solid. LC-MS (m/z): 480 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks δ (ppm): 2.10 (s, 4H), 3.03 (s, 2H), 3.58-3.72 (m, 4H), 3.86 (s, 3H), 4.26 (s, 1H), 5.24 (m, 1H), 6.71 (s, 1H), 6.84 (s, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.55 (s, 1H), 7.86 (s, 1H), 8.38 (m, 2H), 11.43 (s, 1H).

Example 57



[000546] To a solution of Compound **55A** was dissolved in CD_3OD (5 mL) was added NaBD_4 (13 mg, 0.32 mmol) at -30°C under nitrogen atmosphere. The reaction was warmed to 0°C and kept stirring for 1 h. After quenched with 2% CD_3COOD in D_2O , the mixture was extracted with dichloromethane (50 mL x 3) and washed with D_2O . The crude product was purified by prep-HPLC to give Compound **57** (20 mg, yield 25%) as a white solid. LC-MS (m/z): 508 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 3.01 (s, 2H), 3.49 (s, 2H), 3.81 (s, 2H), 4.12-4.17 (m, 4H), 4.47-4.49 (m, 1H), 6.76 (m, 2H), 6.84 (s, 1H), 7.35 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.45 (s, 1H), 7.90 (d, $J = 2.0$ Hz, 1H), 11.95 (s, 1H).

Example 58

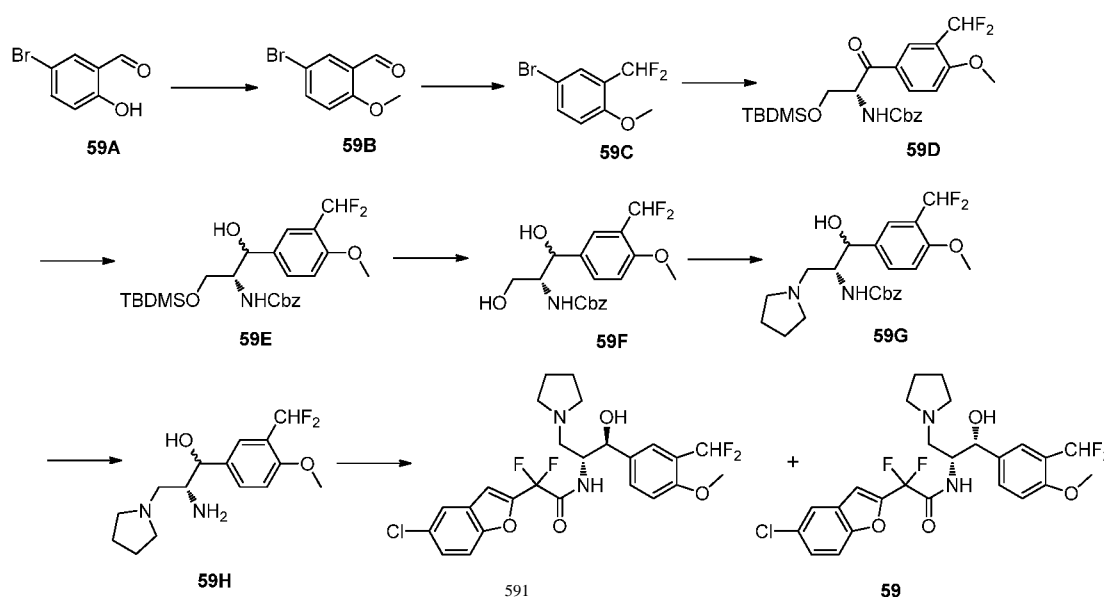


[000547] A solution of Compound **45A** (62 mg, 0.12 mmol) in DMF (2 mL) was added NaN_3 (24 mg, 0.36 mmol) and the mixture was stirred at 50°C for 3 h. The mixture was added H_2O (mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer

was washed with brine, and concentrated to give Compound **58A** (40 mg, yield 63%) as a white solid. LC-MS (m/z): 532 [M+]⁺.

[000548] To a solution of Compound **58A** (40 mg, 0.075 mmol) in THF (1 mL) was added PPh₃ (21 mg, 0.08 mmol), the mixture was stirred at 20 °C for 18 h. It was added H₂O (mL) and stirred for 2 h and concentrated. The crude product was purified by prep-HPLC to give Compound **58** (5 mg, yield 13%) as a white solid. LC-MS (m/z): 506 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.79-1.81 (m, 4H), 2.40-2.45 (m, 1H), 2.56-2.64 (m, 6H), 3.34-3.38 (m, 1H), 4.14-4.34 (m, 5H), 4.90-4.91 (m, 2H), 6.75-6.84 (m, 3H), 7.07 (s, 1H), 7.32-7.35 (m, 1H), 7.45-7.58 (m, 1H), 7.59 (s, 1H), 9.66-9.67 (m, 1H).

Example 59



[000549] To a solution of Compound **59A** (10 g, 50 mmol) and K₂CO₃ (20.7 g, 150 mmol) in DMF (30 mL) was added MeI (21.3 g, 150 mmol), and the mixture was stirred for 15 h at 25 °C. After the TLC showed complete disappearance of the starting material, the reaction was quenched by adding water. It was extracted with ethyl acetate. The extracts were evaporated to dryness to give Compound **59B** (10.6 g, yield 98%>) as a yellow solid. LC-MS (m/z): 215 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.92 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 10.39 (s, 1H).

[000550] To a solution of Compound **59B** (9 g, 42 mmol) in DCM (90 mL) was added DAST (33.7 g, 209 mmol), and the mixture was stirred for 18 h at 25 °C. The mixture was adjusted to pH 8 with saturated NaHCO₃, extracted with DCM, and dried over anhydrous Na₂SO₄. After evaporation, the crude product was purified by column chromatography on

silica gel (ethyl acetate in petroleum ether, 3% v/v) to get Compound **59C** (5.14 g, yield 52%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.85 (s, 3H), 6.82 (d, *J* = 9.2 Hz, 1H), 6.89 (t, *J*_{F-H} = 552 Hz, 1H), 7.52 (dt, *J* = 8.8, 1.2 Hz, 1H), 7.66 (t, *J* = 1.2 Hz, 1H).

[000551] To a solution of Compound **59C** (5 g, 21 mmol) in THF (100 mL) was added *n*-BuLi (2.4 M, 8.75 mL) at -60 °C under N₂. After stirred for 0.5 h, a solution of Compound **A4** (2.77 g, 7 mmol) in THF (50 mL) was added slowly. The mixture was stirred at -60 °C for 1 h, before quenched with saturated aq NH₄Cl solution. It was extracted with ethyl acetate, washed with brine (100 mL) and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to give Compound **59D** (2.65 g, yield 76%) as a yellow oil. LC-MS (m/z): 494 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) -0.15 (s, 3H), -0.12 (s, 3H), 0.74 (s, 9H), 3.85-3.92 (m, 2H), 3.96 (s, 3H), 5.13 (s, 2H), 5.33-5.38 (m, 1H), 5.93 (d, *J* = 7.6 Hz, 1H), 6.79-7.06 (m, 2H), 7.31-7.37 (m, 5H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H).

[000552] Compound **59D** (2.65 g, 5.36 mmol) was dissolved in THF (100 mL) and cooled to -70 °C under nitrogen atmosphere. L-Selectride (1M solution in THF, 10.7 mL) was added dropwise while keeping the temperature at -70 °C. After an hour, the reaction was quenched with saturated aq NH₄Cl solution and the mixture was extracted with ethyl acetate, and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to give Compound **59E** (2.1 g, yield 79%) as a colorless oil. LC-MS (ESI) m/z: 478 [M-17]⁺.

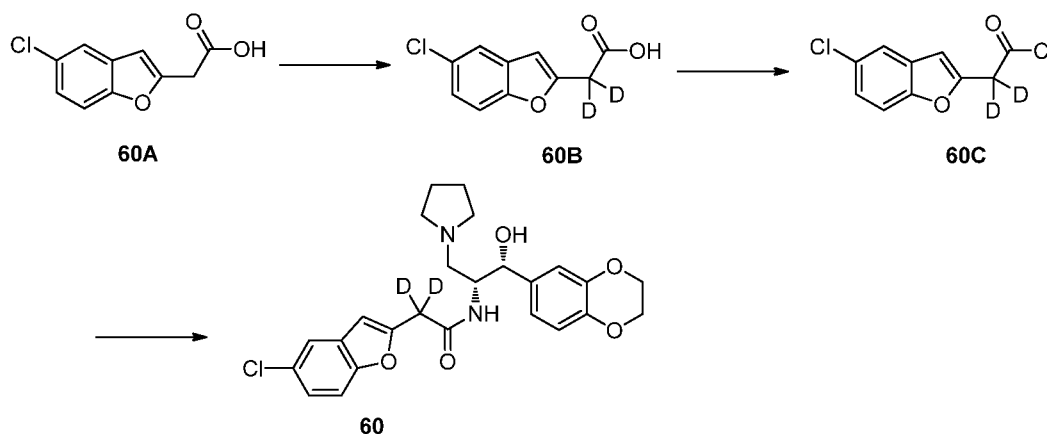
[000553] To a solution of Compound **59E** (2.1 g, 4.23 mmol) in THF (50 mL) was added a solution of TBAF (555 mg, 2.12 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at rt for 18 h, condensed, added water, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na₂SO₄. The crude product was purified by flash column chromatography on silica gel (MeOH in H₂O, 40% v/v) to give Compound **59F** (760 mg, yield 47%) as a colorless oil. LC-MS (m/z): 364 [M-17]⁺.

[000554] To a solution of Compound **59F** (0.76 g, 2 mmol) in THF (50 mL) was added Et₃N (0.6 g, 6 mmol) at -40 °C. MsCl (241 mg, 2.09 mmol) was added slowly and the mixture was stirred at -20 °C for 7 h. Pyrrolidine (1.13 g, 16 mmol) were added and the reaction mixture was allowed to warm up to rt and then heated to 50 °C for 15 h. The crude product was purified by column chromatography silica gel (methanol in dichloromethane, 5% v/v) to give Compound **59G** (270 mg, yield 31%) as colorless oil. LC-MS (m/z): 435 [M+1]⁺.

[000555] To a solution of Compound **59G** (270 mg, 0.62 mmol) in methanol (20 mL) was added Pd(OH)₂ (27 mg) and the mixture was stirred at 25 °C under H₂ for 24 h. The mixture was filtered and evaporated to render Compound **59H** (260 mg, yield 98%) as a white solid. LC-MS (m/z): 301 [M+]⁺.

[000556] The mixture of Compound **59H** (180 mg, 0.6 mmol), EDCI (173 mg, 0.9 mmol), HOBt (122 mg, 0.9 mmol) and Compound **HE** (178 mg, 0.72 mmol) in DCM (15 mL) was stirred for 16 h at 25 °C. The mixture was washed with saturated aq NaHCO₃ and brine. After evaporation, the residues were purified by prep-HPLC to afford Compound **59I** (64 mg, yield 11%) as the white solid and Compound **59** (59 mg, yield 10%>) as the white solid. For Compound **59I**, LC-MS (m/z): 529 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.07-2.19 (m, 4H), 2.77-2.91 (m, 2H), 3.21-3.24 (m, 1H), 3.63-3.64 (m, 1H), 3.76 (s, 3H), 3.80-3.82 (m, 1H), 3.88-3.90 (m, 1H), 4.52 (s, 1H), 5.02 (s, 1H), 6.72-7.00 (m, 3H), 7.31-7.34 (m, 1H), 7.40-7.42 (m, 2H), 7.52-7.62 (m, 2H), 9.15 (d, *J* = 4.8 Hz, 1H), 11.78 (s, 1H). For Compound **59**, LC-MS (m/z): 529 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 2.88-3.04 (m, 2H), 3.53-3.63 (m, 2H), 3.71 (s, 3H), 3.74-3.81 (m, 2H), 4.60 (s, 1H), 5.19 (s, 1H), 6.65-6.98 (m, 3H), 7.32-7.39 (m, 3H), 7.51-7.53 (m, 2H), 7.95 (d, *J* = 6.4 Hz, 1H), 11.69 (s, 1H).

Example 60

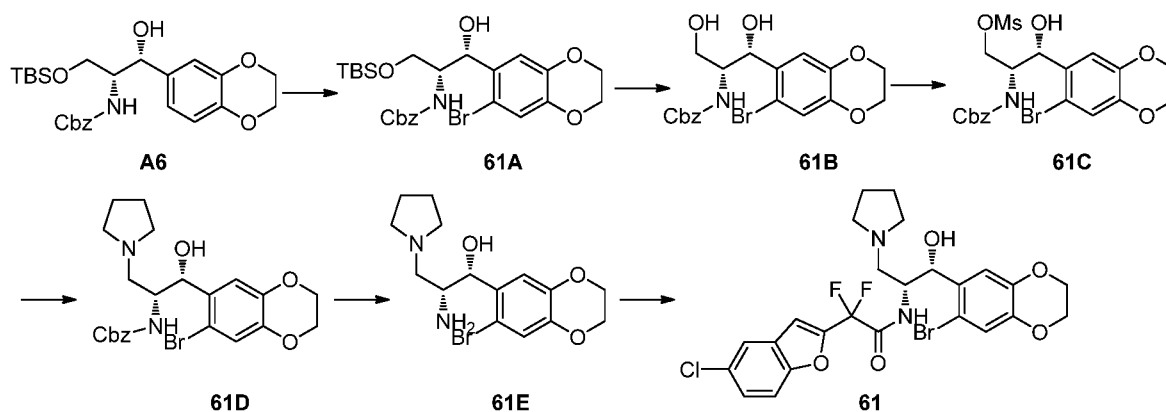


[000557] A solution of Compound **60A** (21 mg, 0.1 mmol) and K₂CO₃ (55 mg, 0.4 mmol) in D₂O (3 mL) was stirred at 110 °C for 16 h under N₂. The mixture was acidified by the addition of 1M HCl solution, extracted with DCM (20 mL x 2), dried over anhydrous Na₂SO₄, and concentrated to yield Compound **60B** (15 mg, yield 71%) as a white solid. LC-MS (m/z): 167 [M-45]⁻; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 6.63 (s, 1H), 7.21 (m, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H).

[000558] A mixture of Compound **60B** (100 mg, 0.47 mmol) in SOCl_2 (3 mL) was stirred at 25 °C for 2 h. The mixture was concentrated to give Compound **60C** (100 mg, crude) as a yellow oil which was used for the next step without further purification.

[000559] Intermediate **A** was dissolved in CD_3OD and the solvent evaporated. To a solution of Intermediate **A** (100 mg, 0.36 mmol) in DCM (3 mL) was added Compound **60C** solution (100 mg, 0.43 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was added water (30 mL), extracted with DCM (30 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to give Compound **60** (19 mg, yield 9%) as a white foam. LC-MS (m/z): 473 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.03 (m, 4H), 2.82 (m, 2H), 3.16 (m, 1H), 3.48 (m, 1H), 3.73 (br, 2H), 4.14 (m, 4H), 4.45 (m, 1H), 4.84 (d, $J = 2.4$ Hz, 1H), 6.41 (s, 1H), 6.64 (s, 2H), 6.76 (s, 1H), 7.18 (m, 1H), 7.32(d, $J = 8.4$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 11.42 (br, 1H).

Example 61



[000560] To a solution of Compound **A6** (1 g, 2 mmol) in CH_3CN (15 mL) was added NBS (564 mg, 3.2 mmol) and the mixture was stirred at 50 °C for 1.5 h. It was cooled to rt, diluted with DCM (50 mL), washed with water (100 mL x 3) and brine (100 mL), dried over Na_2SO_4 , and concentrated to give Compound **61A** (1.2 g, crude) as a yellow solid. LC-MS (m/z): 534 $[\text{M}-18]^+$.

[000561] To a solution of Compound **61A** (1 g, 2.1 mmol) in THF (20 mL) was added TBAF (275 mg, 1.05 mmol) at 0 °C. The mixture was stirred at rt overnight, evaporated to remove solvent, and added water (50 mL). It was extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL), dried over Na_2SO_4 , concentrated and, purified by column chromatography on silica gel (33% ethyl acetate in petroleum) to give Compound **61B** (720 mg, yield 80%) as a white solid. LC-MS (m/z): 420 $[\text{M}-18]^+$.

[000562] To a solution of Compound **61B** (720 mg, 1.6 mmol) in THF (20 mL) was added Et_3N (500 mg, 4.94 mmol). The mixture was cooled to -15 °C, added MsCl (207 mg,

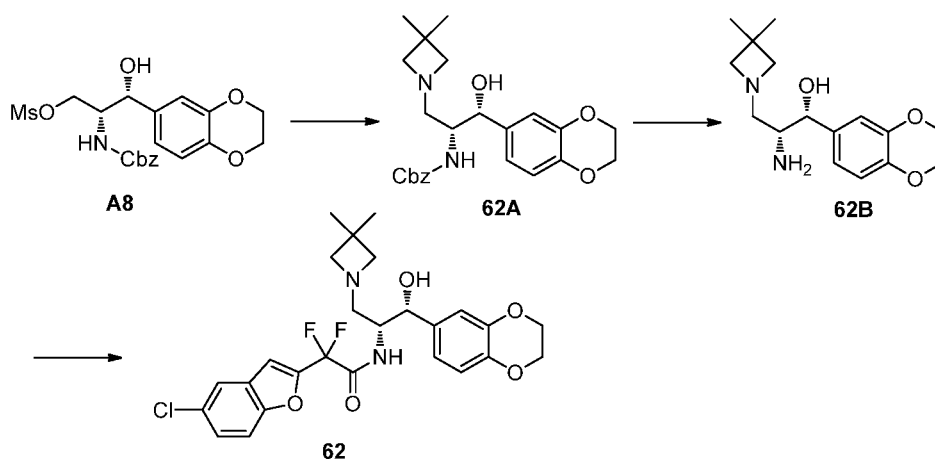
1.8 mmol) slowly, and stirred at -15 °C for half an hour. It was diluted with water, extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated to render Compound **61C** (700 mg, yield 83%), which was used for the next step without further purification. LC-MS (m/z): 498 [M-18]⁺.

[000563] To a solution of Compound **61C** (700 mg, 1.36 mmol) in THF (20 mL) was added pyrrolidine (1 g, 13.6 mmol). The reaction mixture was allowed to warm up to rt and then heated at 50 °C overnight. After cooled to rt and added water (20 mL), the mixture was extracted with ethyl acetate (50 mL x 2), washed with water (50 mL x 3) and brine (50 mL), dried over Na₂SO₄, and concentrated to give Compound **61D** (600 mg, crude). LC-MS (m/z): 491 [M+1]⁺.

[000564] To a solution of Compound **61D** (600 mg, 1.22 mmol) in EtOH (20 mL) and H₂O (2 mL) was added LiOH (154 mg, 3.67 mmol) and then the mixture was stirred at 100 °C overnight. After cooled to rt and added water (50 mL), the mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated to yield Compound **61E** (200 mg, yield 50%) as a yellow liquid. LC-MS (m/z): 357 [M+1]⁺.

[000565] A mixture of Compound **HE** (166 mg, 0.67 mmol), EDCI (216 mg, 1.12 mmol), HOBt (216 mg, 1.12 mmol), and Compound **61E** (200 mg, 0.56 mmol) in DCM (20 mL) was stirred at rt overnight. The mixture was added water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **61** (130 mg, yield 40%>) as a white solid. LC-MS (m/z): 585 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.15 (s, 4H), 2.95 (s, 1H), 3.10 (s, 1H), 2.57 (m, 2H), 3.87 (m, 2H), 3.94 (m, 2H), 4.04 (m, 1H), 4.13 (m, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 5.31 (s, 1H), 6.79 (s, 1H), 7.01 (s, 1H), 7.08 (s, 1H), 7.33 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 11.79 (s, 1H).

Example 62

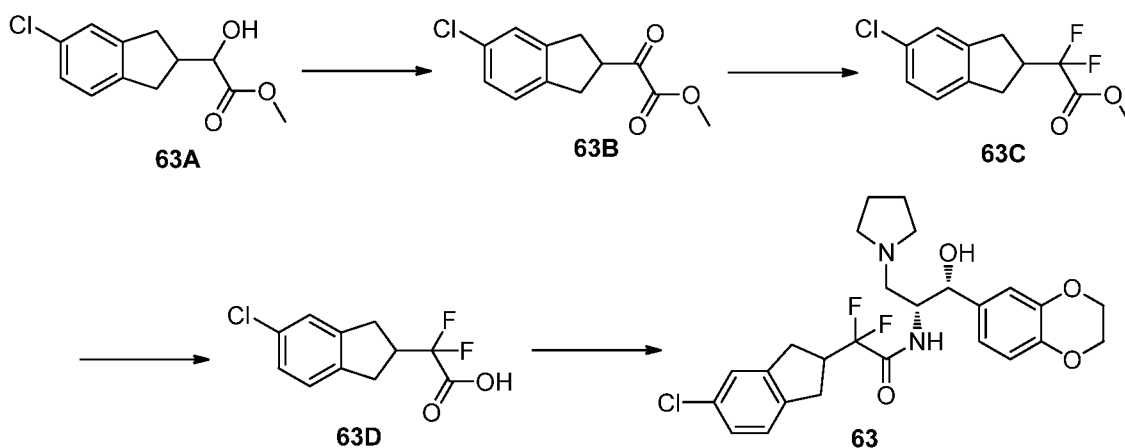


[000566] To a solution of Compound **A8** (437 mg, 1 mmol) in CH_3CN (20 mL) was added 3,3-dimethylazetidine (363 mg, 3 mmol), K_2CO_3 (414 mg, 3 mmol), and NaI (449 mg, 3 mmol). The mixture was heated at 82 °C overnight. It was cooled to rt, filtered and concentrated in vacuum to give a crude Compound **62A** (426 mg, crude) as a yellow oil. LC-MS (m/z): 427 [M+]⁺.

[000567] To a solution of Compound **62A** (426 mg, 1 mmol) in EtOH/water (20 mL, 9:1, v/v) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (420 mg, 10 mmol). The mixture was refluxed for 36 h. It was added water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to yield Compound **62B** (300 mg, crude) as a yellow oil. LC-MS (m/z): 293 [M+]⁺.

[000568] To a mixture of Compound **62B** (292 mg, 1 mmol) in DCM (20 mL) was added EDCI (288 mg, 1.5 mmol), HOBt (202 mg, 1.5 mmol) and Compound **HE** (246 mg, 1 mmol). It was stirred at 25 °C overnight, added water (10 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford a trifluoroacetic acid salt of Compound **62** (139 mg, yield 27%) as a white solid. LC-MS (m/z): 521 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.30 (s, 3H), 1.43 (s, 3H), 3.50 (s, 2H), 3.64 (t, $J = 12$ Hz, 2H), 4.05-4.19 (m, 6H), 4.30 (s, 1H), 5.01 (s, 1H), 6.73 (s, 3H), 6.8 (s, 1H), 7.34 (d, $J = 8$ Hz, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.58 (s, 1H), 7.89 (d, $J = 8$ Hz, 1H), 12.23 (s, 1H).

Example 63



[000569] To a solution of Compound **63A** (3.00 g, 12.50 mmol) in DCM (100 mL) was added DMP (6.36 g, 15.00 mmol) carefully. The mixture was stirred at 25 °C overnight. The mixture was quenched with aq $\text{Na}_2\text{S}_2\text{O}_3$ solution, diluted with ethyl acetate (200 mL), washed with water and brine, and purified with silica gel column chromatography (ethyl acetate in petroleum ether, from 0% to 20% v/v) to render Compound **63B** (2.10 g, yield 70%) as a white solid. LC-MS (m/z): 239 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.06-3.11 (m, 3H), 3.15-3.30 (m, 1H), 3.84 (s, 3H), 3.90-3.93 (m, 0.5H), 4.06-4.10 (m, 0.5H), 7.10-7.20 (m, 3H).

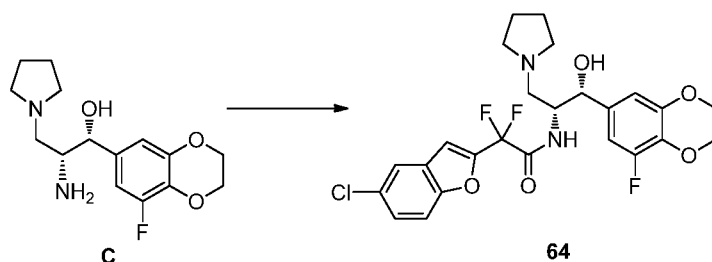
[000570] To a solution of Compound **63B** (200 mg, 1.26 mmol), in DCM (5 mL) was added DAST (1.01 g, 6.30 mmol) dropwise at 20 °C. The mixture was stirred at 20 °C overnight. The mixture was diluted with ethyl acetate (100 mL), washed with water and brine, and purified by silica gel column chromatography (dichloromethane in petroleum ether, from 0% to 8% v/v) to yield Compound **63C** (280 mg, yield 85%) as a colorless oil. LC-MS (m/z): 261 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.06-3.11 (m, 3H), 3.15-3.30 (m, 1H), 3.84 (s, 3H), 3.90-3.93 (m, 0.5H), 4.06-4.10 (m, 0.5H), 7.10-7.20 (m, 3H).

[000571] A mixture of Compound **63C** (280 mg, 1.08 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (136 mg, 3.24 mmol) in THF/MeOH/ H_2O (10/10/5 mL) was stirred at 20 °C overnight. The mixture was acidified to pH 2 with dilute HCl and extracted with DCM. Then organic phase washed with water and brine, dried over anhydrous Na_2SO_4 , and evaporated to give Compound **63D** (230 mg, yield 86%) as white solid. LC-MS (m/z): 465 [M-]⁻.

[000572] A mixture of Compound **63D** (89 mg, 0.36 mmol), Compound **HE** (100 mg, 0.36 mmol), EDCI (104 mg, 0.54 mmol) and HOBt (73 mg, 0.54 mmol) in DCM (10 mL) was stirred at 25 °C overnight. The mixture was diluted with ethyl acetate (150 mL), washed

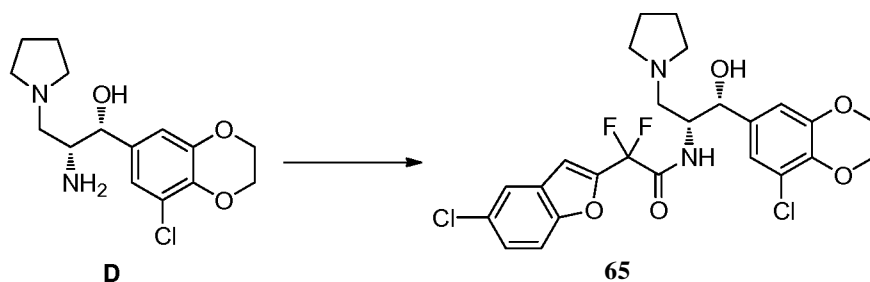
with water and brine, and purified by prep-HPLC to afford Compound **63** (100 mg, yield 55%) as a white solid. LC-MS (m/z): 507 $[M+1]^+$; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 1.88 (br s, 2H), 2.01 (br s, 2H), 2.50-2.83 (m, 4H), 3.00-3.16 (m, 3H), 3.50-3.55 (m, 5H), 4.13-4.20 (m, 4H), 4.42-4.50 (m, 1H), 4.74 (br s, 1H), 5.88 (s, 1H), 6.78-6.84 (m, 3H), 7.20-7.26 (m, 3H), 8.40 (d, $J = 8.8$ Hz, 1H), 9.50 (s, 1H).

Example 64



[000573] To a solution of Intermediate **C** (292 mg, 1 mmol) in DCM (20 mL) was added EDCI (288 mg, 1.5 mmol), HOBt (202 mg, 1.5 mmol) and Compound **HE** (246 mg, 1 mmol) and it was stirred at 25 °C overnight. The mixture was added water (10 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford a trifluoroacetic acid salt of Compound **64** (120 mg, yield 19%) as a white solid. LC-MS (m/z): 525 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.14 (s, 4H), 2.91-3.03 (m, 2H), 3.50 (d, $J = 4$ Hz, 2H), 3.82 (s, 2H), 4.11-4.19 (m, 4H), 4.44 (d, $J = 4$ Hz, 1H), 5.07 (s, 1H), 6.61 (s, 1H), 6.70 (d, $J = 12$ Hz, 1H), 6.86 (s, 1H), 7.34 (d, $J = 12$ Hz, 1H), 7.43 (d, $J = 12$ Hz, 1H), 7.58 (s, 1H), 7.80 (d, $J = 8$ Hz, 1H), 11.76 (s, 1H).

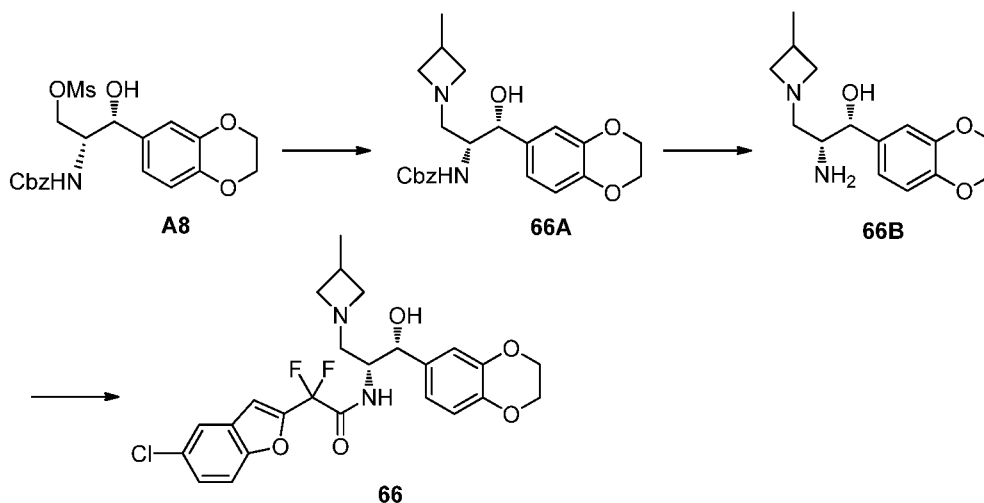
Example 65



[000574] To a solution of Intermediate **D** (250 mg, 0.8 mmol) in dichloromethane (20 mL) was added EDCI (230 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol) and Compound **HE** (196 mg, 0.8 mmol). The mixture was stirred at 25 °C overnight, added water (10 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to afford a trifluoroacetic acid salt of Compound **65** (75 mg, yield 14%) as a white solid. LC-MS (m/z): 541 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic

peaks: δ (ppm) 2.13 (s, 4H), 3.01 (s, 2H), 3.51 (s, 2H), 3.80 (s, 2H), 4.06 (s, 2H), 4.20 (s, 2H), 4.47(d, $J = 4$ Hz, 1H), 5.06 (s, 1H), 6.74 (s, 1H), 6.80 (s, 1H), 6.94 (s, 1H), 7.34 (d, $J = 12$ Hz, 1H), 7.43 (d, $J = 12$ Hz, 1H), 7.58 (s, 1H), 7.80 (d, $J = 8$ Hz, 1H), 11.76 (s, 1H).

Example 66

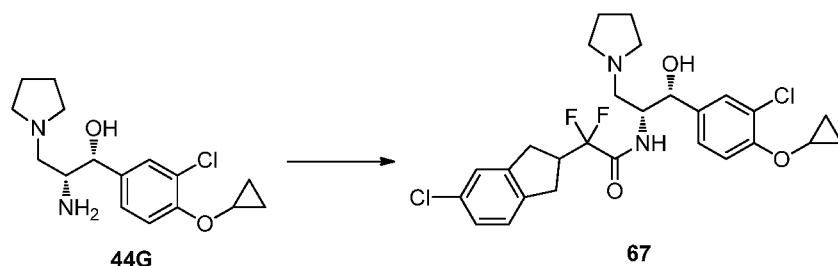


[000575] To a solution of Compound **A8** (437 mg, 1mmol) in CH_3CN (20 mL) was added 3-methylazetidine hydrochloride (321 mg, 3 mmol), K_2CO_3 (414 mg, 3 mmol) and NaI (449 mg, 3 mmol). The mixture was heated at 82 °C overnight. It was cooled to rt, filtered, and concentrated in vacuum to give crude Compound **66A** (426 mg, crude) as a yellow oil. LC-MS (m/z): 413 [M+1]⁺.

[000576] To a solution of Compound **66A** (412 mg, 1 mmol) in EtOH/water (20 mL, 9:1, v/v) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (420 mg, 10 mmol). The mixture was refluxed for 24 h and water (20 mL) was added. It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum to give crude Compound **66B** (280 mg, crude) as a yellow oil. LC-MS (m/z): 278 [M+1]⁺.

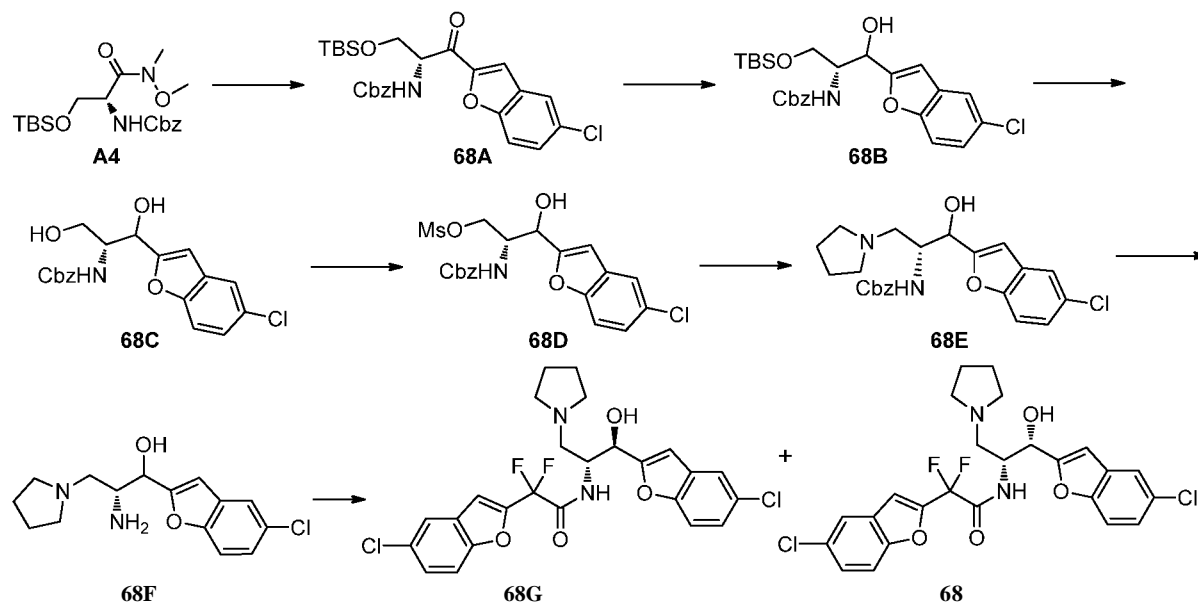
[000577] To a mixture of Compound **66B** (140 mg, 0.5 mmol) in DCM (10 mL) was added EDCI (144 mg, 0.75 mmol), HOBt (100 mg, 0.75 mmol), and Compound **HE** (123 mg, 0.5 mmol) and stirred at 30 °C overnight. It was added water (10 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , and purified by prep-HPLC to give a trifluoroacetic acid salt of Compound **66** (20 mg, yield 6%) as a white solid. LC-MS (m/z): 507 [M+1]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.23-1.38 (m, 3H), 2.92 (s, 1H), 3.15 (s, 1H), 3.49 (s, 3H), 4.01-4.15 (m, 5H), 4.30 (s, 1H), 4.43 (s, 1H), 5.00 (s, 1H), 6.73(s, 3H), 6.80 (s, 1H), 7.34 (d, $J = 8$ Hz, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.58 (s, 1H), 7.85 (s, 1H), 12.34 (s, 1H).

Example 67



[000578] A mixture of Compound **HE** (100 mg, 0.41 mmol), EDCL.HCl (118 mg, 0.62 mmol), HOBT (81 mg, 0.62 mmol), Compound **44G** (126 mg, 0.41 mmol) in DCM (5 mL) was stirred at 28 °C overnight. The mixture was added dropwise sat. aq NaHCO₃, and then extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂S₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **67** (62 mg, yield 28%) as a white solid. LC-MS: 539 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 0.62 (m, 2H), 0.81 (m, 2H), 1.88 (m, 2H), 2.03 (m, 2H), 2.60-2.65 (m, 2H), 2.76-2.80 (m, 2H), 3.06-3.20 (m, 3H), 3.41-3.54 (m, 4H), 3.88 (s, 1H), 5.53 (s, 1H), 8.84 (s, 1H), 6.00 (s, 1H), 7.15-7.21 (m, 3H), 7.27-7.31 (m, 1H), 7.36-7.40 (m, 2H), 8.45 (d, *J* = 9.2 Hz, 1H).

Example 68



[000579] To a solution of Compound **11B** (4.59 g, 30 mmol) in THF (125 mL) was added n-BuLi (2.4 M, 12.5 mL) at -60 °C under N₂ and stirred for 0.5 h and then a solution of Compound **A4** (3.97 g, 10 mmol) in THF (50 mL) was added slowly. The mixture was stirred at -60 °C for 1 h, before quenched by addition of saturate aq NH₄Cl solution. The mixture was extracted with ethyl acetate, brine, and dried over Na₂S₄. The crude product was purified by

column chromatography on silica gel (ethyl acetate in petroleum, 5% v/v) to give Compound **68A** (3.48 g, yield 71%) as a yellow oil. LC-MS (m/z): 488 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) -0.11 (s, 3H), -0.08 (s, 3H), 0.75 (s, 9H), 4.99 (dd, *J* = 4.4, 10.0 Hz, 1H), 4.19 (dd, *J* = 3.6, 10.0 Hz, 1H), 5.14 (s, 2H), 5.26-5.30 (m, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 7.32-7.38 (m, 5H), 7.45-7.57 (m, 3H), 7.70 (d, *J* = 2.0 Hz, 1H).

[000580] A solution of Compound **68A** (3.48 g, 7.14 mmol) in THF (200 mL) was added L-selectride (1M solution in THF, 14.3 mL) dropwise at -70 °C under nitrogen atmosphere. After stirred for one hour, the reaction was quenched with saturated aq NH₄Cl solution and the mixture was extracted with ethyl acetate and dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to give Compound **68B** (3.41 g, yield 97%) as a colorless oil. LC-MS (m/z): 472 [M-17]⁺.

[000581] To a solution of Compound **68B** (3.41 g, 6.95 mmol) in THF (100 mL) was added a solution of TBAF (0.91 mg, 3.48 mmol) in THF (10 mL) at 0 °C. After stirred at rt for 18 h, the mixture was evaporated to remove solvent. The residue was taken up with water, extracted with ethyl acetate, washed with brine, and dried over Na₂SO₄. The crude was purified by flash column chromatography on silica gel (MeOH in DCM, 5% v/v) to render Compound **69C** (2.01 g, yield 76%) as a white solid. LC-MS (m/z): 358 [M-17]⁺.

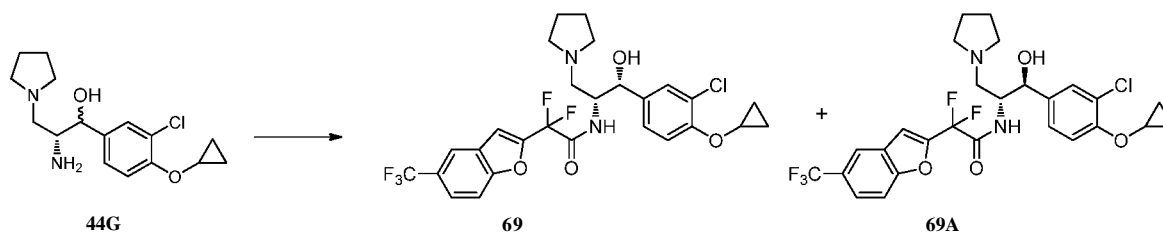
[000582] To a solution of Compound **68C** (2.01 g, 5.35 mmol) in THF (100 mL) was added Et₃N (1.62 g, 16.01 mmol) at -40 °C. MsCl (646 mg, 5.62 mmol) was added slowly and the mixture was stirred at -20 °C for 4 h. After evaporation, Compound **68D** (2.28 g, yield 100%) was obtained as yellow oil, which was used for the next step without purification.

[000583] To a solution of Compound **68D** (2.28 g, 5.35 mmol) in THF (100 mL) was added pyrrolidine (3.03 g, 42.8 mmol). The reaction mixture was heated at 50 °C for 15 h. After evaporation, the crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **68E** (940 mg) as a colorless oil. LC-MS (m/z): 429 [M+H]⁺.

[000584] To a solution of Compound **68E** (310 mg, 0.72 mmol) in ethanol (10 mL) and H₂O (10 mL) was added LiOH (152 mg, 3.61 mmol). The mixture was refluxed for 4 h. After evaporation, the mixture was extracted by DCM, and washed by brine, and dried over anhydrous Na₂SO₄. After filtration and evaporation, Compound **69F** (210 mg, yield 98%) was obtained as a yellow oil. LC-MS (m/z): 295 [M+]⁺.

[000585] A mixture of Compound **68F** (210 mg, 0.71 mmol), EDCI (204 mg, 1.07 mmol), HOBT (145 mg, 1.07 mmol) and Compound **HE** (210 mg, 0.85 mmol) in DCM (10 mL) was stirred at 25 °C for 16 h. The mixture was washed by saturated NaHCO₃ and brine. After evaporation, the crude was purified by prep-HPLC and followed by chiral-prep-HPLC to afford Compound **68G** (77 mg, yield 17%) as a white solid and Compound **68** (82 mg, yield 18%) as a white solid. For Compound **68G**, LCMS (m/z): 523 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.07 (s, 4H), 2.82-2.91 (m, 2H), 3.26-3.29 (m, 1H), 3.70-3.95 (m, 3H), 4.82 (s, 1H), 5.02 (d, *J* = 4.0 Hz, 1H), 6.68 (s, 1H), 6.91 (s, 1H), 7.19-7.21 (m, 1H), 7.28-7.33 (m, 3H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 9.18 (d, *J* = 7.2 Hz, 1H), 11.70 (s, 1H). For Compound **68**, LC-MS (m/z): 523 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.13 (s, 4H), 2.94-3.06 (m, 2H), 3.61 (s, 2H), 3.85 (s, 2H), 4.81 (d, *J* = 6.0 Hz, 1H), 5.33 (s, 1H), 6.64 (s, 2H), 7.06-7.09 (m, 1H), 7.14-7.15 (m, 1H), 7.19-7.21 (m, 1H), 7.28-7.31 (m, 2H), 7.39-7.40 (m, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 11.78 (s, 1H).

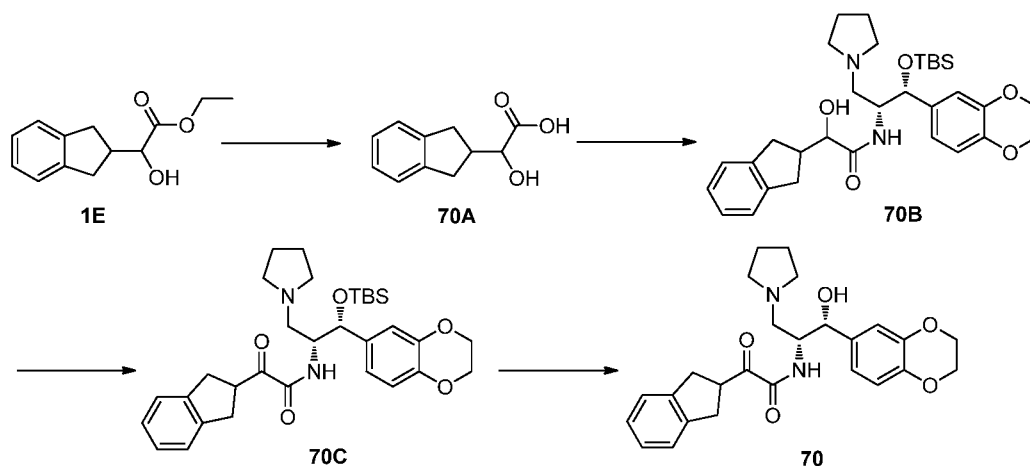
Example 69



[000586] A mixture of Compound **33F** (150 mg, 0.54 mmol), EDCI.HCl (154 mg, 0.81 mmol), HOBT (109 mg, 0.81 mmol), Compound **44G** (166 mg, 0.54 mmol) in DCM (5 mL) was stirred at 28 °C overnight. The reaction was quenched with addition of sat. aq NaHCO₃ and the mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL x 1), dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **70** (42 mg, yield 14.1%) as a white solid and Compound **69A** (42 mg, yield 14.1%) as a white solid. For Compound **69**, LC-MS (m/z): 573 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 0.52-0.61 (m, 2H), 0.73-0.76 (m, 2H), 1.89 (br s, 2H), 2.02 (br s, 2H), 3.08-3.21 (m, 2H), 3.50 (s, 4H), 3.67-3.72 (m, 1H), 4.53 (s, 1H), 4.82 (s, 1H), 6.04 (s, 1H), 7.02 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.32 (s, 1H), 7.86 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 8.16 (s, 1H), 8.93 (d, *J* = 9.2 Hz, 1H), 9.66 (s, 1H). For Compound **69A**, LC-MS (m/z): 573 [M+]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ (ppm) 0.46-0.54 (m, 2H), 0.70-0.74 (m, 2H), 1.89 (br s, 2H), 2.04 (br s, 2H), 3.15 (s, 2H), 3.38-3.48 (m, 4H), 3.60-3.65 (m, 1H), 4.13-4.37 (s, 1H), 4.52 (s, 1H),

6.09 (s, 1H), 6.73 (s, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 7.23 (d, $J = 8.8$ Hz, 1H), 7.82-7.90 (m, 2H), 8.09 (s, 1H), 9.27 (d, $J = 9.2$ Hz, 1H), 9.62 (s, 1H).

Example 70



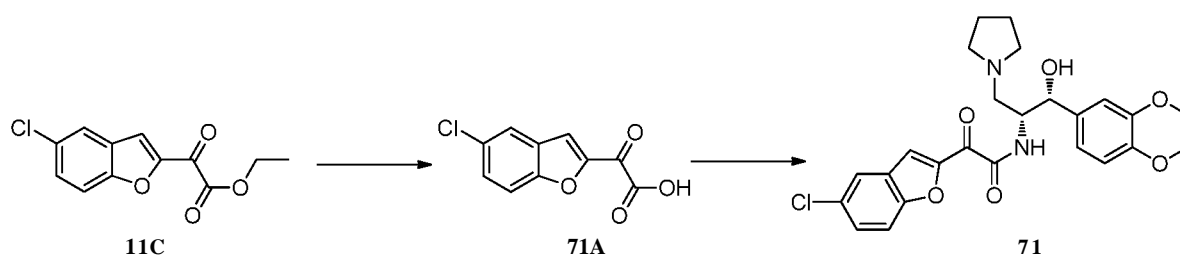
[000587] To a stirred solution of Compound **1E** (500 mg, 2.27 mmol) in THF (8 mL) was added LiOH.H₂O (99 mg, 2.27 mmol) and water (2 mL). The mixture was stirred at room temperature for 3 h. After reaction, the mixture was adjusted pH to 1 with 1 M HCl and concentrated by evaporation. The aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water and brine, dried over anhydrous Na₂S₄, and concentrated to render Compound **70A** (403 mg, yield 92%) as a yellow solid. LCMS: (m/z) 193 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.97 (m, 3H), 3.07-3.09 (m, 2H), 4.39 (d, $J = 4.4$ Hz, 1H), 7.15 - 7.19 (m, 4H).

[000588] To a solution of (*R*,*2R*)-1-((tert-butyldimethylsilyloxy)-1-(2,3-dihydrobenzo[3,4][1,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-2-amine (392 mg, 1.0 mmol) in DCM (20 mL) was added EDCI (288 mg, 1.5 mmol), HOBt (202 mg, 1.5 mmol) and Compound **70A** (192 mg, 1.0 mmol). The mixture was stirred at room temperature overnight and diluted with DCM (20 mL). It was washed with water (50 mL x 2), brine (50 mL x 1), dried over anhydrous Na₂S₄, concentrated, and purified by silica gel column chromatography (methanol in dichloromethane, 5% v/v) to give Compound **70B** (360 mg, yield 64%) as a yellow oil. LC-MS (m/z): 567 [M+]⁺.

[000589] To a stirred solution of Compound **70B** (360 mg, 0.64 mmol) in DCM (20 mL) was added DMP (324 mg, 0.76 mmol). The mixture was stirred at room temperature overnight. It was quenched with sat. aq Na₂S₃ solution and then concentrate by evaporation. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na₂S₄. Filtration and evaporation to dryness gave Compound **70C** (210 mg, yield 60%) as a yellow oil. LCMS: (m/z) 565 [M+]⁺.

[000590] To a solution of Compound **70C** (210 mg, 0.37 mmol) in THF (20 mL) was added TBAF (195 mg, 0.74 mmol). The mixture was stirred at room temperature overnight, quenched with sat. aq NH_4Cl solution, and concentrated by evaporation. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 . Removal of solvent led to a crude product, which was purified by prep-HPLC to give Compound **70** (12 mg, yield 7%) as a yellow solid. LC-MS (m/z): 451 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.07 (s, 4H), 2.87 (m, 3H), 3.21 (m, 4H), 3.82 (m, 3H), 4.08 (m, 1H), 4.21 (s, 4H), 4.45 (m, 2H), 4.96 (m, 1H), 6.76-6.82 (m, 3H), 7.14 (m, 4H), 7.86 (s, 1H), 11.11 (s, 1H).

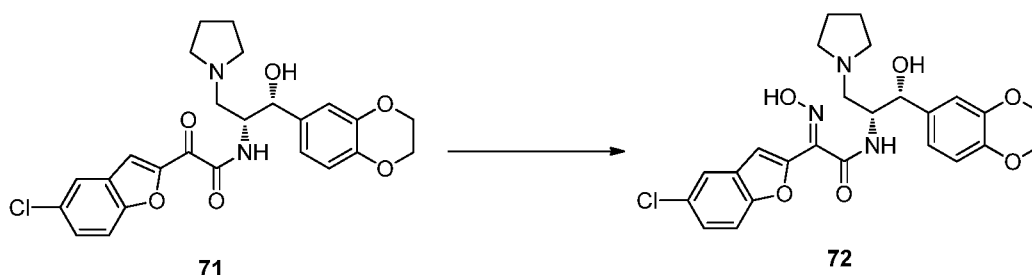
Example 71



[000591] To a solution of Compound **11C** (300 mg, 1.19 mmol) in EtOH (5 mL) was added LiOH (43 mg, 1.78 mmol) in water (5 mL). The mixture was stirred at room temperature overnight. After removal of EtOH by evaporation, the mixture was adjusted to pH 7 with diluted HCl. Lyophilization of the solution gave Compound **71A** (200 mg, crude), which was used for the next step without further purification. LC-MS (m/z): 223 [M-]⁻.

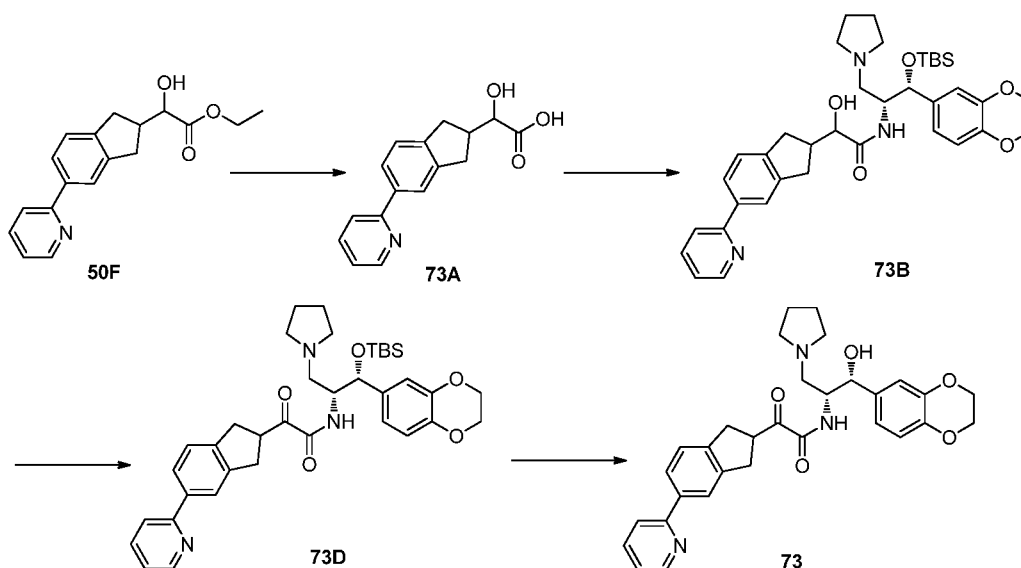
[000592] A mixture of Compound **71A** (100 mg, 0.45 mmol), EDCI (130 mg, 0.68 mmol), HOBT (91 mg, 0.68 mmol), Intermediate **A** (125 mg, 0.45 mmol) in DCM (10 mL) was stirred at room temperature overnight. After addition of sat. aq NaHCO_3 , the mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC to give Compound **71** (68 mg, yield 31%) as a white solid. LC-MS (m/z): 485 [M+]⁺; ¹H-NMR ($\text{DMSO}-d_6$, 400 MHz) major characteristic peaks: δ (ppm) 1.84 (m, 4H), 3.13 (m, 2H), 3.51 (m, 4H), 4.18 (s, 4H), 4.42 (s, 1H), 4.70 (s, 1H), 5.92 (s, 1H), 6.80 (m, 3H), 7.65 (m, 1H), 7.81 (m, 1H), 8.05 (s, 1H), 8.19 (m, 1H), 8.59 (s, 1H), 9.18 (s, 1H).

Example 72



[000593] A mixture of Compound **71** (20 mg, 0.042 mmol) and saturated hydroxylamine solution in methanol (5 mL) was stirred at 70 °C for 5 h. After addition of sat. aq NH_4Cl (10 mL), the mixture was extracted with DCM (10 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-HPLC to give Compound **72** (3 mg, yield 14%) as a white solid. LC-MS (m/z): 500 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) major characteristic peaks: δ (ppm) 1.92 (m, 4H), 3.11 (m, 2H), 3.55 (m, 4H), 4.21 (s, 4H), 4.58 (s, 1H), 4.80 (s, 1H), 5.95 (s, 1H), 6.46 (s, 1H), 6.87 (m, 3H), 7.40 (m, 1H), 7.64 (m, 2H), 8.84 (m, 1H), 10.07 (s, 1H), 12.42 (s, 1H).

Example 73



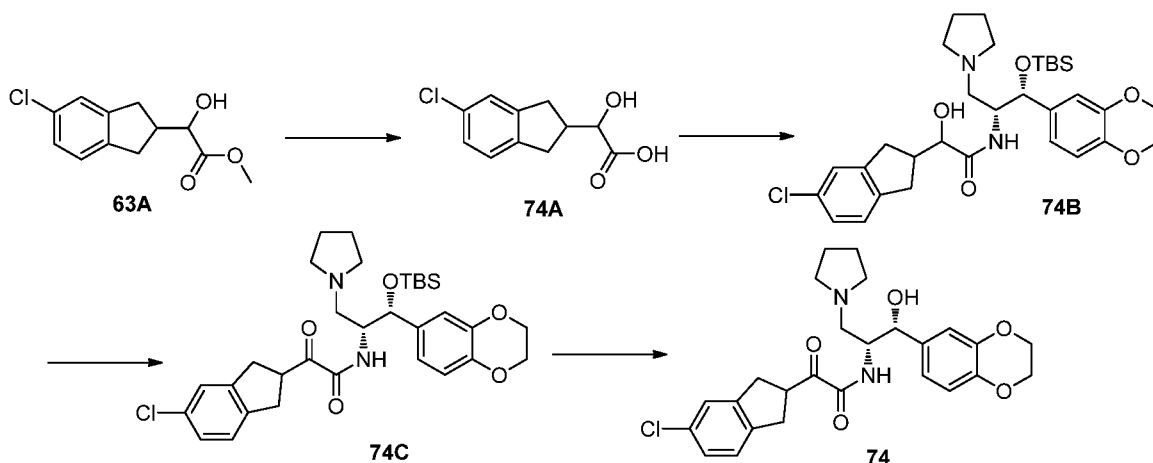
[000594] To a stirred solution of Compound **50F** (250 mg, 0.84 mmol) in THF (10 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (71 mg, 1.68 mmol) and water (2 mL). The mixture was stirred at room temperature for 3 h. After adjusted pH to 1 with 1 M HCl, the mixture was concentrated by evaporation. The aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4 , and concentrated to give Compound **73A** (160 mg, yield 71%) as a yellow solid. LCMS: (m/z) 270 $[\text{M}+1]^+$.

[000595] To a solution of (1*R*,2*R*)-1-((tert-butyldimethylsilyl)oxy)-1-(2,3-dihydrobenzo[3,4][1,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-2-amine (233 mg, 0.59 mmol) in DCM (10 mL) was added EDCI (171 mg, 0.89 mmol), HOBt (120 mg, 0.89 mmol) and Compound **73A** (160 mg, 0.59 mmol). The mixture was stirred at 25 °C overnight. After diluted with DCM (20 mL), it was washed with water (50 mL x 2), brine (50 mL x 1), dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **73B** (120 mg, yield 31%) as a yellow oil. LC-MS (m/z): 644 [M+]⁺.

[000596] To a stirred solution of Compound **73B** (120 mg, 0.19 mmol) in DCM (10 mL) was added DMP (97 mg, 0.23 mmol) and NaHCO₃ (31 mg, 0.37 mmol). The mixture was stirred at 25 °C overnight. After addition with sat. aq Na₂SO₃ solution, the mixture was concentrated by evaporation. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na₂SO₄. Filtration and evaporation of the solution to dryness gave Compound **73C** (110 mg, yield 92%) as a colorless oil. LCMS (m/z): 642 [M+]⁺.

[000597] To a solution of Compound **73C** (110 mg, 0.17 mmol) in THF (10 mL) was added TBAF (22 mg, 0.09 mmol). The mixture was stirred at 25 °C overnight and followed by quenched with sat. aq NH₄Cl solution. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was washed with water, brine, and dried over anhydrous Na₂SO₄. After removal of the solvents, the crude product was purified by prep-HPLC twice to give Compound **73** (5.9 mg, yield 7%) as a white solid. LC-MS (m/z): 528 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.72 (m, 2H), 1.85 (m, 3H), 1.94-1.97 (m, 1H), 2.31 (s, 1H), 2.53 (s, 1H), 2.77 (m, 3H), 2.92-3.12 (m, 3H), 3.26-3.28 (m, 3H), 4.23-4.24 (m, 5H), 4.62 (d, *J* = 4.8 Hz, 0.36 H), 5.03 (m, 0.64H), 6.62-6.72 (m, 1H), 6.79-6.85 (m, 2H), 7.21 (m, 1H), 7.29-7.34 (m, 1H), 7.70-7.72 (m, 3H), 7.83-7.86 (m, 1H), 8.66 (m, 1H).

Example 74



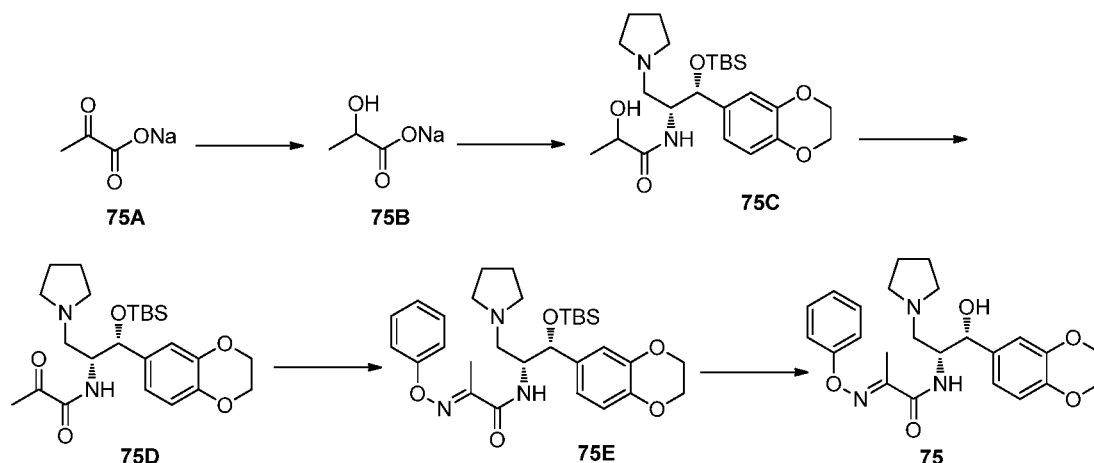
[000598] A mixture of Compound **63A** (1.10 g, 4.58 mmol) and LiOH.H₂O (577 mg, 13.75 mmol) in THF/MeOH/H₂O (20/20/10 mL) was stirred at 25 °C for 3 h. It was diluted with ice-water (150 mL) and adjusted to pH 1 with cone. HCl. Filtration to collect the solid gave Compound **74A** (900 mg, yield 87%) as a white solid. ¹H-NMR (DMSO-d₆, 400 MHz) major characteristic peaks: δ(ppm) 2.75-2.91 (m, 5H), 3.96 (s, 1H), 7.12-7.24 (m, 3H).

[000599] A mixture of Compound **74A** (100 mg, 0.44 mmol), EDCI (127 mg, 0.66 mmol), HOBT (89 mg, 0.66 mmol) and (S)-1-(ter *t*-butyldimethylsilyloxy)-1-(2,3-dihydrobenzo[3,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-2-amine (173 mg, 0.44 mmol) in DCM (10 mL) was stirred at 25 °C overnight. It was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by silica gel column chromatography (methanol in dichloromethane, from 0% to 8% v/v) to give Compound **74B** (230 mg, yield 87%) as a white solid. LC-MS (m/z): 601 [M+]⁺.

[000600] A mixture of Compound **74B** (200 mg, 0.33 mmol) and DMP (212 mg, 0.50 mmol) in DCM (10 mL) was stirred at 25 °C overnight. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by silica gel column chromatography (methanol in dichloromethane, from 0% to 8% v/v) to afford Compound **74C** (160 mg, yield 80%) as a colorless oil. LC-MS (m/z): 599 [M+]⁺.

[000601] A mixture of Compound **74C** (160 mg, 0.27 mmol) and Bu₄NF (50 mg) in THF (20 mL) was stirred at 25 °C overnight. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to yield Compound **74** (60 mg, yield 46%) as a white solid. LC-MS (m/z): 485 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.72 (br s, 4H), 1.87-1.96 (m, 2H), 2.30 (br s, 1H), 2.54-2.65 (m, 2H), 2.95-3.03 (m, 3H), 3.12-3.25 (m, 3H), 3.49-3.56 (m, 1H), 4.59 (s, 5H), 4.60 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 1H), 6.57-6.63 (m, 1H), 6.77-6.85 (m, 2H), 7.10-7.17 (m, 4H).

Example 75



[000602] A mixture of **75A** (1.00 g, 9.09 mmol) and Pd/C (1.00 g, 10%) in MeOH (20 mL) was stirred at 25 °C overnight in the presence of H₂. Then mixture was filtered to remove Pd/C. The filtrate was evaporated to render Compound **75B** (1.00g, yield 100%) as a white solid. LC-MS (m/z): 89 [M-1]⁻.

[000603] A mixture of Compound **75B** (57 mg, 0.51 mmol), (S)-1-(tert-butyl)dimethylsilyloxy)-1-(2,3-dihydrobenzo[3,4]dioxin-6-yl)-3-(pyrrolidin-1-yl)propan-2-amine (200 mg, 0.51 mmol), EDCI (147 mg, 0.76 mmol) and HOBt (103 mg, 0.76 mmol) in DMSO (5 mL) was stirred at 20 °C overnight. It was diluted with ethyl acetate (200 mL), washed with water and brine, and purified by silica gel column chromatography (methanol in dichloromethane, from 0% to 8% v/v) to yield Compound **75C** (180 mg, yield 76%) as colorless oil. LC-MS (m/z): 465 [M+1]⁺.

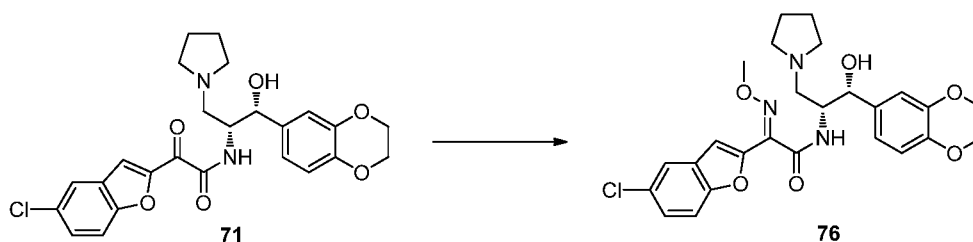
[000604] To a solution of Compound **75C** (470 mg, 1.01 mmol) in DCM (10 mL) was added DMP (478 mg, 1.11 mmol) at 20 °C. The mixture was stirred at 20 °C overnight. The mixture was quenched with Na₂S₂O₃ aqueous solution, diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na₂SO₄, and purified by silica gel column chromatography (methanol in dichloromethane, from 0% to 8% v/v) to afford Compound **75D** (320 mg, yield 68%) as colorless oil. LC-MS (m/z): 463 [M+1]⁺.

[000605] A mixture of Compound **75D** (150 mg, 0.32 mmol), sodium acetate (53 mg, 0.64 mmol) and O-phenylhydroxylamine hydrochloride (91 mg, 0.64 mmol) in EtOH (10 mL) was stirred at 85 °C for 3 h. Purification by prep-HPLC gave Compound **75E** (100 mg, yield 56%) as a colorless oil. LC-MS (m/z): 554 [M+1]⁺.

[000606] A mixture of Compound **75E** (100 mg, 0.23 mmol) and Bu₄NF (10 mg) in THF (10 mL) was stirred at 20 °C overnight. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, and purified by prep-HPLC to give Compound **75** (22 mg,

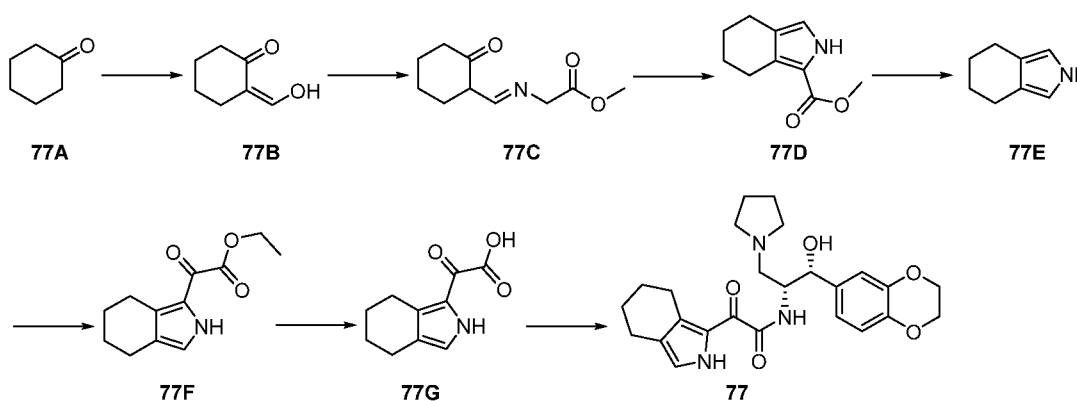
yield 22%) as a white solid. LC-MS (m/z): 440 [M+]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.99-2.06 (m, 2H), 2.17 (s, 5H), 3.14-3.23 (m, 2H), 3.43-3.49 (m, 1H), 3.59-3.68 (m, 2H), 3.80-3.87 (m, 1H), 4.21 (s, 4H), 4.50-4.55 (m, 1H), 4.83 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.87-6.90 (m, 1H), 6.96 (s, 1H), 7.12-7.16 (m, 1H), 7.30-7.33 (m, 2H), 7.38-7.42 (m, 2H).

Example 76



[000607] A mixture of Compound **71** (30 mg, 0.062 mmol), O-methylhydroxylamine (29 mg, 0.62 mmol) in methanol (5 mL) was stirred at 60 °C for 5 h. After addition of sat. aq NH₄Cl (10 mL), the mixture was extracted with DCM (10 mL x 2), washed with brine (30 mL x 1), dried over Na₂S₄, and concentrated. The crude product was purified by prep-HPLC to give Compound **76** (10 mg, yield: 31%) as a white solid. LC-MS (m/z): 514 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.88 (m, 4H), 3.10 (m, 2H), 3.61 (m, 4H), 3.96 (m, 3H), 4.20 (m, 4H), 4.48 (m, 1H), 4.83 (m, 1H), 5.98 (s, 1H), 6.44 (s, 1H), 6.91 (m, 3H), 7.61 (m, 1H), 8.40 (m, 1H), 9.61 (m, 1H).

Example 77



[000608] A mixture of NaH (60%, 20 g, 500 mmol), THF (3 L), EtOH (2.5 mL) was cooled to 0 °C, ethyl formate (55.5 g, 750 mmol) and Compound **77A** (49 g, 500 mmol) were added. The mixture was stirred for 6 hrs, and stood for 24 hrs. After the addition of EtOH (10 mL), the mixture was stirred for 1 hr, added water (1L) and EA (1L), washed with water (500 mL x 2). The aqueous layer was acidified with 6 N HCl, extracted with EA (300 mL x 2),

washed with brine (300 mL x 1), dried over anhydrous Na_2SO_4 , and purified by column chromatography on silica (ethyl acetate in Petroleum ether, 10% v/v) to give Compound **77B**.

[000609] To a solution of Compound **77B** (23 g, 183 mmol) in MeOH (300 mL) was added 2-aminoacetate hydrochloride (23 g, 183 mmol) and NEt_3 (18.4 g, 183 mmol). The mixture was stirred at 25 °C for 16 hrs. The mixture was concentrated and added water (100 mL), extracted with DCM (100 mL x 3), washed with brine (100 mL x 1), dried over anhydrous Na_2SO_4 , concentrated to give Compound **77C**.

[000610] To a solution of NaOMe (6.86 g, 127 mmol) in MeOH (200 mL) was added Compound **77C** (25 g, 127 mmol). The mixture was stirred at 90 °C for 3 hrs. The mixture was poured into water (500 mL), extracted with EA (100 mL x 3), washed with water (50 mL x 1), dried over anhydrous Na_2SO_4 , purified by column chromatography (dichloromethane, 100% v/v) to give Compound **77D**.

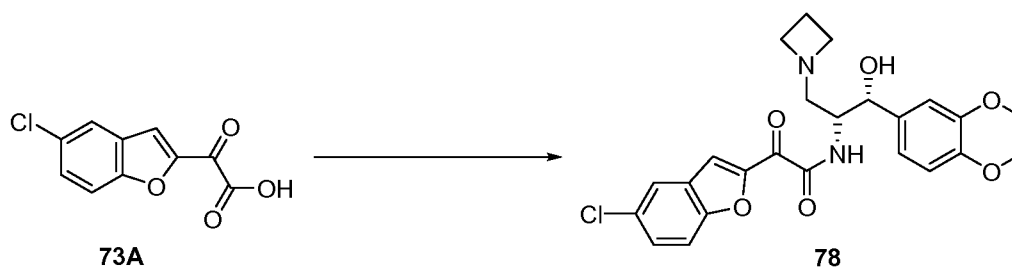
[000611] A mixture of Compound **77D** (1 g, 5.6 mmol) and KOH (0.6 g, 11.2 mmol) in ethane-1,2-diol (20 mL) was stirred at 200 °C for 3 hrs. The mixture was cooled down, added DCM (50 mL), washed with water (50 mL x 3), brine (50 mL x 1), dried over anhydrous Na_2SO_4 , purified by FCC (ethyl acetate in petroleum ether, 0-20% v/v) to give Compound **77E**.

[000612] To a solution of Compound **77E** (200 mg, 1.7 mmol) and NEt_3 (550 mg, 5.1 mmol) in DCM (20 mL) was added ethyl 2-chloro-2-oxoacetate (455 mg, 3.4 mmol) and stirred at 25 °C for 3 hrs. The mixture was added DCM (50 mL), washed with water (50 mL x 3), brine (50 mL x 1), dried over anhydrous Na_2SO_4 , purified by FCC (ethyl acetate in petroleum ether, 0-20% v/v) to give Compound **77F**.

[000613] To a solution of Compound **77F** (350 mg, 1.58 mmol) in EtOH (30 mL) and H_2O (3 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (133 mg, 3.17 mmol) and stirred at 25 °C for 10 min, concentrated and added water (30 mL), extracted with DCM (20 mL x 2). The aqueous layer was acidified via the addition of 1 N HCl, extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4 , concentrated to give Compound **77G**.

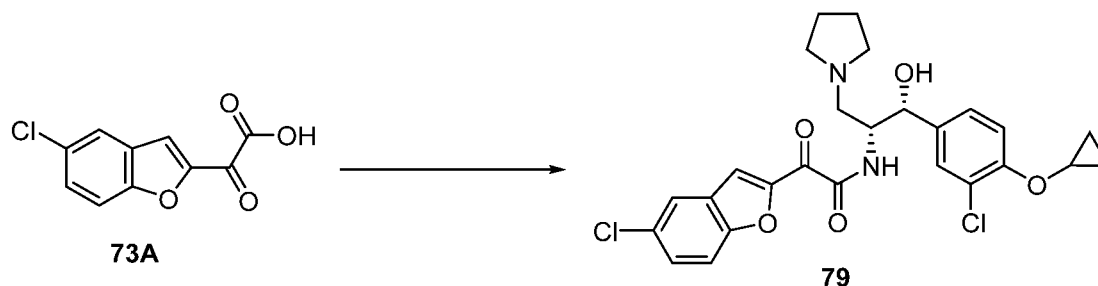
[000614] To a solution of Compound **77G** (100 mg, 0.5 mmol), EDCI (144 mg, 0.75 mmol), HOBT (100 mg, 0.75 mmol) in DCM (10 mL) was added Intermediate A (140 mg, 0.5 mmol). The mixture was stirred at 25 °C for 24 hrs, added water (50 mL), extracted with DCM (30 mL x 3), dried over anhydrous Na_2SO_4 , purified by prep-HPLC to give Compound **77**. LCMS: 454 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 1.73 (m, 4H), 2.10 (m, 5H), 2.51 (m, 2H), 2.84 (m, 2H), 2.97 (br, 1H), 3.40 (m, 2H), 3.92 (m, 2H), 4.21 (s, 4H), 4.44 (s, 1H), 5.10 (s, 1H), 6.80 (m, 3H), 6.88 (s, 1H), 8.20 (br, 1H), 11.02 (br, 1H), 11.49 (br, 1H).

Example 78



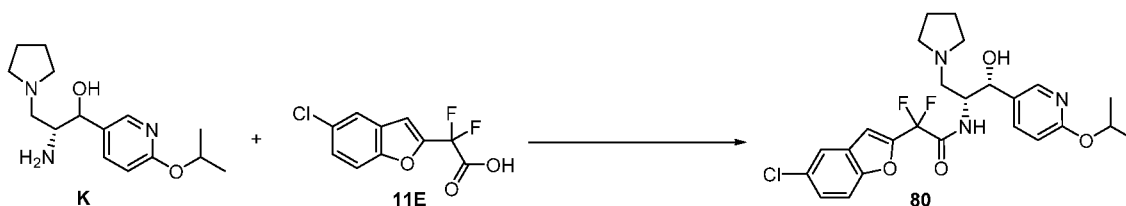
[000615] A mixture of Compound **73A** (200 mg, 0.75 mmol), EDCI (218 mg, 1.13 mmol), HOBt (154 mg, 1.13 mmol), Intermediate **F** (168 mg, 0.75 mmol) in DCM (20 mL) was stirred at room temperature overnight. Then added water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , concentrated. The crude product was purified by pre-HPLC to give Compound **78**. LC-MS (ESI) m/z : 471 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 2.43 (m, 2H), 3.14 (s, 3H), 3.58 (m, 2H), 4.13 (s, 4H), 4.41 (m, 2H), 4.99 (s, 1H), 6.83 (m, 3H), 7.44 (s, 2H), 7.67 (s, 1H), 8.01 (s, 1H), 8.19 (s, 1H), 10.96 (s, 1H).

Example 79



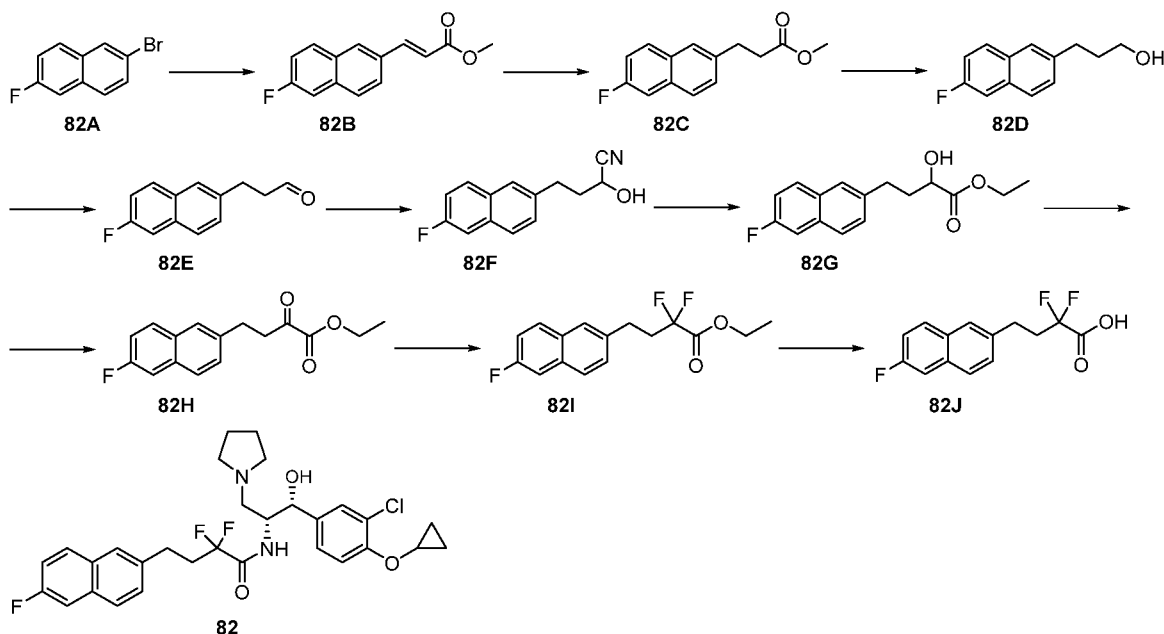
[000616] A mixture of Compound **73A** (254 mg, 1.13 mmol), EDCI.HCl (325 mg, 1.69 mmol), HOBt (230 mg, 1.69 mmol) and Intermediate **I** (350 mg, 1.13 mmol) in DCM (25 mL) was stirred at room temperature overnight. Then the mixture was treated with water, extracted with DCM (150 mL x 2), washed with brine (100 mL x 1), dried over Na_2SO_4 and concentrated. The crude product was purified with Prep-HPLC to provide Compound **79**. LC-MS (ESI) m/z : 517.0 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 0.74-0.76 (d, $J = 5.2$ Hz, 4H), 2.15 (s, 4H), 2.98-2.99 (m, 3H), 3.66 (s, 1H), 3.68-3.77 (m, 2H), 3.91 (s, 2H), 4.53 (s, 1H), 5.14 (s, 1H), 7.17-7.22 (m, 2H), 7.35 (s, 1H), 7.43-7.49 (m, 2H), 7.685-7.688 (d, $J = 1.2$ Hz, 1H), 8.11-8.18 (m, 2H), 11.77 (s, 1H).

Example 80



[000618] To a solution of Intermediate **K** (200 mg, 0.72 mmol) and Compound **HE** (176 mg, 0.72 mmol) in DCM (10 mL) was added EDCI.HCl (207 mg, 1.08 mmol) and HOBt (146 mg, 1.08 mmol) under N₂. The mixture was stirred at 30 °C overnight. TLC and LC-MS showed the starting material was consumed completely, then water (3 mL) was added to the mixture and then extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over anhydrous Na₂SO₄, and concentrated to provide the crude product. The crude product was purified with Prep-HPLC to provide a racemic mixture (45 mg, Yield: 12%) as a white solid, which was further purified by chiral HPLC (AD-H, 0.1% DEA in methanol) to furnish Compound **80**. LC-MS (ESI) m/z: 508 [M+H]⁺; ¹H NMR (MeOD, 400 MHz) δ (ppm) 1.29 (m, 6H), 1.83 (s, 4H), 2.69-2.73 (m, 4H), 2.91 (d, *J* = 6.8 Hz, 2H), 4.41 (m, 1H), 4.93 (d, *J* = 3.6 Hz, 1H), 5.08 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 7.45 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 2.8 Hz, 1H).

Example 82



[000619] A mixture of Compound **82A** (20 g, 89 mmol), methyl acrylate (23 g, 268 mmol), Pd(PPh₃)₂Cl₂ (3 g, 45 mmol) and K₂CO₃ (30 g, 223 mmol) in DMF (100 mL) was stirred at 100 °C for 12 h, then cooled to room temperature, then filtered. The filtrate was

treated with water, extracted with DCM (100 mL x 2), washed with water (100 mL x 3), brine (100 mL), dried over Na_2SO_4 , and concentrated to furnish the solid, then the solid was washed with PE, filtered to furnish the crude Compound **82B**.

[000620] To a solution of Compound **82B** (17 g, 74 mmol) in MeOH (200 mL) and THF (80 mL) was added Pd/C (2 g), then the mixture was stirred at room temperature for 12 h under H_2 , then filtered. The filtrate was concentrated to furnish the crude Compound **82C**.

[000621] To a solution of LiAlH_4 (3 g, 73 mmol) in THF (100 mL) was added dropwise Compound **82C** (17 g, 73 mmol) in THF (50 mL) at $-78\text{ }^\circ\text{C}$ under N_2 , then the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min, then quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ and filtered. The filtrate was concentrated to furnish the crude Compound **82D**.

[000622] To a solution of Compound **82D** (13 g, 64 mmol) in DCM (100 mL) was added DMP (32 g, 76 mmol) at $0\text{ }^\circ\text{C}$, then the mixture was stirred at room temperature for 2 h, then filtered. The filtrate was concentrated and the residue was purified with column chromatography (ethyl acetate in petroleum, 10% v/v) to furnish Compound **82E**.

[000623] Compound **82E** (25 g, 0.12 mol) was added to a solution of $\text{Na}_2\text{S}_2\text{O}_5$ (24 g, 0.12 mol) in water (300 mL), then the mixture was stirred for 2 h at room temperature. And after the addition of NaCN (12 g, 0.24 mol) for 15 h, the mixture was diluted with EA (50 mL), extracted with EA (100 mL x 2), washed with sat. NaHCO_3 (100 mL x 2), brine (100 mL), dried over Na_2SO_4 , and concentrated to furnish the crude product Compound **82F**.

[000624] To a solution of Compound **82F** (5 g, 22 mmol) in EtOH (50 mL) was bubbled a gentle stream of HCl gas (dried over con. H_2SO_4) at $0\text{ }^\circ\text{C}$ for 5 h. Then the mixture was treated with water slowly at $0\text{ }^\circ\text{C}$, stirred at room temperature for 2 h, then extracted with DCM (100 mL x 2), washed with brine (100 mL), dried over Na_2SO_4 , concentrated and purified with column chromatography (ethyl acetate in petroleum, 10% v/v) to furnish Compound **82G**.

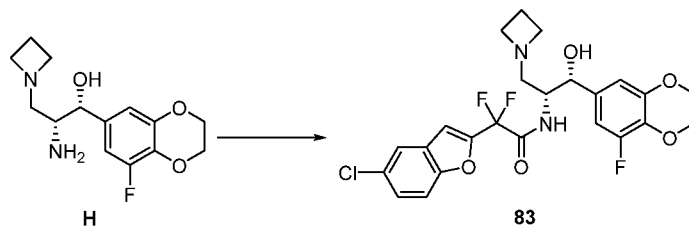
[000625] To a solution of Compound **82G** (4 g, 14.5 mmol) in DCM (100 mL) was added DMP (7.4 g, 17.4 mmol), then the mixture was stirred at room temperature for 1 h, then filtered. The filtrate was concentrated and the residue was purified with column chromatography (10% ethyl acetate in petroleum) to furnish Compound **82H**.

[000626] To a solution of Compound **82H** (2 g, 7.3 mmol) in DCM (50 mL) was added DAST (5.9 g, 36 mmol), then the mixture was stirred at room temperature for 12 h, poured into ice water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 , concentrated and purified with column chromatography (10% ethyl acetate in petroleum) to furnish Compound **82I**.

[000627] To a solution of Compound **82I** (1.8 g, 6.07 mmol) in THF (30 mL) was added LiOH (383 mg, 9.1 mmol) in water (2 mL), then the mixture was stirred at room temperature for 2 h, then evaporated to remove solvent. The mixture was treated with water, adjusted PH to 2 with diluted HCl, then extracted with EA (50 mL x 2), washed with brine (50 mL), dried over Na₂S₄, and concentrated to furnish the Compound **82J**.

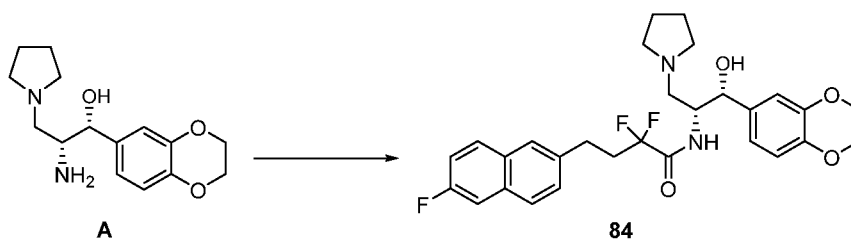
[000628] To a solution of Compound **82J** (173 mg, 0.64 mmol) in DCM (50 mL) was added EDCI.HCl (186 mg, 0.97 mmol), HOBt (132 mg, 0.97 mmol), and (1R,2R)-2-amino-1-(3-chloro-4-cyclopropoxyphenyl)-3-(pyrrolidin-1-yl)propan-1-ol (200 mg, 0.97 mmol), then the mixture was stirred at room temperature overnight. The mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂S₄ and concentrated. The crude product was purified with Prep-HPLC to provide Compound **82**. LC-MS (ESI) m/z: 561 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 0.56 (m, 4H), 2.13 (m, 4H), 2.41 (m, 2H), 2.60 (m, 2H), 2.90 (m, 2H), 3.43 (s, 3H), 3.81 (s, 2H), 4.47 (s, 1H), 5.16 (s, 1H), 7.16 (m, 3H), 7.40 (m, 2H), 7.49 (s, 1H), 7.56 (s, 1H), 7.68 (s, 1H), 7.75 (m, 1H), 7.79 (m, 1H), 11.99 (s, 1H).

Example 83



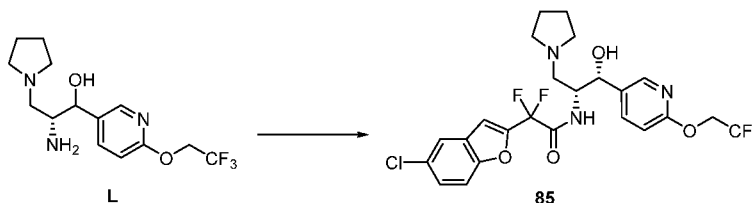
[000629] To a mixture of Compound **HE** (106 mg, 0.3 mmol) in dichloromethane (20 mL) was added EDCI.HCl (86 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol) and **Intermediate H** (74 mg, 0.3 mmol). It was stirred at 30 °C for 5 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous Na₂S₄, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **83**. LC-MS (ESI) m/z: 493 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.42 (s, 1H), 2.60 (s, 1H), 3.55-3.58 (m, 2H), 4.05-4.13 (m, 4H), 4.24 (s, 1H), 4.41(t, *J* = 8 Hz, 1H), 4.80 (s, 1H), 6.64 (s, 1H), 6.72 (d, *J* = 12 Hz, 1H), 6.90 (s, 1H), 7.43 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.70 (s, 1H).

Example 84



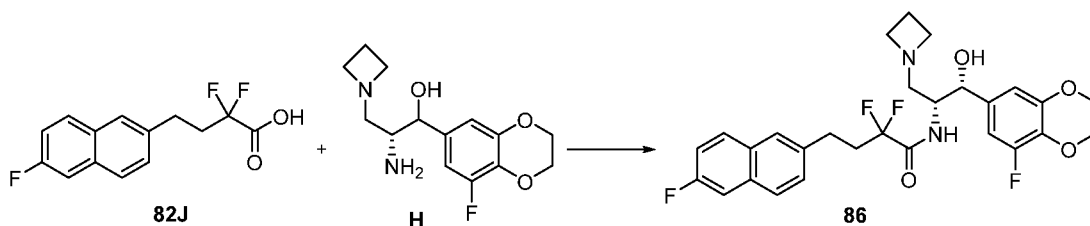
[000630] A mixture of Intermediate A (100 mg, 0.36 mmol), Compound **82J** (96 mg, 0.36 mmol), EDCI.HCl (104 mg, 0.54 mmol) and HOBt (73 mg, 0.54 mmol) in DCM (20 mL) was stirred at room temperature overnight. The mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified with Prep-HPLC to provide Compound **84**. LC-MS (ESI) m/z : 529 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 2.09 (s, 4H), 2.22 (m, 2H), 2.49 (m, 1H), 2.65 (m, 1H), 3.45 (m, 4H), 3.89 (m, 4H), 4.48 (s, 1H), 5.05 (s, 1H), 6.80 (s, 2H), 6.90 (s, 1H), 7.24 (m, 2H), 7.41 (m, 1H), 7.52 (s, 1H), 7.79 (m, 2H), 7.76 (m, 1H), 11.76 (s, 1H).

Example 85



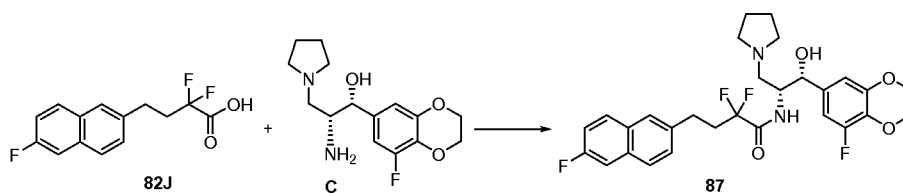
[000631] To a solution of Intermediate **L** (200 mg, 0.63 mmol) and **HE** (185 mg, 0.75 mmol) in DCM (10 mL) was added EDCI.HCl (181 mg, 0.94 mmol) and HOBt (127 mg, 0.94 mmol) under N_2 . The mixture was stirred at 30 °C overnight. TLC and LC-MS showed the starting material was consumed completely, and sat. NaHCO_3 (3 mL) was added to the mixture and then extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over anhydrous Na_2SO_4 , and concentrated to provide the crude product. The crude product was purified with Prep-HPLC to provide Compound **85**. LC-MS (ESI) m/z : 548 $[\text{M}+\text{H}]^+$; ^1H NMR (MeOD, 400 MHz) δ (ppm) 2.08-2.22 (m, 4H), 3.25 (m, 2H), 3.65-3.77 (m, 4H), 4.55-4.57 (m, 1H), 4.67-4.72 (m, 2H), 6.71 (d, $J = 2.8$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 7.02 (s, 1H), 7.48 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.59 (d, $J = 9.2$ Hz, 1H), 7.71 (dd, $J = 2.4, 8.4$, 1H), 7.75 (d, $J = 2.0$, Hz, 1H), 8.15 (d, $J = 2.4$ Hz, 1H).

Example 86



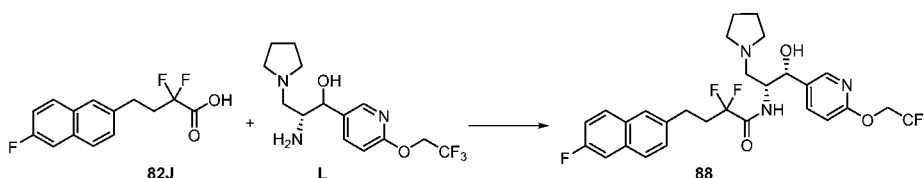
[000632] To a mixture of Compound **82J** (99 mg, 0.35 mmol) in dichloromethane (10 mL) was added EDCI.HCl (99 mg, 0.52 mmol), HOBt (71 mg, 0.52 mmol) and Intermediate **H** (94 mg, 0.35 mmol). It was stirred at 30 °C for 2 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous Na₂S₄, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **86**. LC-MS (ESI) *m/z*: 533 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) of Compound **86** δ (ppm) 2.18-2.68 (m, 6H), 3.56-3.59 (m, 2H), 3.72-3.95 (m, 4H), 4.25-4.45 (m, 4H), 4.46 (m, 1H), 4.85-4.86 (d, *J* = 2.8 Hz, 1H), 6.75-6.82 (m, 2H), 7.28-7.34 (m, 2H), 7.49-7.52 (m, 1H), 7.63 (s, 1H), 7.79-7.90 (m, 2H).

Example 87



[000634] To a mixture of Compound **82J** (80 mg, 0.3 mmol) in dichloromethane (10 mL) was added EDCI.HCl (86 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol) and Intermediate **C** (118 mg, 0.4 mmol) and the resultant mixture was stirred at 30 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous Na₂S₄, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **87**. LC-MS (ESI) *m/z*: 557 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.12-2.31 (m, 3H), 2.45-2.52 (m, 1H), 2.62-2.70 (m, 1H), 2.90 (s, 1H), 3.01-3.11 (m, 5H), 3.46 (m, 2H), 3.79-3.98 (m, 6H), 4.45 (s, 1H), 5.50 (s, 1H), 6.68-6.74 (m, 2H), 7.22-7.24 (m, 1H), 7.39 (d, *J* = 12 Hz, 1H), 7.53-7.58 (m, 2H), 7.70 (d, *J* = 12 Hz, 1H), 7.76 (t, *J* = 8 Hz, 1H), 11.62 (s, 1H).

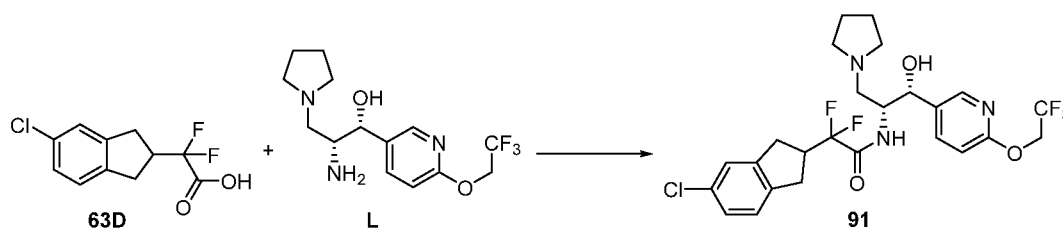
Example 88



for 30 min, then added ice water, adjusted pH 2 with diluted HCl, extracted with EtOAc (50 mL x 2). The organic layer was concentrated to form a solid, washed with PE, filtered to furnish Compound **90A**.

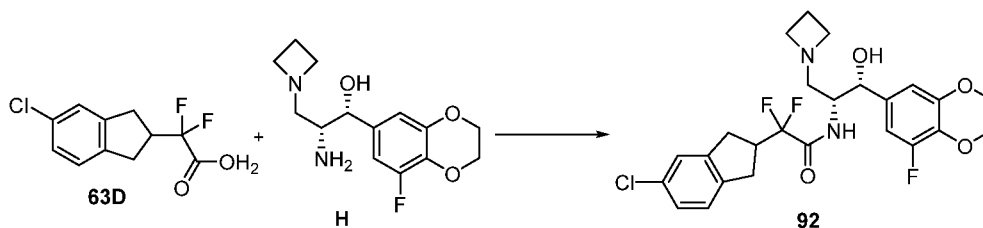
[000638] A mixture of Compound **90A** (177 mg, 0.72 mmol), Intermediate **A** (200 mg, 0.72 mmol), EDCI.HCl (207 mg, 1.08 mmol), HOBt (147 mg, 1.08 mmol) in DMF (20 mL) was stirred at room temperature overnight, then purified with Prep-HPLC to offer Compound **90**. LC-MS (ESI) m/z : 507 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.05 (s, 4H), 2.85 (m, 6H), 3.22 (s, 2H), 3.65 (s, 1H), 3.83 (s, 1H), 4.18 (s, 4H), 4.40 (s, 1H), 4.92 (s, 1H), 6.77 (s, 2H), 6.84 (s, 1H), 7.30 (m, 1H), 7.38 (m, 2H), 7.59 (s, 1H), 7.73 (m, 3H), 11.58 (s, 1H).

Example 91



[000639] The solution of Compound **63D** (60 mg, 0.24 mmol), Intermediate **L** (77 mg, 0.24 mmol), EDCI.HCl (68 mg, 0.36 mmol) and HOBt (49 mg, 0.36 mmol) in DCM (5 mL) was stirred at 25 °C for 16 h. Then it was diluted with EA (150 mL), washed with water (50 mL x 3) and brine (50 x 2 mL), dried over sulphate, evaporated and purified with Prep-HPLC to furnish Compound **91**. LC-MS (ESI) m/z : 548 [M+H]⁺; ¹H NMR (MeOD, 400 MHz) δ 2.06 (br s, 2H), 2.19 (br s, 2H), 2.68-2.76 (m, 3H), 2.84-2.92 (m, 2H), 2.97-3.07 (m, 2H), 2.56-3.69 (m, 3H), 3.75 (br s, 1H), 4.65-4.72 (m, 2H), 4.74-4.83 (m, 1H), 5.02 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.10-7.15 (m, 3H), 7.83 (d, J = 8.8 Hz, 1H), 8.24 (s, 1H).

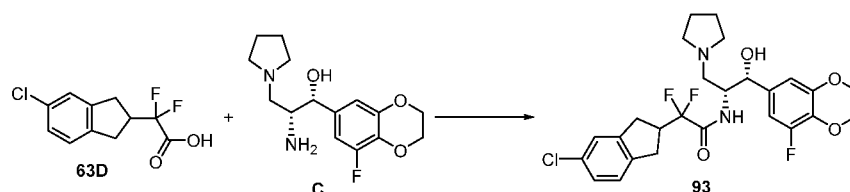
Example 92



[000640] To a mixture of Compound **63D** (59 mg, 0.24 mmol) and Intermediate **H** (59 mg, 0.2 mmol) in dichloromethane (9 mL) was added EDCI.HCl (58 mg, 0.3 mmol), HOBt (41 mg, 0.3 mmol). It was stirred at 30 °C for 2 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **92**. LC-MS (ESI) m/z : 511 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.38-3.07 (m, 7H),

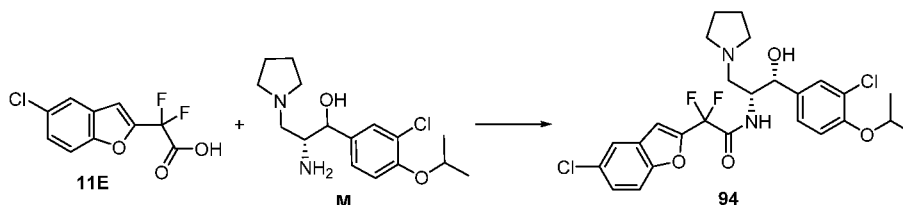
3.48 (s, 2H), 3.96-4.39 (m, 9H), 5.00 (s, 1H), 6.65-6.73 (m, 2H), 7.03-7.12 (m, 3H), 7.50-7.52 (d, $J = 4$ Hz, 1H), 12.33 (br, 1H).

Example 93



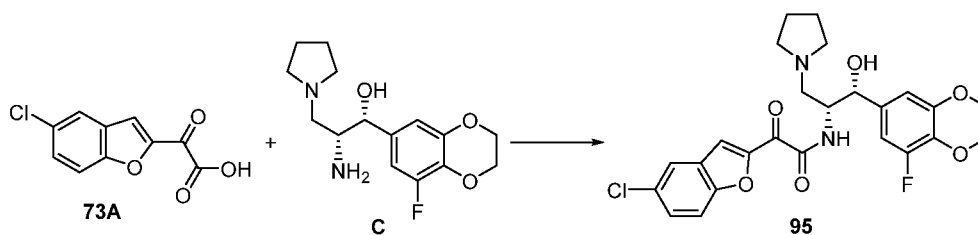
[000641] To a mixture of Compound **63D** (118 mg, 0.48 mmol) in dichloromethane (10 mL) was added EDCI.HCl (115 mg, 0.60 mmol), HOBt (81 mg, 0.60 mmol) and Intermediate C (118 mg, 0.4 mmol). It was stirred at 30 °C for 2 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **93**. LC-MS (ESI) m/z : 525 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.12 (s, 4H), 2.57-2.66 (m, 2H), 2.80-2.93 (m, 5H), 3.47 (s, 2H), 3.77 (s, 2H), 4.16-4.24 (m, 4H), 4.44 (s, 1H), 5.06 (s, 1H), 6.68-6.75 (m, 2H), 7.03-7.11 (m, 3H), 7.58 (s, 1H), 11.69 (s, 1H).

Example 94



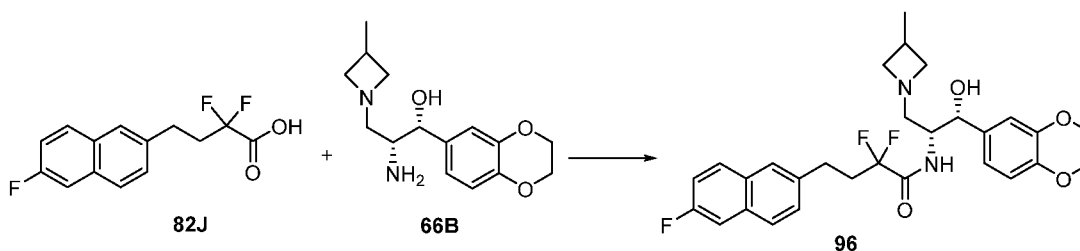
[000642] A mixture of Intermediate **M** (150 mg, 0.48 mmol), EDCI.HCl (138 mg, 0.72 mmol), HOBt (97 mg, 0.72 mmol) and Compound **11E** (142 mg, 0.58 mmol) in DCM (15 mL) was stirred for 18 h at 25 °C. Then the mixture was washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous sodium sulphate. After evaporation, the crude compound was purified with Prep-HPLC to furnish Compound **94**. LC-MS (ESI) m/z : 541 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.26-1.34 (m, 6H), 2.11 (m, 4H), 2.93-3.01 (m, 4H), 3.52-3.55 (m, 1H), 3.79 (m, 1H), 4.37-4.43 (m, 1H), 4.52 (m, 1H), 5.13 (s, 1H), 6.67 (s, 1H), 6.71 (d, $J = 4.4$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.32-7.43 (m, 3H), 7.94 (d, $J = 6.4$ Hz, 1H), 11.80 (s, 1H).

Example 95



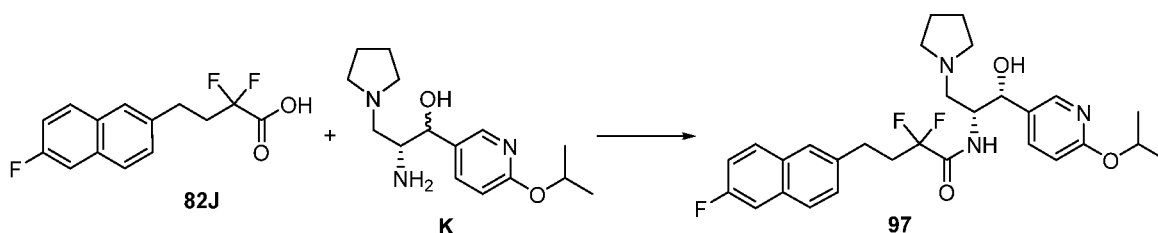
[000643] To a mixture of Compound **73A** (180 mg, 0.8 mmol) in dichloromethane (20 mL) was added HATU (456 mg, 1.2 mmol), DMF (0.1 mL) and Intermediate **C** (237 mg, 0.8 mmol). It was stirred at 30 °C for 2 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish the mixture. Then the mixture was further purified with chiral separation, Prep-HPLC to furnish trifluoroacetic acid salt of Compound **95**. LC-MS (ESI) m/z : 503 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.18 (s, 4H), 2.95-3.08 (m, 2H), 3.52 (s, 2H), 3.93 (s, 2H), 4.23 (s, 4H), 4.47 (s, 1H), 5.13 (s, 1H), 6.73 (d, $J = 12$ Hz, 2H), 7.46-7.53(m, 2H), 7.70 (s, 1H), 7.99 (s, 1H), 8.25 (s, 1H), 11.86 (s, 1H).

Example 96



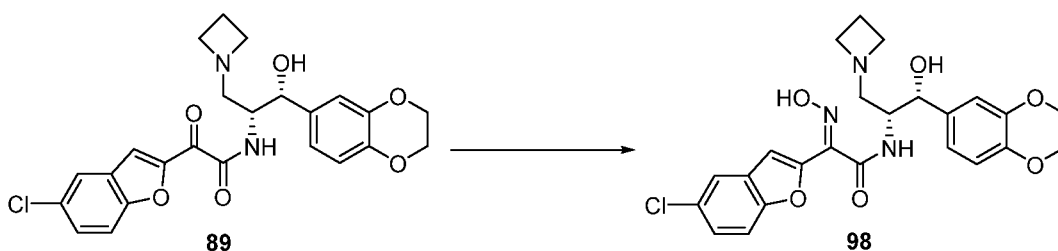
[000644] A mixture of Compound **82J** (80 mg, 0.3 mmol), EDCI.HCl (86 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol) and Compound **66B** (83 mg, 0.3 mmol) in DCM (10 mL) was stirred at room temperature for 5 h. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulphate and concentrated under vacuum. The residue was purified with Prep-HPLC to offer Compound **96**. LC-MS (ESI) m/z : 529 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.21-1.35 (m, 3H), 2.21 (s, 2H), 2.47 (s, 1H), 2.61 (s, 1H), 3.10 (s, 2H), 3.39-3.49 (m, 3H), 3.81-3.96 (m, 5H), 4.30-4.38 (m, 2H), 4.98 (s, 1H), 6.78-6.86 (m, 3H), 7.25(d, $J = 8$ Hz, 1H), 7.51 (s, 1H), 7.68-7.77 (m, 3H), 12.13 (s, 1H).

Example 97



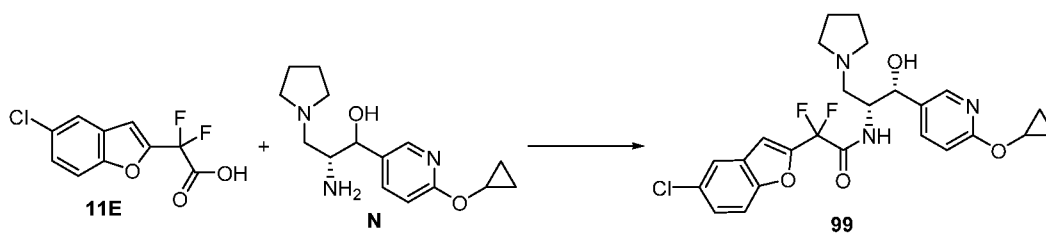
[000645] A mixture of Intermediate **K** (200 mg, 0.72 mmol), **82J** (192 mg, 0.72 mmol), EDCI.HCl (206 mg, 1.07 mmol), HOBt (146 mg, 1.07 mmol) in DCM (20 mL) was stirred at 25 °C for 4 h, added water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulphate, concentrated, and purified with Prep-HPLC to offer Compound **97**. LC-MS (ESI) m/z : 529 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.20-1.23 (m, 6H), 2.07 (s, 4H), 2.23-2.28 (m, 2H), 2.64-2.69 (m, 2H), 3.00 (s, 2H), 3.62-3.82 (m, 4H), 4.63 (s, 1H), 4.94 (s, 1H), 5.26 (s, 1H), 6.85 (s, 1H), 7.19-7.23 (m, 2H), 7.36-7.39 (m, 1H), 7.52 (s, 1H), 7.65-7.74 (m, 2H), 8.04 (s, 2H), 8.41 (s, 1H), 11.54 (s, 1H).

Example 98



[000646] To a solution of **89** (12 mg, 0.025 mmol) in MeOH (6 mL) was added hydroxylamine hydrochloride (34 mg, 0.5 mmol) at 30 °C, then the reaction was stirred at 55 °C for 4 h. Then it was purified with Prep-HPLC to furnish Compound **98**. LC-MS (ESI) m/z : 504 $[M+H]^+$; 1H NMR (MeOD, 400 MHz) δ (ppm) 2.21-2.61 (m, 2H), 3.37-3.41 (m, 2H), 4.12-4.18 (m, 9H), 4.74-4.79 (m, 1H), 6.36 (s, 1H), 6.63-6.71 (m, 2H), 7.26-7.27 (m, 1H), 7.28-7.54 (m, 3H).

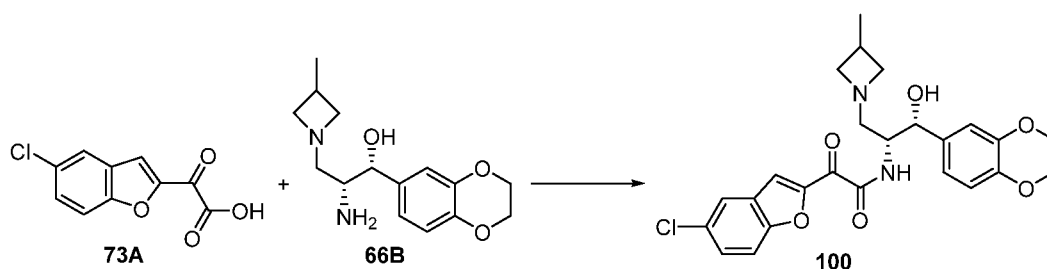
Example 99



[000647] To a solution of Intermediate **N** (110 mg, 0.397 mmol) in CH_2Cl_2 (5 mL) was added Compound **11E** (97 mg, 0.397 mmol), EDCI.HCl (113 mg, 0.595 mmol) and HOBt (80 mg, 0.595 mmol). The reaction mixture was stirred for 10 hours at 30 °C. The solvent

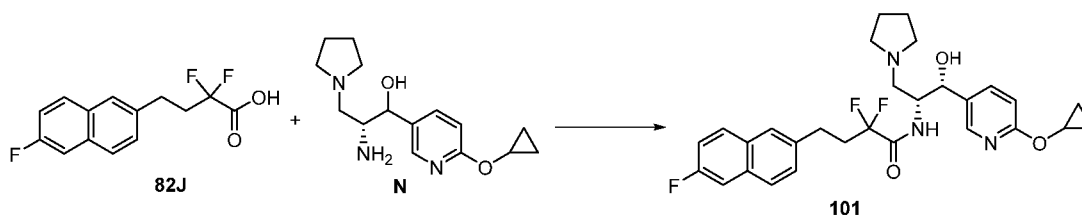
was removed under reduced pressure, and the residue was purified successively by prep. TLC (MeOH in CH₂Cl₂, 10% v/v) and chiral HPLC (co-solvent MeOH (0.1% DEA), column, AD-H 4.6 * 250mm, 5 urn) to offer desired product Compound **99**. LC-MS (ESI) m/z: 506 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 0.73-0.79 (m, 4H), 1.78-1.82 (m, 4H), 2.64-2.67 (m, 2H), 2.74-2.76 (m, 2H), 2.97-3.07 (m, 2H), 4.07-4.10 (m, 1H), 4.23 (br, 1H), 5.17 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 7.32-7.35 (m, 1H), 7.41-7.44 (m, 1H), 7.53-7.58 (m, 2H), 8.21 (d, *J* = 2.0 Hz, 1H).

Example 100



[000648] A mixture of Compound **73A** (145 mg, 0.65 mmol), HATU (370 mg, 0.97 mmol), and Compound **66B** (180 mg, 0.65 mmol) in DCM (20 mL) and DMF (2 mL) was stirred at room temperature for 2 h. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulphate and concentrated. The crude product was purified with Prep-HPLC to offer Compound **100**. LC-MS (ESI) m/z: 485 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.25-1.37 (m, 3H), 2.31-2.45 (m, 1H), 3.01-3.15 (m, 1H), 3.47-3.59 (m, 3H), 4.08-4.16 (m, 5H), 4.33 (s, 1H), 4.51 (s, 1H), 5.01 (s, 1H), 6.78-6.85 (m, 3H), 7.43-7.49 (m, 2H), 7.69 (s, 1H), 7.95 (s, 1H), 8.24 (s, 1H), 11.32 (s, 1H).

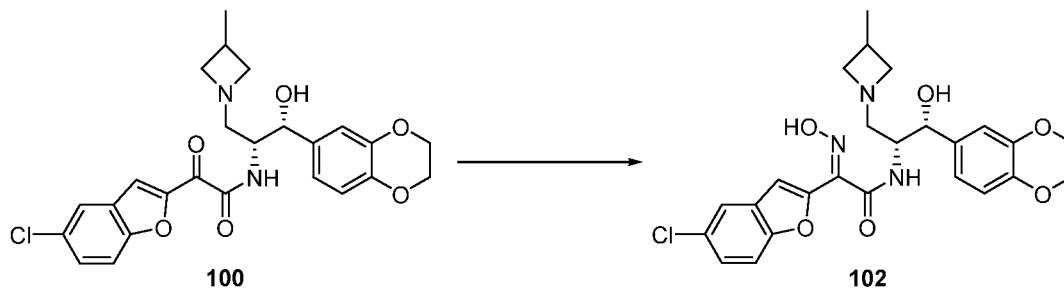
Example 101



[000650] A mixture of Intermediate N (100 mg, 0.36 mmol), Compound **82J** (96 mg, 0.36 mmol), EDCI.HCl (104 mg, 0.54 mmol), HOBt (74 mg, 0.54 mmol) in DCM (20 mL) was stirred at 25 °C overnight, added water, extracted with DCM (50 mL x 2), Brine (50 mL), dried over sodium sulphate, concentrated and purified with Prep-HPLC to offer Compound **101**. LC-MS (ESI) m/z: 528 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 0.67-0.72 (m, 4H), 2.06 (s, 4H), 2.17-2.27 (m, 2H), 2.57-2.71 (m, 2H), 3.04 (s, 2H), 3.53-3.67 (m, 3H), 3.88

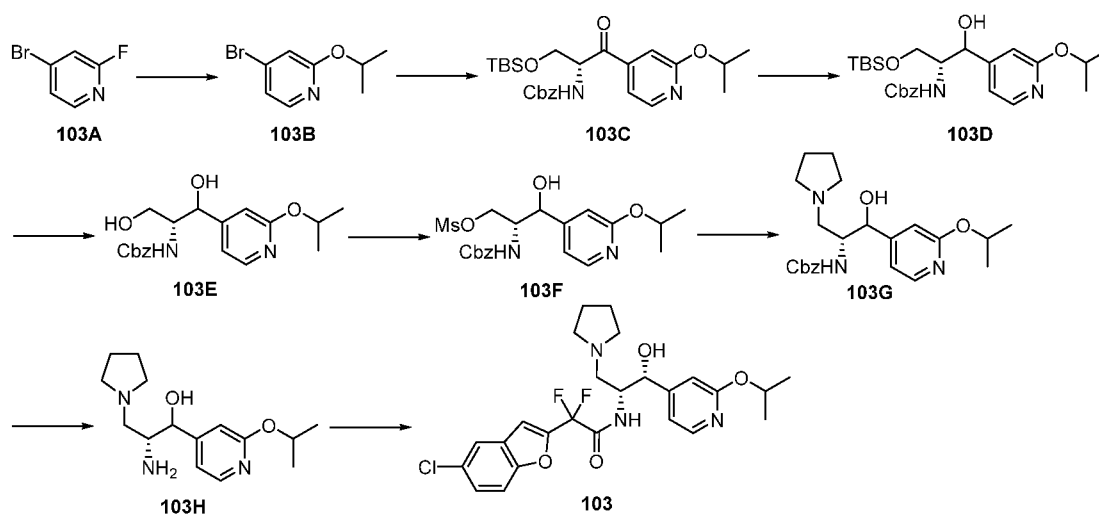
(s, 2H), 4.67 (s, 1H), 5.23 (s, 1H), 6.01 (s, 1H), 7.10 (s, 1H), 7.19-7.24 (m, 2H), 7.37-7.39 (m, 1H), 7.51 (s, 1H), 7.66-7.68 (m, 1H), 7.70-7.74 (m, 1H), 8.10 (s, 2H), 8.50 (s, 1H), 11.31 (s, 1H).

Example 102



[000651] A mixture of **100** (12 mg, 0.025 mmol) and hydroxylamine hydrochloride (17 mg, 0.25 mmol) in MeOH (3 mL) was stirred at room temperature for 4 h. Then it was purified with Prep-HPLC directly to offer Compound **102**. LC-MS (ESI) m/z: 500 [M+H]⁺; ¹H NMR (MeOD, 400 MHz) δ (ppm) 1.26-1.35 (m, 3H), 3.12 (s, 1H), 3.45-3.52 (m, 2H), 3.78-4.14 (m, 4H), 4.38-4.52 (m, 5H), 4.86-4.93 (m, 1H), 6.23 (s, 1H), 6.80-6.94 (m, 3H), 7.29 (s, *J* = 8 Hz, 1H), 7.34-7.41 (m, 1H), 7.44-7.62 (m, 2H).

Example 103



[000653] 60% NaH (1.04 g, 26 mmol) was added in two portions to isopropyl alcohol (30 mL) at room temperature (about 30 °C) under N₂. The mixture was stirred at 60 °C for 30 min. Compound **103A** (2 g, 11.36 mmol) was added in two portions and the mixture was stirred at reflux 4 h and at 80 °C overnight. The solution was concentrated in vacuo. Water (100 mL) and ethyl acetate (200 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (10 mL x 2), brine (10 mL x 2) and dried over anhydrous sodium sulphate.

After filtration the solvent was removed in vacuo. The crude product was subjected to flash chromatography (silica, ethyl acetate in petroleum, 0-10% v/v) to offer Compound **103B**.

[000654] To a solution of Compound **103B** (13 g, 60 mmol) in THF (300 mL) was added n-BuLi (2.4 M, 25 mL) at -60 °C under N₂ and the resultant mixture was stirred for 0.5 h, then a solution of Compound **A4** (8 g, 20 mmol) in THF (50 mL) was added, then the mixture was stirred at -60 °C for 1 h. After reaction monitored by LC-MS and TLC, added saturated NH₄Cl solution (50 mL), extracted with ethyl acetate (100 mL x 3), washed with brine (100 mL x 2), and dried over anhydrous sodium sulphate. The crude product was purified with column chromatography (ethyl acetate in petroleum, 0-20% v/v) to offer Compound **103C**.

[000655] Compound **103C** (472 mg, 1 mmol) was dissolved in anhydrous THF (10 mL) and cooled down to -70 °C under nitrogen atmosphere. L-Selectride (2 mL, 1M solution in THF, 2 mmol) was added dropwise while keeping the temperature at -70 °C. Then the reaction was stirred for 0.5 h at -70 °C. After reaction was monitored by TLC, the reaction was quenched with saturated NH₄Cl solution (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed water (30 mL), brine (30 mL x 2), and dried over anhydrous sodium sulphate. The crude product was purified with column chromatography (ethyl acetate in petroleum, 0-20% v/v) to offer Compound **103D**.

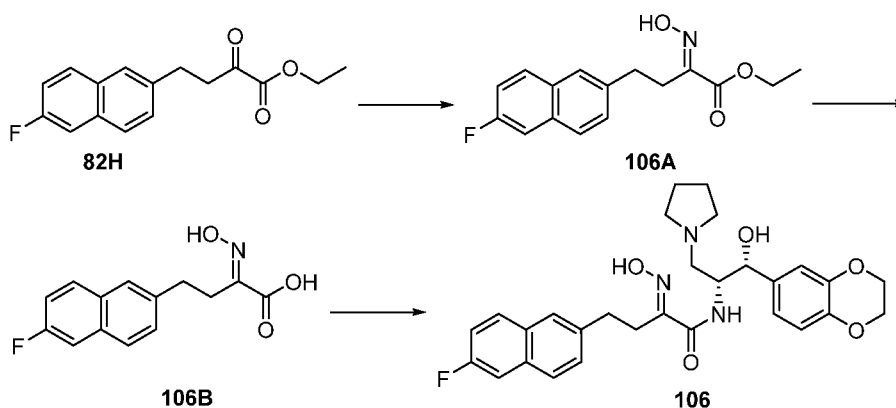
[000656] To a solution of Compound **103D** (2.1 g, 4.4 mmol) in THF (40 mL) was added a solution of TBAF (0.58 g, 2.2 mmol) in THF (10 mL) at 0 °C, then the mixture was stirred at 30 °C overnight. After the reaction was monitored by TLC and LC-MS. THF was evaporated. Then the residue was treated with water (50 mL) and extracted with ethyl acetate (50 mL x 3), washed with brine (50 mL), and dried over anhydrous sodium sulphate. The crude product was purified with flash column (silica, methanol in dichloromethane, 0-10% v/v) to offer Compound **103E**.

[000657] To a solution of Compound **103E** (1.2 g, 3.3 mmol) in dry DCM (20 mL) was added Et₃N (1 mL) under N₂, then the mixture was cooled to -40 °C, MsCl (0.31 mL, 4 mmol) was added slowly. Then the mixture was stirred at -40 °C about an hour. After reaction was monitored by TLC, the mixture was treated with water (10 mL) and extracted with DCM (50 mL x 3), washed with brine (50 mL), dried over anhydrous sodium sulphate. The crude product was purified with flash column (silica, methanol in dichloromethane, 0-30% v/v) to offer Compound **103F**.

[000658] To a solution of Compound **103F** (1 g, 2.3 mmol) in THF (40 mL) was added pyrrolidine (2 mL) under N₂, then the mixture was stirred at 50 °C for 16 h. After reaction

[000662] The mixture of Intermediate **O** (120 mg, 0.34 mmol), EDCI.HCl (98 mg, 0.51 mmol), HOBt (69 mg, 0.51 mmol) and Compound **HE** (101 mg, 0.41 mmol) in DCM (15 mL) was stirred for 18 h at 25 °C. Then the mixture was washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate. After evaporation, the crude compound was purified with Prep-HPLC to furnish Compound **105**. LC-MS (ESI) m/z: 583 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.75-1.84 (m, 2H), 1.96-2.14 (m, 6H), 2.77-2.87 (m, 2H), 3.17-3.20 (m, 1H), 3.55-3.60 (m, 3H), 3.76 (m, 1H), 3.88-4.02 (m, 3H), 4.41-4.48 (m, 2H), 4.95 (d, *J* = 4.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 7.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.42 (d, *J* = 9.2 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 9.23 (d, *J* = 8.0 Hz, 1H), 11.87 (s, 1H).

Example 106



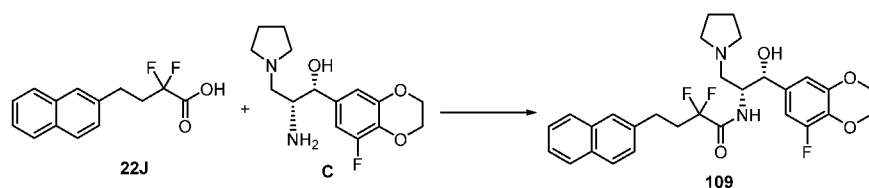
[000663] To a solution of Compound **82H** (310 mg, 1.13 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (102 mg, 1.47 mmol) and K₂CO₃ (203 mg, 1.47 mmol), then the mixture was stirred at 25 °C for 12 h and filtered. The filtrate was concentrated to furnish the Compound **106A**. LC-MS (ESI) m/z: 290 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.25 (t, *J* = 6.8 Hz, 3H), 2.98 (s, 4H), 4.17-4.23 (m, 2H), 7.18-7.26 (m, 1H), 7.37-7.41 (m, 2H), 7.63 (s, 1H), 7.70-7.73 (m, 2H).

[000664] To a solution of Compound **106A** (1500 mg, 0.52 mmol) in THF (15 mL) was added LiOH (65 mg, 1.55 mmol) in water (2 mL), then the mixture was stirred at 25 °C for 12 h, then added water, diluted with EA (20 mL), adjusted to PH = 2 with diluted HCl, extracted with EA (50 mL x 2), brine (50 mL), dried over sodium sulphate, and concentrated to furnish crude Compound **106B**.

[000665] A mixture of Compound **106B** (135 mg, 0.52 mmol), Intermediate **A**, EDCI.HCl (149 mg, 0.77 mmol), HOBt (106 mg, 0.77 mmol) in DMF (8 mL) was stirred at 25 °C overnight, purified with Prep-HPLC to offer Compound **106**. LC-MS (ESI) m/z: 522 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.97 (s, 4H), 2.83-2.87 (m, 6H), 3.09 (s, 1H),

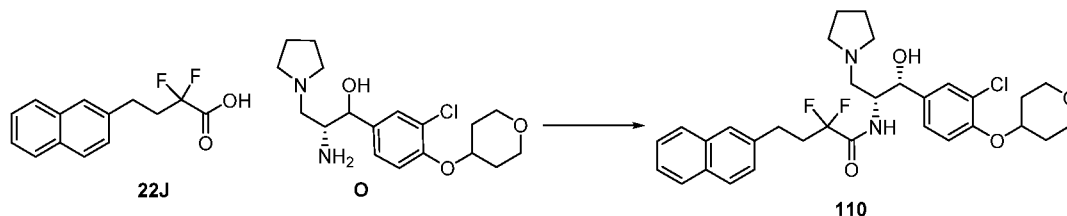
5.18 (s, 1H), 6.80-6.82 (m, 1H), 7.19-7.21 (m, 1H), 7.43-7.46 (m, 2H), 7.53 (s, 1H), 7.61-7.63 (m, 2H), 7.75-7.80 (m, 3H), 8.14 (s, 1H), 11.88 (s, 1H).

Example 109



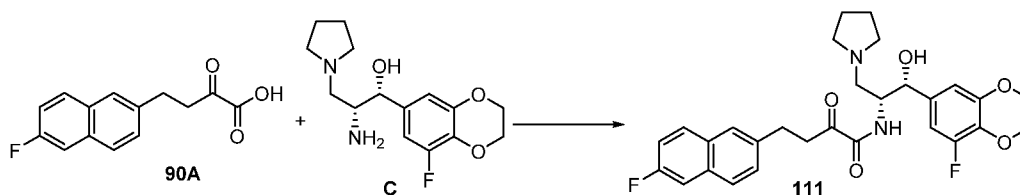
[000668] A mixture of Compound **22J** (100 mg, 0.40 mmol), EDCl.HCl (115 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) in Dichloromethane (20 mL) was stirred at 30 °C for 15 min. Intermediate **C** (148 mg, 0.50 mmol) was added. The reaction was stirred at 30 °C for 15 h. It was treated with water (20 mL), extracted with dichloromethane (20 mL x 3). The organic layer was washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish Compound **109**. LC-MS (ESI) m/z : 529 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.10 (m, 4H), 2.27 (s, 1H), 2.45-2.54 (m, 1H), 2.63-2.71 (m, 1H), 2.84 (s, 1H), 2.98 (s, 1H), 3.42 (s, 2H), 3.77-3.95 (m, 6H), 4.43 (s, 1H), 5.04 (s, 1H), 6.68-6.73 (m, 2H), 7.22-7.24 (m, 1H), 7.41-7.47 (m, 2H), 7.54 (s, 2H), 7.75-7.80 (m, 3H), 11.59 (s, 1H).

Example 110



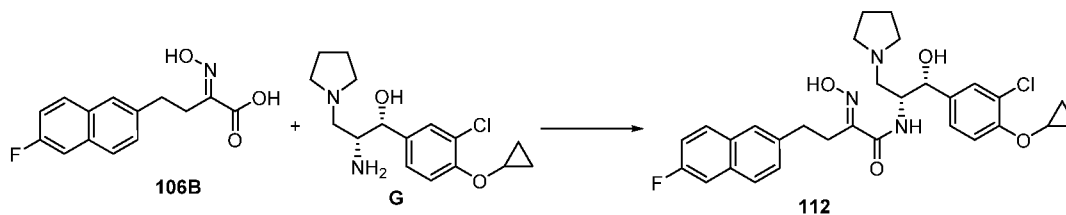
[000669] The mixture of Intermediate **O** (120 mg, 0.34 mmol), EDCl.HCl (98 mg, 0.51 mmol), HOBt (69 mg, 0.51 mmol) and Compound **22J** (103 mg, 0.41 mmol) in DCM (15 mL) was stirred for 3 h at 25 °C. Then the mixture was washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate. After evaporation, the crude compound was purified with Prep-HPLC to furnish Compound **110**. LC-MS (ESI) m/z : 587 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.57 (m, 2H), 1.71 (m, 2H), 2.10 (m, 4H), 2.23-2.33 (m, 2H), 2.44-2.68 (m, 2H), 2.81-2.95 (m, 2H), 3.32-3.42 (m, 4H), 3.77-3.79 (m, 4H), 4.21 (m, 1H), 4.45 (m, 1H), 5.12 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 7.14-7.22 (m, 2H), 7.41-7.48 (m, 3H), 7.59 (s, 1H), 7.63 (s, 1H), 7.74-7.80 (m, 3H), 11.7 (s, 1H).

Example 111



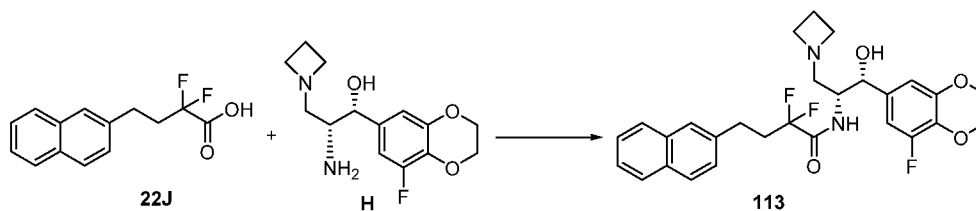
[000670] A mixture of Compound **90A** (160 mg, 0.65 mmol), HATU (370 mg, 0.97 mmol) and DMF (0.5 mL) in Dichloromethane (20 mL) was stirred at 30 °C for 15 min. Intermediate **C** (192 mg, 0.65 mmol) was added. The reaction was stirred at 30 °C for 4 h. Then water (20 mL) was added to reaction mixture. The resulting mixture was extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish trifluoroacetic acid salt of Compound **111**. LC-MS (ESI) m/z : 525 $[M+H]^+$; 1H NMR ($CDCl_3$ & MeOD, 400 MHz) δ (ppm) 1.97-2.05 (m, 4H), 2.93-2.97 (m, 3H), 3.12-3.16 (m, 3H), 3.09-3.33 (m, 1H), 3.47 (t, $J = 12$ Hz, 1H), 3.62 (s, 1H), 3.76 (s, 1H), 4.14-4.18 (m, 4H), 4.23-4.27 (m, 1H), 4.74 (s, 1H), 6.60-6.65 (m, 2H), 7.16 (t, $J = 8$ Hz, 1H), 7.27 (d, $J = 8$ Hz, 1H), 7.34 (d, $J = 12$ Hz, 1H), 7.56 (s, 1H), 7.61-7.71 (m, 2H).

Example 112



[000672] A mixture of Compound **106B** (150 mg, 0.57 mmol), Intermediate **G** (178 mg, 0.57 mmol), EDCl.HCl (165 mg, 0.86 mmol), HOBt (117 mg, 0.86 mmol) in DMF (5 mL) was stirred at 25 °C for 12 h, purified with Prep-HPLC to offer Compound **112**. LC-MS (ESI) m/z : 529 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.72 (s, 4H), 1.97 (s, 4H), 2.77-2.82 (m, 7H), 3.66 (s, 4H), 4.52 (s, 1H), 4.92 (s, 1H), 7.16-7.21 (m, 3H), 7.34-7.38 (m, 3H), 7.57 (s, 1H), 7.63-7.65 (m, 1H), 7.68-7.72 (m, 2H), 8.15 (s, 1H), 10.90 (s, 1H).

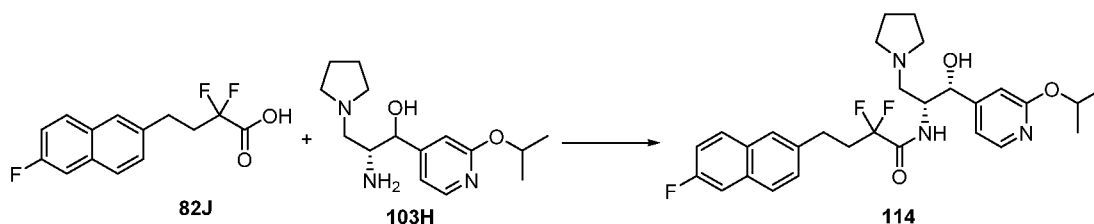
Example 113



[000673] To a solution of Compound **22J** (100 mg, 0.40 mmol) in Dichloromethane (20 mL) was added EDCl.HCl (115 mg, 0.60 mmol), HOBt (81 mg, 0.60 mmol), and the

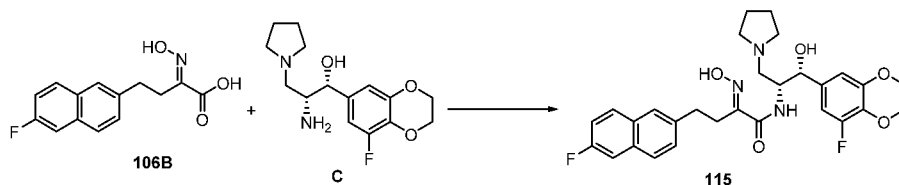
resultant mixture was stirred at 30 °C for 15 min. then Intermediate **H** (140 mg, 0.50 mmol) was added. The reaction was stirred at 30 °C for 15 h. It was poured into ice water (20 mL), extracted with dichloromethane (20 mL x 3). The organic layer was washed with water (50 mL x 2) and brine (30 mL), dried over anhydrous sodium sulphate, evaporated and purified with Prep-HPLC to furnish Compound **113**. LC-MS (ESI) m/z : 515 $[M+H]^+$; **H** NMR (CDCl₃, 400 MHz) δ (ppm) 2.56-2.66 (m, 6H), 3.43 (s, 2H), 3.82-3.95 (m, 6H), 4.18-4.45 (m, 3H), 4.98 (s, 1H), 6.66-6.72 (m, 2H), 7.21-7.25 (m, 1H), 7.43-7.54 (m, 4H), 7.75-7.81 (m, 3H), 12.25 (s, 1H).

Example 114



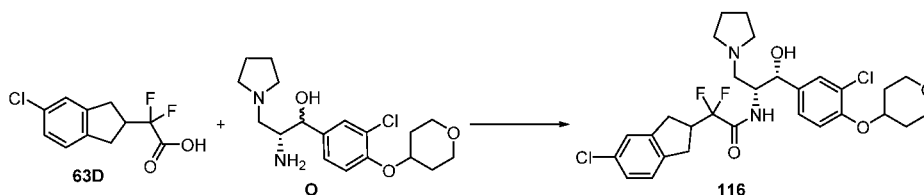
[000675] To a solution of Intermediate **103H** (140 mg, 0.5 mmol) and Compound **82J** (134 mg, 0.5 mmol) in DCM (5 mL) was added EDCI.HCl (144 mg, 0.75 mmol) and HOBT (101 mg, 0.75 mmol) under N₂. The mixture was stirred at 30 °C overnight. TLC and LC-MS showed the starting material was consumed completely, EA (50 mL) was added to the mixture and then washed with water (50 mL x 3), brine (50 mL x 1), dried over anhydrous sodium sulphate, and concentrated to offer crude product. The crude product was purified with Prep-HPLC to offer a mixture (50 mg, Yield: 57%) as a white solid, then the mixture was separated by Chiral-HPLC (Co-solvent EtOH (0.1% DEA), column OZ-H 250 * 4.6 mm 5 urn) to offer Compound **114**. LC-MS (ESI) m/z : 530 $[M+H]^+$; **H** NMR (CDCl₃, 400 MHz) δ (ppm) 1.12 (d, $J = 6.0$ Hz, 3H), 1.20 (d, $J = 6.4$ Hz, 3H), 2.00 (m, 4H), 2.26 (m, 2H), 2.50 (m, 1H), 2.67 (m, 1H), 3.14 (m, 4H), 3.30 (m, 1H), 3.47 (m, 1H), 4.47 (m, 1H), 5.11 (m, 2H), 6.73 (s, 1H), 6.82 (m, 1H), 7.21 (m, 2H), 7.41 (m, 1H), 7.51 (m, 2H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.74 (m, 1H), 8.05 (d, $J = 5.2$ Hz, 1H). Co-solvent: EtOH (0.1% DEA), column: OZ-H 250 * 4.6 mm 5 um, Rt: 3.56 min.

Example 115



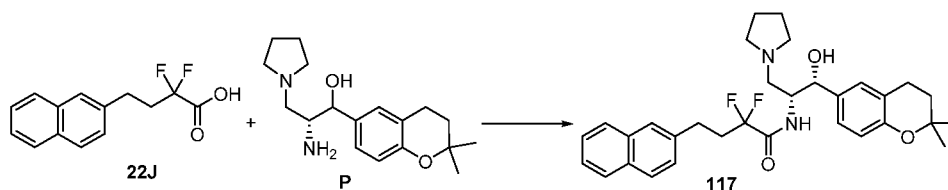
[000676] A mixture of Intermediate C (200 mg, 0.67 mmol), Compound **106B** (176 mg, 0.67 mmol), EDCl.HCl (194 mg, 1.01 mmol), HOBt (137 mg, 1.01 mmol) in DMF (5 mL) was stirred at 25 °C for 12 h, purified with Prep-HPLC to offer Compound **115**. LC-MS (ESI) m/z : 540 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.99 (s, 4H), 2.84 (s, 6H), 3.14 (s, 1H), 3.45 (s, 1H), 3.74 (s, 2H), 4.19 (s, 4H), 4.45 (s, 1H), 4.87 (s, 1H), 6.66-6.69 (m, 2H), 7.18-7.23 (m, 1H), 7.35-7.40 (m, 2H), 7.59-7.71 (m, 3H), 7.73-7.75 (m, 1H), 11.19 (s, 1H).

Example 116



[000677] The mixture of Compound **63D** (150 mg, 0.42 mmol), EDCl.HCl (121 mg, 0.63 mmol), HOBt (85 mg, 0.63 mmol) and Intermediate **O** (152 mg, 0.62 mmol) in DCM (15 mL) was stirred for 16 h at 25 °C. Then the mixture was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate. After evaporation, the crude compound was purified with Prep-HPLC to furnish Compound **116**. LC-MS (ESI) m/z : 583 $[M+H]^+$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.84 (m, 2H), 1.99 (m, 2H), 2.16 (m, 4H), 2.45 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 2.83-3.04 (m, 5H), 3.43-3.58 (m, 4H), 3.82 (m, 2H), 4.01 (m, 2H), 4.48-4.54 (m, 2H), 5.18 (s, 1H), 6.91-6.93 (m, 1H), 7.04-7.11 (m, 3H), 7.18-7.19 (m, 1H), 7.43 (s, 1H), 7.50 (s, 1H), 11.75 (s, 1H).

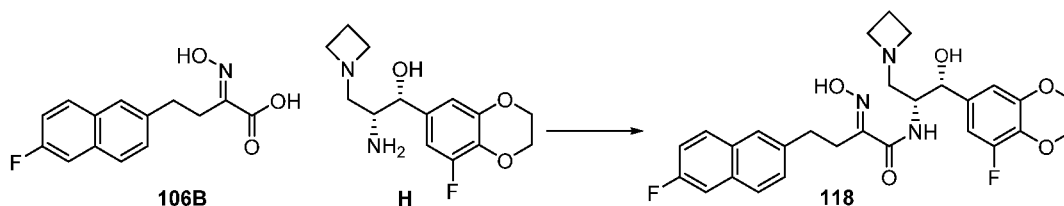
Example 117



[000678] A mixture of Compound **22J** (188 mg, 0.618 mmol), Intermediate **P** (155 mg, 0.618 mmol), EDCl.HCl (176 mg, 0.927 mmol) and HOBt (125 mg, 0.927 mmol) in DCM (10 mL) was stirred at 25 °C for 16 h. Then it was diluted with ethyl acetate (100 mL), washed with water (50 mL x 3) and brine (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **117**. LC-MS (ESI) m/z : 537 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz) δ (ppm) 1.03 (s, 3H), 1.05 (s, 3H), 1.47-1.52 (m, 2H), 1.83-1.82 (m, 2H), 1.98-2.02 (m, 2H), 2.27-2.29 (m, 2H), 2.53-2.60 (m, 2H), 2.63-2.76 (m, 2H), 3.06-3.40 (m, 2H), 3.43-3.48 (m, 4H), 4.52 (s, 1H), 4.72 (s, 1H), 5.82 (s, 4H),

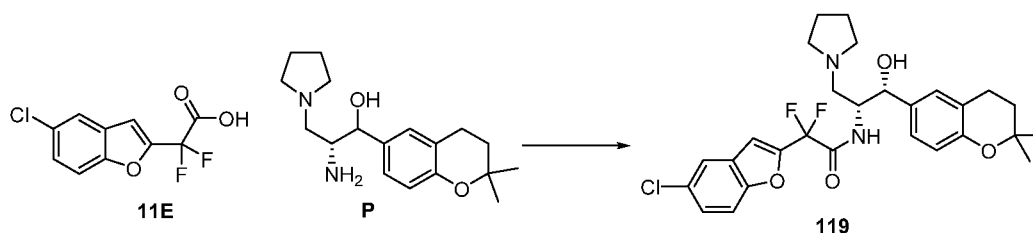
6.63 (d, $J = 8.8$ Hz, 1H), 7.00-7.12 (m, 2H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.45-7.52 (m, 2H), 7.68 (s, 1H), 7.84-7.90 (m, 3H), 8.35 (d, $J = 8.8$ Hz, 1H), 9.49 (s, 1H).

Example 118



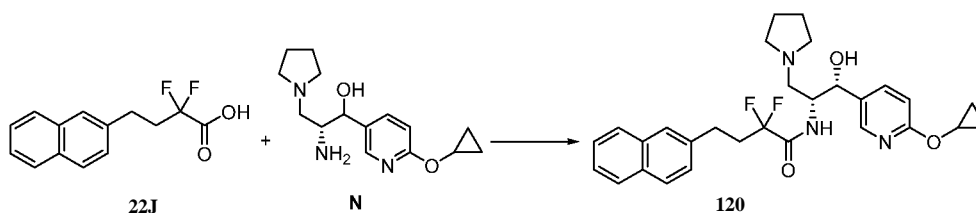
[000679] A mixture of Intermediate **H** (200 mg, 0.71 mol), EDCl.HCl (204, 1.06 mmol), HOBt (145, 1.01 mmol) and Compound **106B** (185mg, 0.71 mol) in DMF (5 mL) was stirred at room temperature overnight. Then the reaction mixture was purified with prep-HPLC to give Compound **118**. LC-MS (ESI) m/z : 526 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 2.15 (s, 1H), 2.50 (m, 1H), 2.81-2.90 (m, 4H), 3.27-3.37 (m, 2H), 3.76 (s, 3H), 4.15-4.17 (m, 5H), 4.29 (s, 1H), 4.82 (s, 1H), 6.61-6.64 (m, 2H), 7.18-7.22 (m, 1H), 7.34-7.39 (m, 2H), 7.52(s, 1H), 7.59 (s, 1H), 7.65-7.67 (m, 1H), 7.71-7.74 (m, 1H), 11.37 (s, 1H).

Example 119



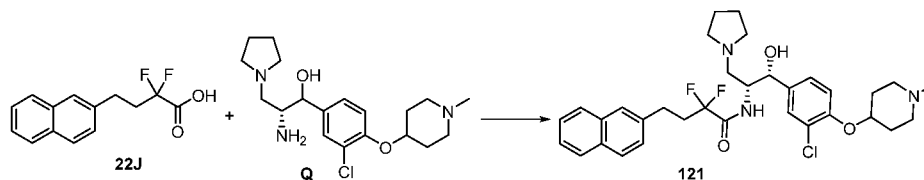
[000680] A mixture of Intermediate **P** (150 mg, 0.490 mmol), Compound **11E** (121 mg, 0.490 mmol), EDCl.HCl (140 mg, 0.740 mmol) and HOBt (100 mg, 0.740 mmol) in DCM/Et₃N (10/0.5 mL) was stirred at 25 °C for 16 h. Then it was diluted with ethyl acetate (100 mL), washed with water (50 mL x 3) and brine (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **119**. LC-MS (ESI) m/z : 533 [M+H]⁺; ¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm) 1.24 (s, 6H), 1.62-1.67 (m, 2H), 1.84-1.90 (m, 2H), 2.00 (s, 2H), 2.57-2.60 (m, 2H), 3.06-3.18 (m, 2H), 3.41-3.47 (m, 4H), 4.46-4.51 (m, 1H), 4.72 (s, 1H), 5.82 (s, 1H), 5.58 (d, $J = 8.4$ Hz, 1H), 6.82 (s, 1H), 6.95-7.00 (m, 2H), 7.53 (d, $J = 6.8$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.82 (s, 1H), 8.86 (d, $J = 9.2$ Hz, 1H), 9.48 (s, 1H).

Example 120



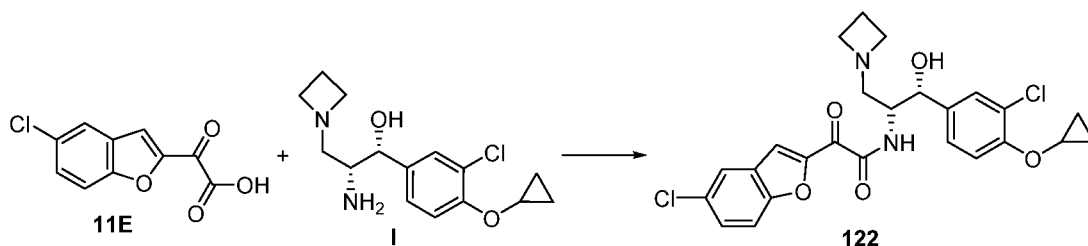
[000681] To a solution of Intermediate **N** (130 mg, 0.52 mmol) in dichloromethane (5 mL) was added Compound **22J** (120 mg, 0.433 mmol), EDCI.HCl (149 mg, 0.7794 mmol), and HOBt (107 mg, 0.7794 mmol). The mixture was stirred at 30 °C for 2h. The mixture was evaporated in *vacuo* to furnish the crude compound. The crude compound was purified with prep-HPLC to furnish a white solid (83 mg, yield 37 %), which was separated by chiral HPLC (co-solvent IPA (0.5% DEA), column AD-H 250 * 4.6 mm 5 urn) to give Compound **120**. LC-MS (ESI) *m/z*: 510 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 0.46-0.61 (m, 4H), 1.78-1.80 (m, 4H), 2.26-2.30 (m, 2H), 2.56-2.63 (m, 5H), 2.73-2.81 (m, 3H), 3.76-3.79(m, 1H), 4.36 (brs, 1H), 4.96 (d, *J* = 2.8 Hz, 1H), 6.88-6.89 (m, 1H), 7.27-7.29 (m, 1H), 7.41-7.45 (m, 2H), 7.59 (s, 1H), 7.75-7.81 (m, 4H), 8.16 (s, 1H). Co-solvent: IPA (0.5% DEA), column: AD-H 250 * 4.6 mm 5 urn, Rt: 3.51 min.

Example 121



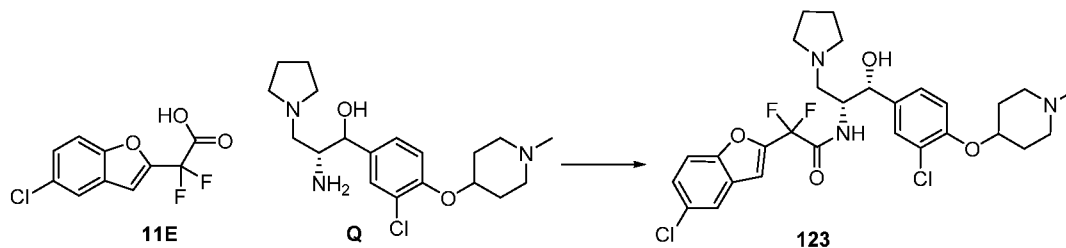
[000682] A mixture of Intermediate **Q** (150 mg, 0.41 mmol), EDCI.HCl (118 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol) and Compound **22J** (103 mg, 0.41 mmol) in DCM (5 mL) was stirred for 18 h at 25 °C. Then the mixture was washed with water (50 mL) and brine (50 mL) and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **121**. LC-MS (ESI) *m/z*: 600 [M+H]⁺; ¹H-NMR (MEOD, 400 MHz) δ (ppm) 1.65-2.11 (m, 11H), 2.49-3.20 (m, 10H), 3.54-3.66 (m, 4H), 4.31 (s, 1H), 4.58-4.61 (d, *J* = 10 Hz, 1H), 4.91 (s, 1H), 6.93-6.95 (m, 1H), 7.19-7.30 (m, 2H), 7.39-7.52 (m, 4H), 7.74-7.76 (m, 3H).

Example 122



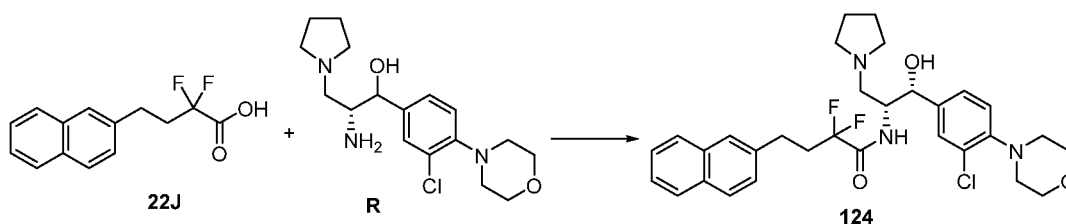
[000683] A mixture of Intermediate **I** (117 mg, 0.4 mmol), EDCl.HCl (114 mg, 0.59 mmol), HOBt (78 mg, 0.59 mmol) and Compound **HE** (88.5 mg, 0.4 mmol) in DCM (15 mL) was stirred at room temperature overnight. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **122**. LC-MS (ESI) m/z : 503 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.67-0.75 (m, 4H), 2.35-2.36 (m, 1H), 2.64 (s, 1H), 3.48 (s, 1H), 3.59-3.69 (m, 2H), 4.0 (s, 2H), 4.35-4.63 (m, 5H), 4.99 (s, 1H), 7.09-7.11 (m, 1H), 7.30 (s, 1H), 7.35-7.40 (m, 2H), 7.60 (s, 1H), 8.04-8.06 (d, $J = 8.0$ Hz, 1H), 8.21 (s, 1H), 11.38 (s, 1H).

Example 123



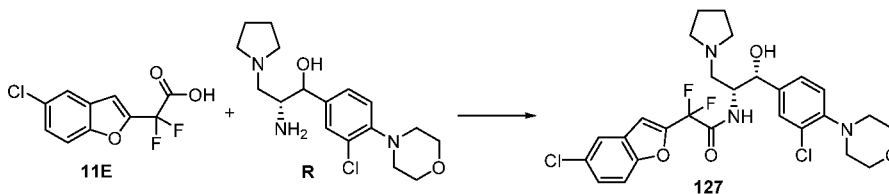
[000684] A mixture of Intermediate **Q** (150 mg, 0.41 mmol), EDCl.HCl (118 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol) and Compound **HE** (101 mg, 0.41 mmol) in DCM (5 mL) was stirred for 18 h at 25 °C. Then the mixture was washed with water (50 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **123**. LC-MS (ESI) m/z : 596 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.06-2.28 (m, 8H), 2.92 (s, 3H), 3.13-3.32 (m, 4H), 3.42-3.76 (m, 6H), 4.60-4.68 (m, 2H), 4.96 (s, 1H), 6.69-6.78 (m, 1H), 6.87-6.95 (m, 1H), 7.27-7.29 (m, 1H), 7.28 (s, 2H), 7.57-7.59 (m, 1H), 7.74 (m, 1H).

Example 124



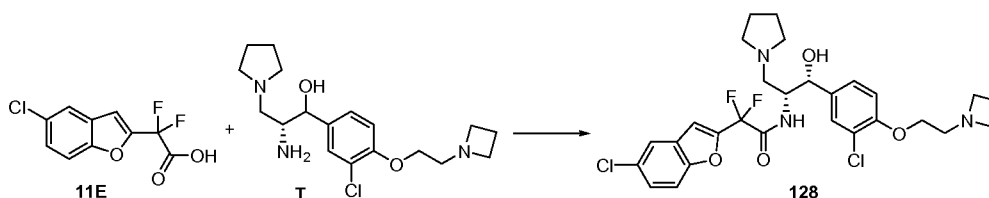
3.65 (m, 5H), 4.47 (s, 1H), 5.10 (s, 1H), 6.74 (s, 1H), 6.68-7.15 (m, 3H), 7.32-7.35 (m, 1H), 7.39-7.41 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 1.6$ Hz, 1H), 7.99 (d, $J = 6.0$ Hz, 1H), 11.45 (s, 1H).

Example 127



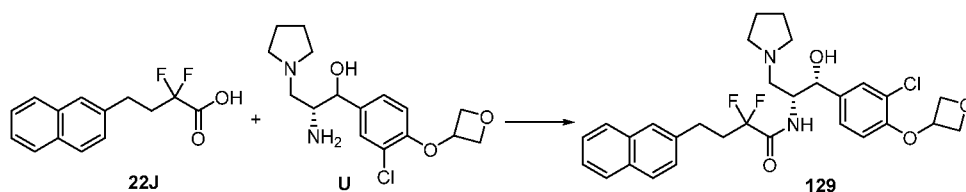
[000688] A mixture of Intermediate **R** (150 mg, 0.442 mmol), Compound **11E** (109 mg, 0.442 mmol), EDCI.HCl (127 mg, 0.663 mmol) and HOBt (90 mg, 0.663 mmol) in DCM/Et₃N (10/0.3 mL) was stirred at 25 °C for 16 h. Then it was diluted with ethyl acetate (100 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **127**. LC-MS (ESI) m/z : 568 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.06 (s, 2H), 2.20 (s, 2H), 2.75-2.88 (m, 4H), 3.17-3.22 (m, 2H), 3.58-3.70 (m, 4H), 3.75-3.83 (m, 4H), 4.65-4.69 (m, 1H), 4.93 (s, 1H), 6.68 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.42-7.48 (m, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.79 (s, 1H).

Example 128



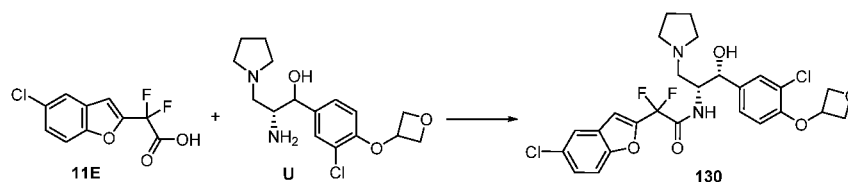
[000689] To a solution of Intermediate **T** (100 mg, 0.28 mmol) and Compound **11E** (69 mg, 0.28 mmol) in DMF (10 mL) was added EDCI.HCl (82 mg, 0.42 mmol) and HOBt (58 mg, 0.42 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. TLC and LC-MS showed the starting material was consumed completely, sat. sodium bicarbonate (3 mL) was added to the mixture and then extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), dried over anhydrous sodium sulfate, and concentrated to offer the crude product. The crude product was purified with prep-HPLC to offer Compound **128**. LC-MS (ESI) m/z : 582 [M+H]⁺. ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 2.16-2.17 (m, 4H), 2.39-2.44 (m, 1H), 2.75-2.83 (m, 1H), 2.92-3.01 (m, 2H), 3.45-3.54 (m, 4H), 3.76 (s, 2H), 4.14-4.16 (m, 4H), 4.44-4.53 (m, 3H), 5.08 (d, $J = 2.8$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 6.81 (s, 1H), 7.12 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.34-7.38 (m, 2H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 2.0, 1H$), 8.08 (d, $J = 8.8$ Hz, 1H), 11.95 (brs, 1H), 13.25 (brs, 1H).

Example 129



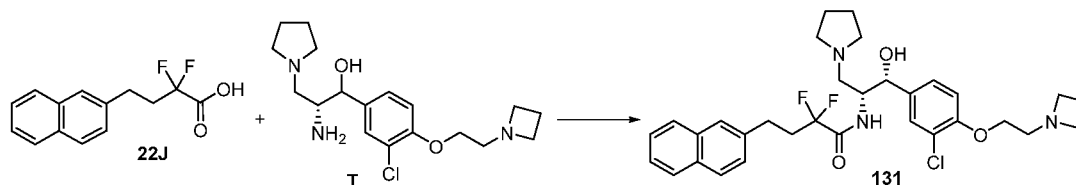
[000690] A mixture of Intermediate U (108 mg, 0.33 mmol), EDCI.HCl (96 mg, 0.50 mmol), HOBt (67 mg, 0.50 mmol) and Compound **22J** (84 mg, 0.33 mmol) in DCM (15 mL) was stirred at room temperature for 4 hours. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **129**. LC-MS (ESI) m/z : 559 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.04-2.40 (m, 7H), 2.52-2.59 (m, 1H), 2.85-2.97 (m, 2H), 3.34-3.77 (m, 4H), 4.46-4.60 (m, 6H), 5.11 (s, 1H), 6.24-6.26 (d, $J = 8.0$ Hz, 1H), 7.14-7.20 (m, 2H), 7.42-7.48 (m, 4H), 7.60-7.63 (m, 1H), 7.75-7.81 (m, 3H).

Example 130



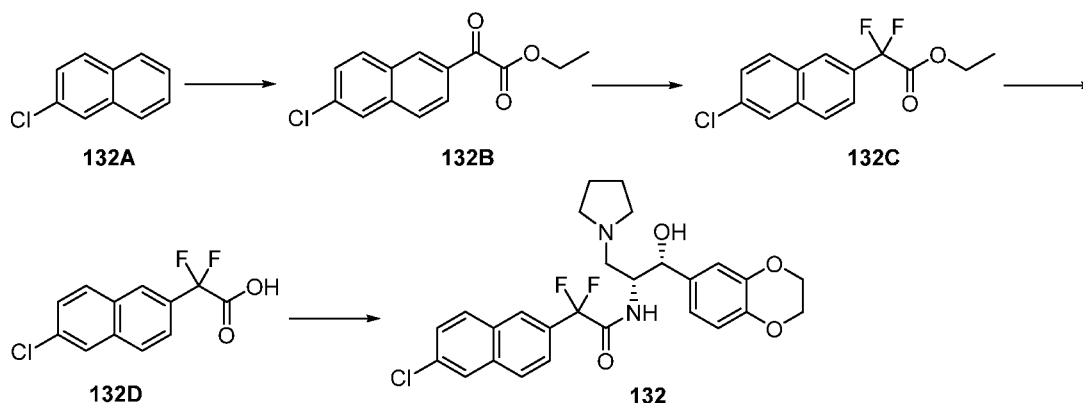
[000691] A mixture of Intermediate U (108 mg, 0.33 mmol), EDCI.HCl (96 mg, 0.50 mmol), HOBt (67 mg, 0.50 mmol) and Compound **11E** (82 mg, 0.33 mmol) in DCM (15 mL) was stirred at room temperature for 4 hours. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **130**. LC-MS (ESI) m/z : 555 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.13 (s, 4H), 2.96-3.09 (m, 2H), 3.22-3.88 (m, 4H), 4.52 (s, 1H), 4.67-4.74 (m, 2H), 4.91-4.96 (m, 3H), 5.12 (s, 1H), 6.18-6.20 (d, $J = 8.4$ Hz, 1H), 6.72 (s, 1H), 7.06-7.08 (m, 1H), 7.33-7.42 (m, 3H), 7.58 (s, 1H), 7.96 (m, 1H), 11.65 (s, 1H).

Example 131



[000692] To a solution of Intermediate **T** (100 mg, 0.28 mmol) and Compound **22J** (71 mg, 0.28 mmol) in DCM (10 mL) was added EDCI.HCl (81 mg, 0.42 mmol) and HOBT (57 mg, 0.42 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. TLC and LC-MS showed the starting material was consumed completely, then sat. sodium bicarbonate (5 mL) was added to the mixture and then extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, and concentrated to offer the crude product. The crude product was purified with prep-HPLC to offer Compound **131**. LC-MS (ESI) m/z : 586 $[M+H]^+$. 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.03-2.22 (m, 8H), 2.34-2.42 (m, 1H), 2.51-2.59 (m, 1H), 2.90-3.01 (m, 2H), 3.15-3.17 (m, 1H), 3.23-3.24 (m, 1H), 3.54-3.58 (m, 1H), 3.63-3.68 (m, 3H), 3.74-3.78 (m, 2H), 3.82-3.93 (m, 2H), 4.01-4.04 (m, 2H), 4.64 (d, $J = 10.4$ Hz, 1H), 4.96 (d, $J = 2.4$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 7.24 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.34 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.46-7.52 (m, 3H), 7.57 (s, 1H), 7.81-7.88 (m, 3H).

Example 132



[000693] To a suspension of aluminum trichloride (1.61 g, 12 mmol) and ethyl chloroacetate (1.63 g, 12 mmol) in dichloromethane (60 mL) was added Compound **132A** (1.62 g, 10 mmol) in dichloromethane (15 mL) dropwise at room temperature overnight. After 24 h a solution of ice water (100 mL) and saturated sodium bicarbonate solution (100 mL) was added dropwise. The aqueous layer was extracted with dichloromethane (50 mL x 3). The combined organics were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 2% v/v) to give the Compound **132B**.

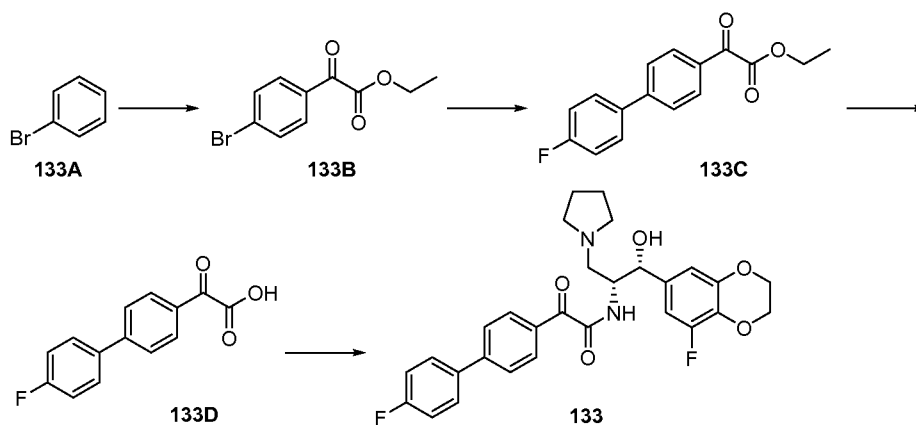
[000694] To a solution of Compound **132B** (2.62 g, 10 mmol) in dichloromethane (350 mL) was added DAST (4 mL) at room temperature. The reaction mixture was stirred at room temperature. After 14 h, the mixture was poured into ice water (50 mL) and extracted with

dichloromethane (50 mL x 2). The combined organics were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (ethyl acetate in petroleum ether, 2% v/v) gave the Compound **132C**.

[000695] To a solution of Compound **132C** (284 mg, 1 mmol) in ethanol/water (16 mL) was added LiOH·H₂O (84 mg, 2 mmol). The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was adjusted to pH 2 with aqueous HCl solution (3 N, 40 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **132D**.

[000696] To a solution of **132D** (256 mg, 1 mmol) in DCM (30 mL) was added Intermediate A (278 mg, 1 mmol), EDCI.HCl (286 mg, 1.5 mmol), HOBT (202 mg, 1.5 mmol), and DIPEA (1 mL). The mixture was stirred at room temperature overnight. The reaction mixture was diluted by DCM (30 mL), washed with brine (50 mL), dried over sodium sulfate, and concentrated to furnish the crude product, which was purified with prep-HPLC to furnish Compound **132**. LC-MS (ESI) m/z: 517 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.65-1.68 (m, 4H), 2.53-2.63 (m, 4H), 2.86-2.88 (m, 2H), 4.02-4.15 (m, 5H), 4.94-4.95 (m, 1H), 6.66-6.69 (m, 3H), 6.89-6.70 (m, 1H), 7.33-7.40 (m, 2H), 7.64-7.79 (m, 4H).

Example 133



[000697] To a stirred suspension of AlCl₃ (8.5 g, 64 mmol) in dichloromethane (40 mL) was added dropwise ethyl 2-chloro-2-oxoacetate (8.7 g, 64 mmol) at -10 °C. The mixture was stirred at -10 °C for 15 minutes. Compound **133A** (5 g, 32 mmol) was added dropwise at -10 °C. The resulting mixture was stirred at 20 °C for 15 hours. The mixture was poured into ice water (100 mL) to quench the reaction and extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with saturated sodium bicarbonate solution (200 mL)

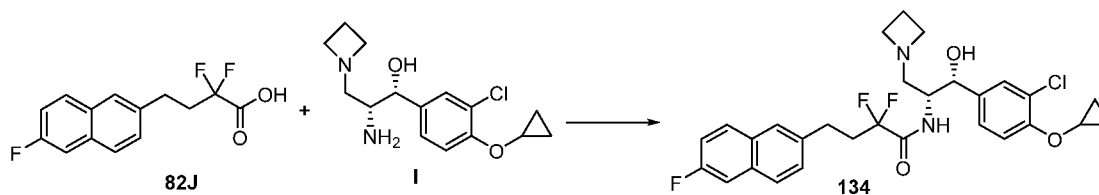
and brine (200 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **133B**.

[000698] A mixture of Compound **133B** (3.7 g, 14.4 mmol), 4-fluorophenylboronic acid (2.4 g, 17.3 mmol), Pd(PPh₃)₄ (497 mg, 0.4 mmol) and K₃P0₄ in toluene (40 mL) was heated to reflux, stirred for 3 h, and filtered. The filtrate was concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **133C**.

[000699] To a solution of Compound **133C** (1.1 g, 4 mmol) in THF/water (30 mL, 15:1, v/v) was added LiOH·H₂O (250 mg, 6 mmol). The mixture was stirred at -10 °C for 3 h. After the reaction was completed, it was adjusted to pH 6 with 3 N HCl and extracted with ethyl acetate (20 mL x 3). The combined organic layers were concentrated in *vacuo* to give Compound **133D**.

[000700] A mixture of Compound **133D** (195 mg, 0.8 mmol), Intermediate **C** (237 mg, 0.8 mmol), HATU (456 mg, 1.2 mmol) and in dichloromethane (20 mL) was stirred at 30 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to furnish Compound **133**. LC-MS (ESI) m/z: 524 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 2.14 (s, 5H), 3.11 (s, 2H), 3.51 (s, 1H), 3.79 (s, 1H), 3.93 (s, 2H), 4.16-4.21 (m, 4H), 4.52 (s, 1H), 5.04 (s, 1H), 6.72 (t, *J* = 8 Hz, 2H), 7.14 (t, *J* = 8 Hz, 2H), 7.54-7.57 (m, 4H), 7.82 (d, *J* = 8 Hz, 1H), 8.08 (d, *J* = 8 Hz, 2H), 9.21 (s, 1H).

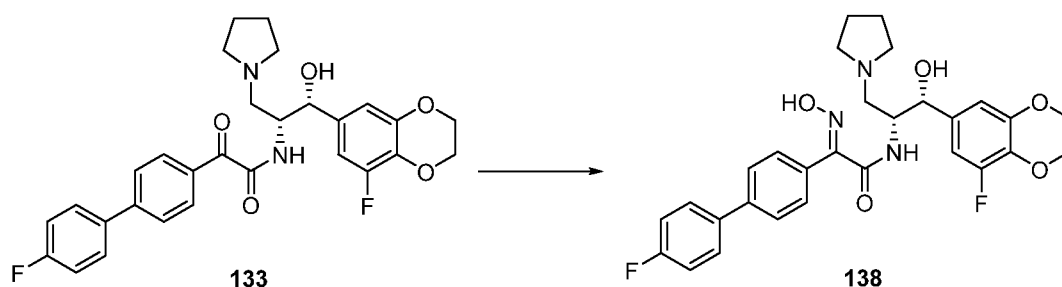
Example 134



[000701] A mixture of Intermediate **I** (100 mg, 0.33 mmol), EDCl·HCl (97 mg, 0.51 mmol), HOBT (69 mg, 0.51 mmol) and Compound **82J** (91 mg, 0.33 mmol) in DMF (5 mL) was stirred at room temperature overnight. Then the reaction mixture was purified with prep-HPLC to offer Compound **134**. LC-MS (ESI) m/z: 547 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.47-0.55 (m, 4H), 2.22 (s, 2H), 2.40 (s, 2H), 2.56 (s, 2H), 3.40-3.50 (m, 3H), 3.96 (s, 2H), 4.34 (s, 3H), 5.05 (s, 1H), 7.15-7.22 (m, 4H), 7.37-7.42 (m, 2H), 7.48 (s, 1H), 7.61 (s, 1H), 7.68-7.71 (m, 1H), 7.75-7.79 (s, 1H), 12.13 (s, 1H).

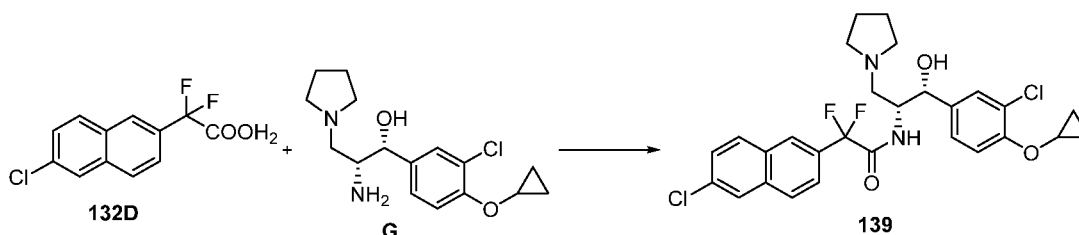
[000704] A mixture of Intermediate **I** (100 mg, 0.33 mmol), EDCL.HCl (97 mg, 0.51 mmol), HOBT (69 mg, 0.51 mmol) and Compound **106B** (88 mg, 0.33 mmol) in DMF (5 mL) was stirred at room temperature overnight. Then the reaction mixture was purified with prep-HPLC to offer Compound **137**. LC-MS (ESI) m/z: 540 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.71-0.72 (m, 4H), 1.26 (s, 1H), 2.11 (s, 1H), 2.46 (s, 1H), 2.78-2.82 (m, 4H), 3.22 (s, 1H), 3.65 (s, 3H), 4.10-4.18 (m, 2H), 4.33 (s, 1H), 4.83 (s, 1H), 7.10-7.22 (m, 3H), 7.32-7.38 (m, 3H), 7.58 (s, 1H), 7.62-7.65 (m, 1H), 7.71-7.75 (m, 1H), 11.02 (s, 1H).

Example 138



[000705] A mixture of Compound **133** (41 mg, 0.078 mmol) and hydroxylamine hydrochloride (109 mg, 1.56 mmol) in MeOH (10 mL) was stirred at room temperature for 4 h. Then it was purified with prep-HPLC directly to offer Compound **138**. LC-MS (ESI) m/z: 538 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.02 (s, 2H), 2.20 (s, 2H), 3.12-3.28 (m, 2H), 3.45-3.87 (m, 4H), 4.26-4.60 (m, 5H), 4.78-4.82 (m, 1H), 6.82 (t, *J* = 12 Hz, 2H), 7.17-7.42 (m, 4H), 7.53-7.68 (m, 4H).

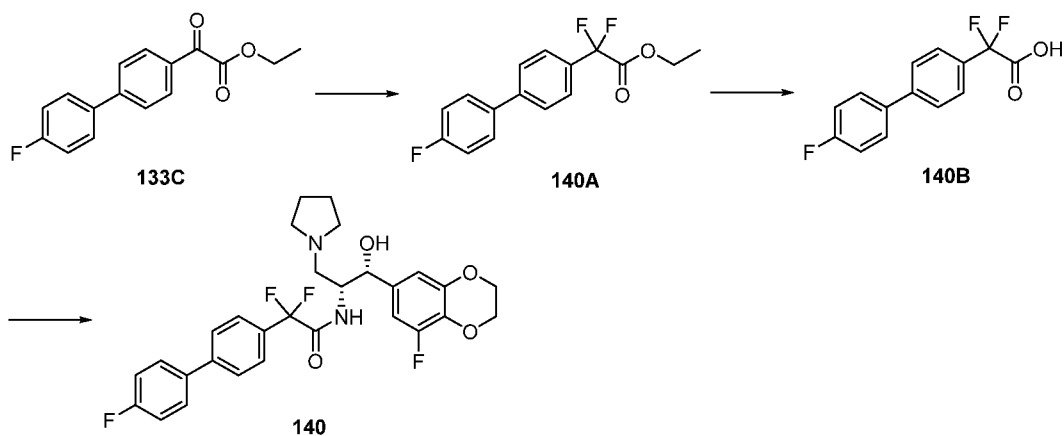
Example 139



[000706] A mixture of Compound **132D** (256 mg, 1 mmol), Intermediate **G** (296 mg, 1 mmol), EDCL.HCl (286 mg, 1.5 mmol) and HOBT (202 mg, 1.5 mmol) in DCM (30 mL) was stirred at 25 °C for 16 h. Then it was diluted with DCM (70 mL), washed with water (50 mL x 3) and brine (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **139**. LC-MS (ESI) m/z: 549 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.69-0.71 (m, 4H), 1.65-1.68 (m, 4H), 2.34-2.37 (m, 4H), 2.64-2.68 (m, 2H), 3.51-3.52 (m, 1H), 4.15 (s, 1H), 5.09 (s, 1H), 6.91-6.92 (m, 1H), 7.12-7.13 (m,

2H), 7.35 (s, 1H), 6.94 (m, 1H), 7.50-7.52 (t, $J = 4.8$ Hz, 2H), 7.78-7.86 (m, 3H), 7.96 (s, 1H).

Example 140

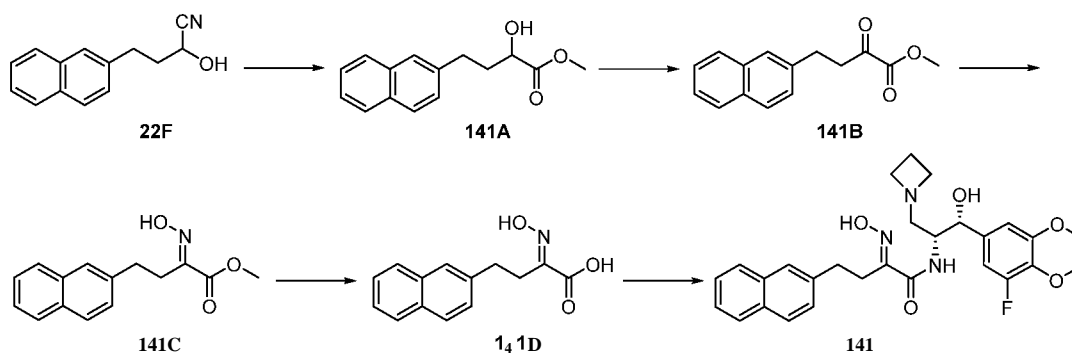


[000707] To a solution of Compound **133C** (1.78 g, 6.54 mmol) in dry dichloromethane (40 mL) was added DAST (2.2 mL, 16.36 mmol). Then the mixture was stirred at 25 °C for 14 h. After the reaction was completed, dichloromethane (25 mL) was added. The organic layer was washed with water (50 mL), followed by aq. sodium bicarbonate (30 mL) and brine (50 mL), dried over sodium sulfate and concentrated to provide the crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20 % v/v) to provide Compound **140A**.

[000708] To a solution of Compound **140A** (2.3 g, 7.8 mmol) in THF/water/MeOH (30 mL, 1:1: 1, v/v) was added LiOH.H₂O (493 mg, 11.7 mmol). The mixture was stirred at 28 °C for 1 h. After the reaction was completed, it was adjusted to pH to 6 with 2 N HCl and extracted with ethyl acetate (60 mL x 3). The combined organic layers were concentrated in vacuum to provide the crude product Compound **140B**.

[000709] To a solution of Compound **140B** (133 mg, 0.5 mmol), Intermediate **C** (156 mg, 0.53 mmol), and EDCI.HCl (144 mg, 0.75 mmol) in dichloromethane (20 mL) was added HOBt (102 mg, 0.75 mmol) at 19 °C, then the reaction was stirred at 19 °C for 4 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to furnish Compound **140**. LC-MS (ESI) m/z : 545 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.12 (m, 4H), 2.90-3.10 (m, 2H), 3.45-3.48 (m, 2H), 3.75-3.85 (m, 2H), 4.11-4.12 (m, 4H), 4.15-4.22 (m, 1H), 4.90-4.91 (d, $J = 2.8$ Hz, 1H), 6.57-6.67 (m, 2H), 7.14-7.19 (m, 2H), 7.43-7.46 (m, 2H), 7.55-7.61 (m, 4H).

Example 141



[000710] A solution of Compound **22F** (6.6 g, 31.27 mmol) in methanol (150 mL) was stirred under HCl gas at room temperature for 6 h. It was quenched with water (30 mL) and stirred at room temperature for 1 h. After removal of solvent, the residue was dissolved in ethyl acetate (200 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **141A**.

[000711] A solution of Compound **141A** (6.7 g, 27.46 mmol) and Dess-Martin periodinane (14 g, 33 mmol) in DCM (50 mL) was stirred at room temperature for 2 h. After removal of solvent, the residue was dissolved in ethyl acetate (200 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 20% to 30% v/v) to afford Compound **141B**.

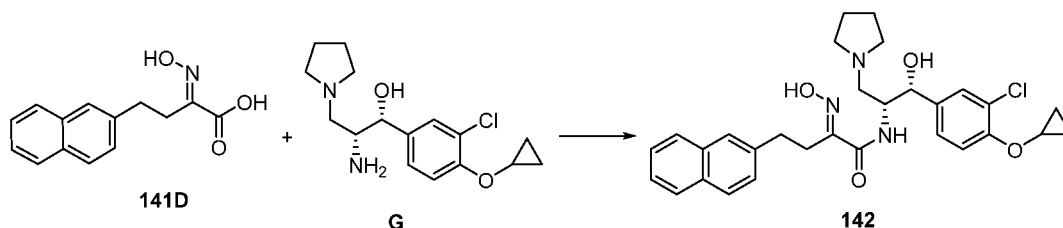
[000712] A solution of Compound **141B** (2.0 g, 8.26 mmol) in EtOH (20 mL) was added potassium carbonate (1.48 g, 10.7 mmol) and hydroxylamine hydrochloride (0.74 g, 10.7 mmol) at room temperature, then stirred at room temperature overnight. Then it was filtered and concentrated to obtain Compound **141C**.

[000713] A mixture of Compound **141C** (2.0 g, 7.78 mmol) and LiOH.H₂O (1.0 g, 23.3 mmol) in THF/MeOH/H₂O (10/10/4 mL) was stirred at room temperature for 3 h. The solution was concentrated to remove organic solvent, then it was adjusted to PH 6 with 3 M HCl (5 mL), filtered and washed with PE (100 mL), dried to obtain Compound **141D**.

[000714] To a solution of Compound **141D** (72 mg, 0.3 mmol) and Intermediate **H** (90 mg, 0.3 mmol) in DMF was added EDCl.HCl (86 mg, 0.45 mmol), followed by HOBt (62 mg, 0.45 mmol). Then the reaction was stirred at room temperature for 15 hours. Then the reaction mixture was treated with water (40 mL), extracted with DCM (100 mL x 2), washed with brine (50 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **141**. LC-MS (ESI) m/z: 508 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.15-2.20 (m, 1H), 2.41-2.55 (m, 1H), 3.15-3.27 (m, 2H),

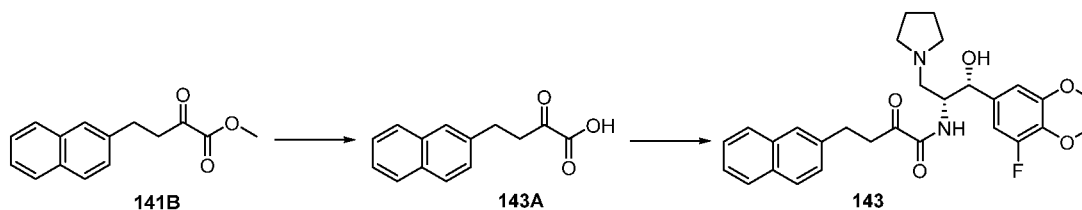
3.65-3.90 (m, 2H), 4.12-4.15 (m, 3H), 4.24 (s, 4H), 4.75-4.76 (d, $J = 2.8$ Hz, 1H), 6.65-6.71 (m, 2H), 7.36-7.46 (m, 3H), 7.64 (s, 1H), 7.75-7.82 (m, 3H).

Example 142



[000715] A mixture of Compound **141D** (150 mg, 0.62 mmol), EDCI.HCl (178 mg, 0.93 mmol), HOBT (126 mg, 0.92 mmol) and Intermediate **G** (230 mg, 0.7 mmol) in DMF (8 mL) was stirred at room temperature overnight. Then the reaction mixture was purified with prep-HPLC to provide Compound **142**. LC-MS (ESI) m/z : 536.2 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.63-0.73 (m, 4H), 1.95-2.09 (m, 4H), 2.65-3.14 (m, 7H), 3.43-3.47 (m, 1H), 3.55-3.58 (m, 2H), 3.70-3.77 (m, 2H), 4.47-4.50 (m, 1H), 4.84-4.85 (d, $J = 2.4$ Hz, 1H), 7.25-7.32 (m, 3H), 7.40-7.45 (m, 3H), 7.74 (s, 1H), 7.76-7.80 (m, 3H).

Example 143

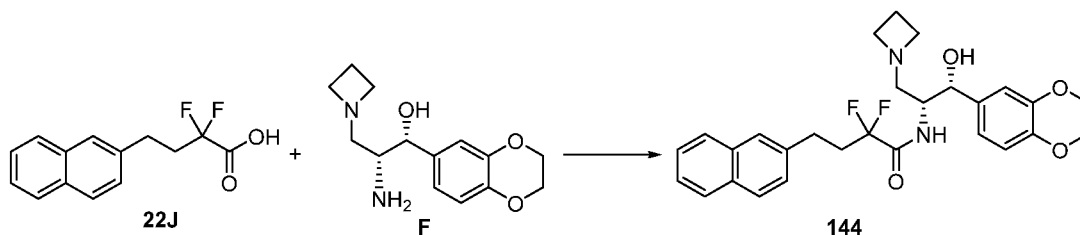


[000716] A mixture of Compound **141B** (2.0 g, 8.26 mmol) and LiOH·H₂O (1.0 g, 24.8 mmol) in THF/MeOH/H₂O (10/10/4 mL) was stirred at room temperature for 5 h. The mixture was adjusted to pH 6 with aqueous HCl solution (6 N, 1.0 mL). After removal of solvent the residue was dissolved in ethyl acetate (100 mL), washed with water (50 mL x 2) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 30% v/v) to afford Compound **143A**.

[000717] A mixture of Compound **143A** (90 mg, 0.4 mmol), Intermediate **C** (118 mg, 0.4 mmol), and HATU (228 mg, 0.6 mmol) in dichloromethane (10 mL) was stirred at 30 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to furnish Compound **143**. LC-MS (ESI) m/z : 506 $[M+H]^+$; 1H -NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 1.77 (s, 2H), 1.93 (s, 2H), 2.87-2.96 (m, 2H), 3.00-3.10 (m, 4H), 3.21-3.27 (m, 4H), 4.18-4.30 (m, 5H), 4.61 (s, 1H), 5.95 (s, 1H), 6.67 (t, $J = 12$ Hz, 2H), 7.36 (d, $J = 8$ Hz,

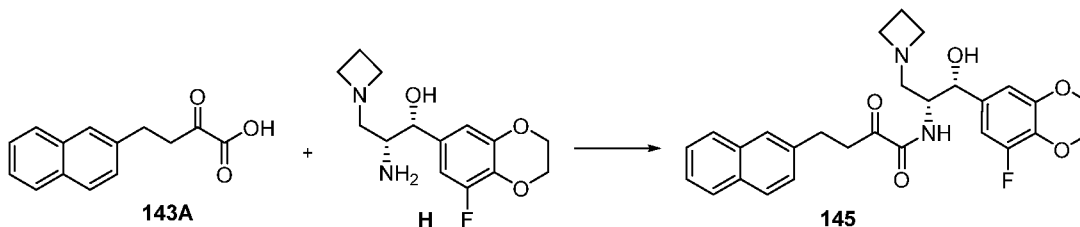
1H), 7.40-7.47 (m, 2H), 7.67 (s, 1H), 7.78-7.84 (m, 3H), 8.14 (d, $J = 12$ Hz, 1H), 9.03 (s, 1H).

Example 144



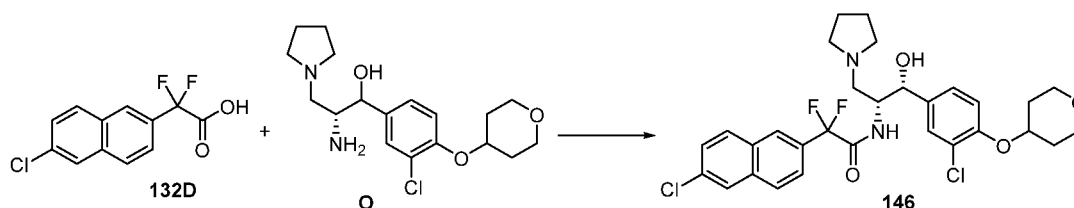
[000718] A mixture of Compound **22J** (0.1 g, 0.4 mmol), Intermediate **F** (0.11 g, 0.4 mmol), DIPEA (0.10 g, 0.8 mmol), EDCI.HCl (0.11 g, 0.6 mmol) and HOBT (0.08 g, 0.6 mmol) in DCM (2 mL) was stirred at 25 °C for 16 h. Then the mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **144**. LC-MS (ESI) m/z : 497 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.15-2.22 (m, 2H), 2.41-2.71 (m, 4H), 3.54-3.63 (m, 3H), 3.77-3.89 (m, 3H), 4.20-4.23 (m, 4H), 4.39-4.42 (m, 1H), 4.85 (d, $J = 3.2$ Hz, 1H), 6.77-6.79 (m, 1H), 6.84-6.90 (m, 2H), 7.26-7.29 (m, 1H), 7.44-7.48 (m, 2H), 7.59 (s, 1H), 7.80-7.83 (m, 3H).

Example 145



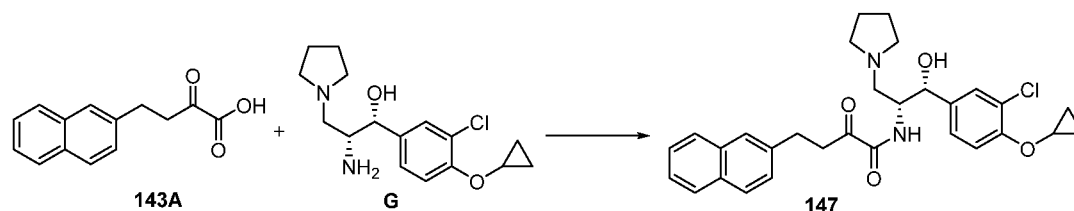
[000719] To a solution of Compound **143A** (90 mg, 0.4 mmol) in dry dichloromethane (8 mL) and DMF (2 mL) was added HATU (228 mg, 0.6 mmol), followed by Intermediate **H** (90 mg, 0.3 mmol) in DMF. Then EDCI.HCl (86 mg, 0.45 mmol) and HOBT (62 mg, 0.45 mmol) was added. The reaction was stirred at room temperature for 15 hours, filtered, and evaporated to furnish the crude product in DMF (3 mL). It was purified with prep-HPLC to furnish Compound **145**. LC-MS (ESI) m/z : 493 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 2.20-2.35 (m, 2H), 2.90-3.00 (m, 2H), 3.12-3.35 (m, 4H), 3.80-4.20 (m, 5H), 4.25 (s, 4H), 4.62 (s, 1H), 5.96 (s, 1H), 6.65-6.74 (m, 2H), 7.38-7.51 (m, 3H), 7.71 (s, 1H), 7.82-7.88 (m, 3H), 8.09-8.12 (d, $J = 9.6$ Hz, 1H), 9.35 (br, 1H).

Example 146



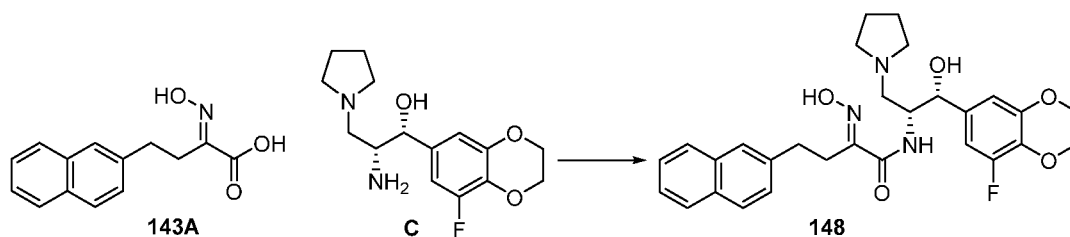
[000720] A mixture of Intermediate **O** (120 mg, 0.34 mmol), EDCl.HCl (98 mg, 0.51 mmol), HOBT (69 mg, 0.51 mmol) and Compound **132D** (120 mg, 0.34 mmol) in DCM (10 mL) was stirred h at 25 °C for 12. Then the mixture was washed with saturated sodium bicarbonate (15 mL) and brine (15 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **146**. LC-MS (ESI) m/z : 593 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.63-1.70 (m, 2H), 1.78-1.84 (m, 2H), 2.03 (m, 4H), 2.83 (m, 1H), 2.93 (m, 1H), 3.71-3.92 (m, 8H), 4.17-4.22 (m, 1H), 4.37 (m, 1H), 5.00 (s, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.25 (s, 1H), 7.31 (d, $J = 9.2$ Hz, 1H), 7.41 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.65 (d, $J = 8.8$ Hz, 1H), 7.72 (d, $J = 8.8$ Hz, 1H), 7.76 (m, 1H), 7.82-7.86 (m, 2H), 11.44 (s, 1H).

Example 147



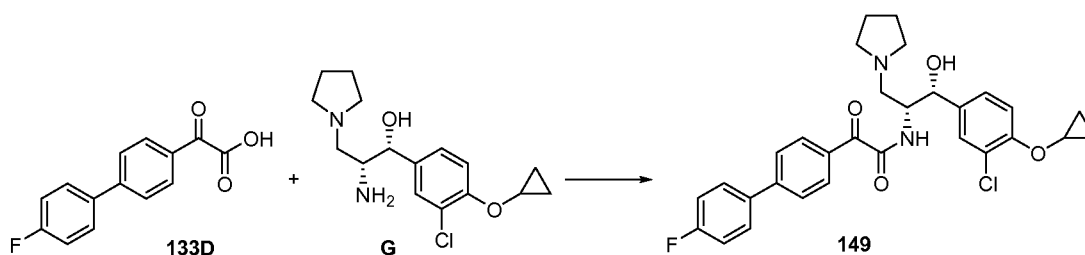
[000721] A mixture of Compound **143A** (152 mg, 0.67 mmol), HATU (456 mg, 1.2 mmol), DCM (16 mL) and Intermediate **G** (248 mg, 0.8 mmol) in DMF (6 mL) was stirred at room temperature overnight. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to provide Compound **147**. LC-MS (ESI) m/z : 521.3 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 0.63-0.78 (m, 4H), 1.82-1.98 (m, 4H), 2.94-3.12 (m, 5H), 3.21-3.24 (m, 1H), 3.46-3.49 (m, 3H), 3.83-3.86 (m, 2H), 4.31-4.36 (m, 1H), 4.74 (d, $J = 2.8$ Hz, 1H), 6.01 (s, 1H), 7.21-7.24 (m, 1H), 7.30-7.40 (m, 3H), 7.45-7.50 (m, 2H), 7.70 (s, 1H), 7.82-7.88 (m, 3H), 8.20 (d, $J = 9.6$ Hz, 1H), 9.38 (s, 1H).

Example 148



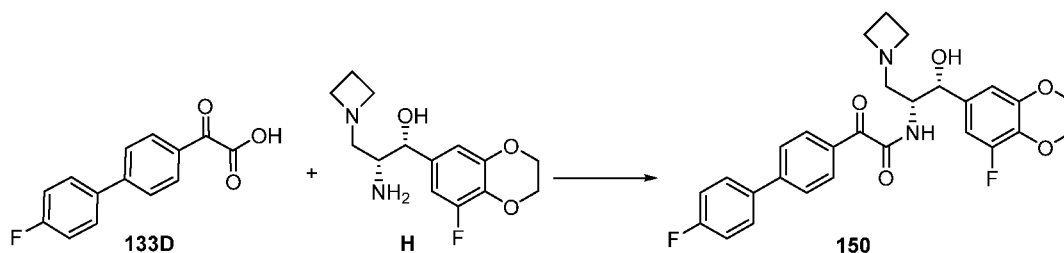
[000722] A mixture of Compound **143A** (97 mg, 0.4 mmol), Intermediate **C** (118 mg, 0.4 mmol), HOBt (81 mg, 0.6 mmol), and EDCI.HCl (115 mg, 0.6 mmol) in DMF (10 mL) was stirred at 30 °C for 8 h. The mixture was purified with prep-HPLC directly to furnish Compound **148**. LC-MS (ESI) m/z : 522 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 1.93 (s, 2H), 2.09 (s, 2H), 2.68-2.95 (m, 4H), 3.04-3.17 (m, 2H), 3.40-3.44 (m, 1H), 3.54 (t, $J = 12$ Hz, 2H), 3.69 (s, 1H), 4.14-4.21 (m, 4H), 4.44-4.49 (m, 1H), 4.75 (s, 1H), 6.74 (d, $J = 12$ Hz, 2H), 7.33 (d, $J = 8$ Hz, 1H), 7.38-7.45 (m, 2H), 7.62 (s, 1H), 7.70 (d, $J = 8$ Hz, 0.5H), 7.70-7.85 (m, 3H).

Example 149



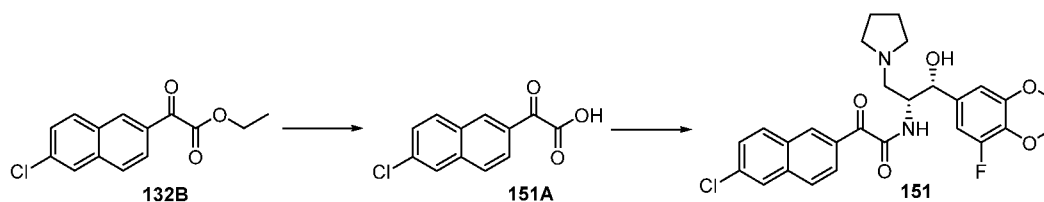
[000723] A mixture of Compound **133D** (230 mg, 0.94 mmol), HATU (515 mg, 1.36 mmol), and Intermediate **G** (324 mg, 1.05 mmol) in DCM (25 mL) was stirred at room temperature overnight. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to provide Compound **149**. LC-MS (ESI) m/z : 537.2 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.69-0.83 (m, 4H), 1.82-1.98 (m, 4H), 2.94-3.12 (m, 5H), 3.21-3.24 (m, 1H), 3.46-3.49 (m, 3H), 2.04-2.08 (m, 3H), 2.19-2.22 (m, 2H), 3.23-3.33 (m, 1H), 3.58-3.75 (m, 4H), 3.82-3.86 (m, 2H), 4.70-4.73 (m, 2H), 5.01 (s, 1H), 7.23-7.27 (m, 2H), 7.39 (d, $J = 0.8$ Hz, 1H), 7.64-7.70 (m, 4H), 7.73-7.76 (m, 2H).

Example 150



[000724] A mixture of Compound **133D** (195 mg, 0.8 mmol), Intermediate **H** (225 mg, 0.8 mmol), and HATU (456 mg, 1.2 mmol) in dichloromethane (20 mL) was stirred at 30 °C for 8 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to furnish Compound **150**. LC-MS (ESI) *m/z*: 509 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 2.47 (s, 2H), 3.46-3.65 (m, 2H), 4.12-4.34 (m, 9H), 4.89 (s, 1H), 6.69 (d, *J* = 12 Hz, 2H), 7.12 (t, *J* = 8 Hz, 2H), 7.55 (t, *J* = 8 Hz, 4H), 7.90 (d, *J* = 8 Hz, 2H).

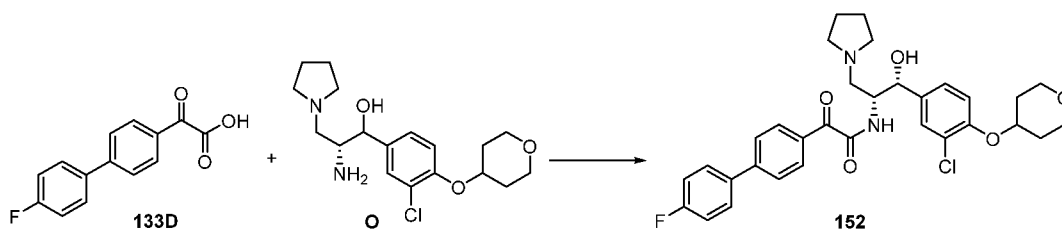
Example 151



[000725] To a solution of Compound **132B** (262 mg, 1 mmol) in ethanol/water (16 mL, 15/1 v/v) was added LiOH·H₂O (84 mg, 2 mmol). The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was adjusted to pH 2 with aqueous HCl solution (3 N, 40 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated to yield the Compound **151A**.

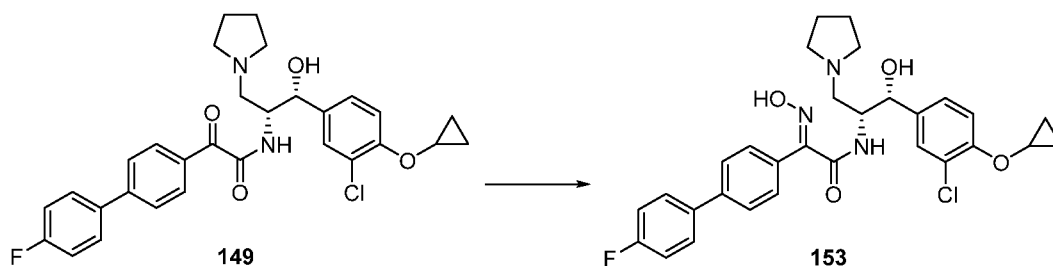
[000726] To a solution of Compound **151A** (170 mg, 0.73 mmol) and Intermediate **C** (216 mg, 0.73 mmol) in dichloromethane (6 mL) was added HATU (414 mg, 1.09 mmol) at 25 °C. Then the reaction was stirred at 25 °C for 15 hours. Then the reaction mixture was treated with water (40 mL), extracted with DCM (10 mL x 2), washed with brine (10 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **151**. LC-MS (ESI) *m/z*: 513 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 2.05-2.07 (m, 2H), 2.22-2.25 (m, 1H), 3.20-3.22 (m, 2H), 3.58-3.95 (m, 4H), 4.05-4.24 (m, 4H), 4.56-4.59 (d, *J* = 10.4 Hz, 1H), 4.95-4.96 (d, *J* = 2.4 Hz, 1H), 6.75-6.81 (m, 2H), 7.52-7.55 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1H), 7.79-7.97 (m, 4H), 8.49 (s, 1H).

Example 152



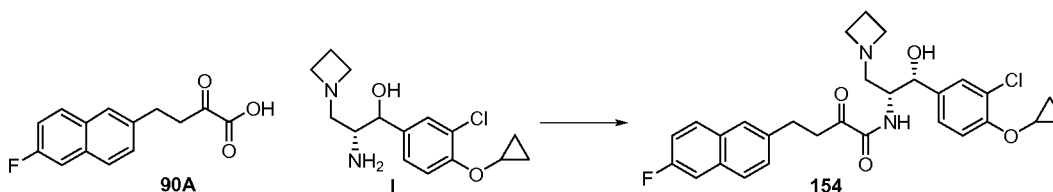
[000727] A mixture of Compound **133D** (82.5 mg, 0.34 mmol), HATU (193.8 mg, 0.51 mmol) and Intermediate **O** (120 mg, 0.34 mmol) in DCM (10 mL) was stirred for 12 h at 25 °C. Then the mixture was washed with water (15 mL) and brine (15 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **152**. LC-MS (ESI) m/z : 581 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.68-1.75 (s, 2H), 1.88-1.90 (s, 2H), 2.08-2.15 (m, 4H), 3.14-3.26 (m, 4H), 3.47-3.52 (m, 2H), 3.87-3.91 (m, 4H), 4.41-4.45 (m, 1H), 4.55-4.57 (m, 1H), 5.08 (s, 1H), 6.85 (d, $J = 17.2$ Hz, 1H), 7.10-7.14 (m, 2H), 7.20-7.22 (m, 1H), 7.40 (s, 1H), 7.50-7.54 (m, 4H), 7.90-7.94 (m, 3H), 9.01 (s, 1H).

Example 153



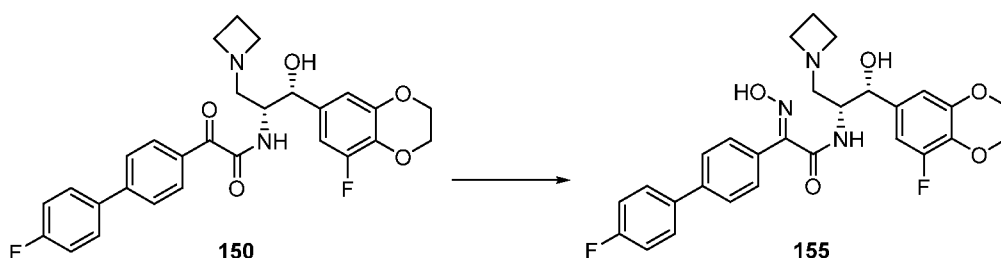
[000728] A mixture of **149** (36 mg, 0.07 mmol) and hydroxylamine hydrochloride (69 mg, 1.0 mmol) in methanol (6 mL) was stirred at 50 °C for 16 hours. Then the reaction mixture was purified with prep-HPLC to provide Compound **153**. LC-MS (ESI) m/z : 552.1 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.72-0.83 (m, 4H), 1.82-1.98 (m, 4H), 2.94-3.12 (m, 5H), 3.21-3.24 (m, 1H), 3.46-3.49 (m, 3H), 2.04-2.08 (m, 3H), 2.04-2.21 (m, 4H), 3.20-3.33 (m, 2H), 3.59-3.89 (m, 5H), 4.83-4.87 (m, 1H), 5.03 (d, $J = 2.4$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 2H), 7.38-7.42 (m, 2H), 7.48-7.52 (m, 3H), 7.66-7.69 (m, 2H).

Example 154



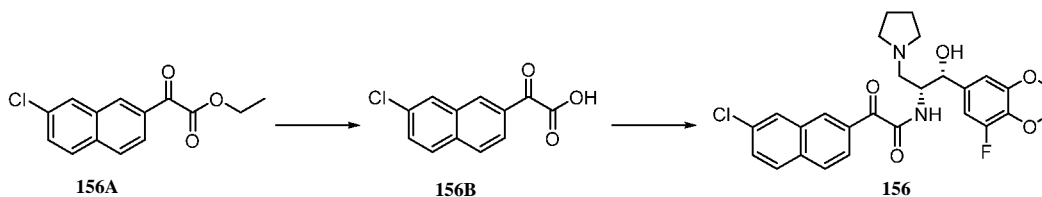
[000729] A mixture of Intermediate **I** (145 mg, 0.49 mmol), HATU (278 mg, 0.73 mmol), and Compound **90A** (100 mg, 0.406 mmol) in DMF (3 mL) and DCM (6 mL) was stirred at 25 °C overnight. Then the reaction mixture was concentrated to remove DCM. The residue was purified with prep-HPLC to provide Compound **154**. LC-MS (ESI) *m/z*: 525 [M+H]⁺; 1H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 0.61-0.65 (m, 2H), 0.76-0.81 (m, 2H), 2.16-2.25 (m, 1H), 2.31-2.39 (m, 1H), 2.93-2.98 (m, 2H), 3.05-3.14 (m, 1H), 3.20-3.42 (m, 3H), 3.84-3.88 (m, 1H), 3.92-3.99 (m, 2H), 4.05-4.18 (m, 3H), 4.69 (s, 1H), 5.97 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.31-7.33 (m, 2H), 7.39-7.45 (m, 2H), 7.66 (d, *J* = 12.8 Hz, 1H), 7.75 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.91-7.94 (m, 1H), 8.13 (d, *J* = 9.6 Hz, 1H), 9.34 (s, 1H).

Example 155



[000730] A mixture of **150** (90 mg, 0.18 mmol) and hydroxylamine hydrochloride (248 mg, 3.54 mmol) in MeOH (10 mL) was stirred at room temperature for 4 h. Then it was purified with prep-HPLC directly to provide Compound **155**. LC-MS (ESI) *m/z*: 523 [M+H]⁺; 1H-NMR (MeOD, 400 MHz) δ (ppm) 2.44 (s, 1H), 2.56-2.66 (m, 1H), 3.53-3.67 (m, 2H), 4.18-4.45 (m, 9H), 4.45 (s, 0.5H), 4.81 (s, 0.5H), 6.77-6.83 (m, 2H), 7.17-7.23 (m, 3H), 7.40-7.69 (m, 5H).

Example 156

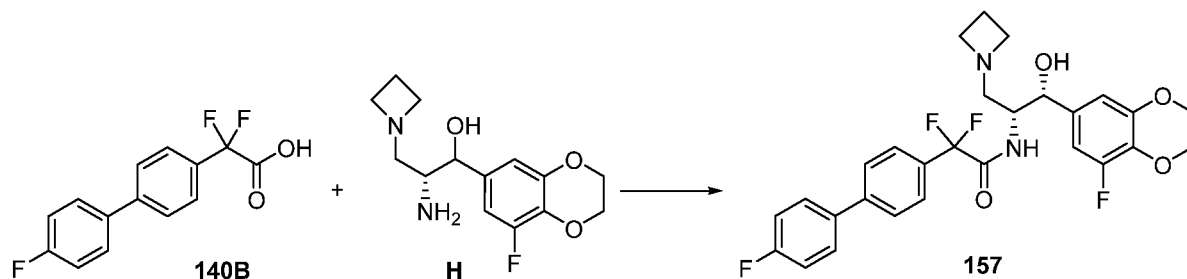


[000731] To a solution of Compound **156A** (100 mg, 0.38 mmol) in THF/water (8 mL, 15:1, v/v) was added LiOH.H₂O (25 mg, 0.58 mmol). The mixture was stirred at -10 °C for 1 h. After the reaction was completed, it was adjusted to pH to 6 with 3 N HCl and extracted with ethyl acetate (15 mL x 3). The combined organic layers were concentrated in vacuum without dryness to provide the desired product Compound **156B**.

[000732] To a solution of Compound **156B** (85 mg, 0.36 mmol) and Intermediate **C** (108 mg, 0.36 mmol) in dichloromethane (3 mL) was added HATU (207 mg, 0.54 mmol) at 25 °C. Then the reaction was stirred at 25 °C for 15 hours. Then the reaction mixture was

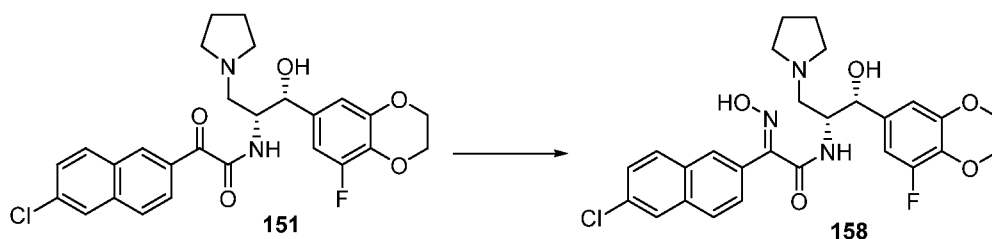
treated with water (20 mL), extracted with DCM (10 mL x 2), washed with brine (10 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **156**. LC-MS (ESI) m/z : 513 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.05-2.17 (m, 4H), 3.11-4.12 (m, 6H), 4.17-4.31 (m, 4H), 4.55-4.57 (m, 1H), 4.95 (d, $J = 2.0$ Hz, 1H), 6.75-6.83 (m, 2H), 7.48-7.56 (m, 2H), 7.75-7.98 (m, 4H), 8.55 (d, $J = 9.2$ Hz, 1H).

Example 157



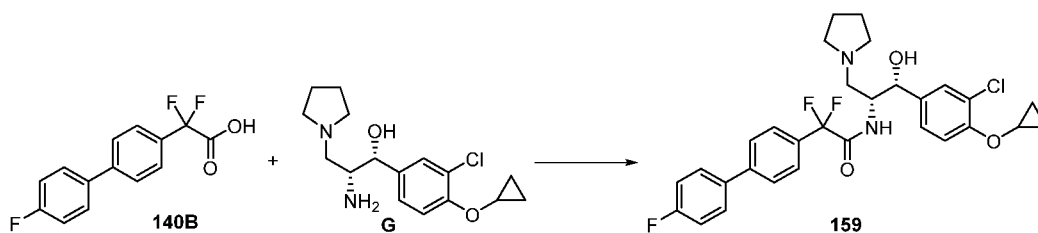
[000733] To a solution of Compound **140B** (67 mg, 0.25 mmol), Intermediate **H** (78 mg, 0.26 mmol), and EDCl.HCl (72 mg, 0.375 mmol) in dichloromethane (10 mL) was added HOBT (51 mg, 0.375 mmol) at 19 °C, then the reaction was stirred at 19 °C for 4 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to furnish Compound **157**. LC-MS (ESI) m/z : 531 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.29-2.38 (m, 2H), 2.72 (br, 1H), 4.08-4.37 (m, 10H), 4.91 (s, 1H), 6.54-6.66 (m, 2H), 7.12-7.17 (m, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.53-7.58 (m, 4H).

Example 158



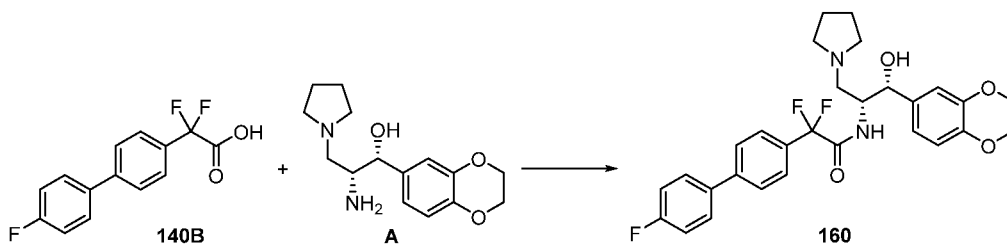
[000734] To a solution of **151** (40 mg, 0.064 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (90 mg, 1.28 mmol) at 30 °C, then the reaction was stirred at 55 °C for 4 h. Then it was purified with prep-HPLC to furnish Compound **158**. LC-MS (ESI) m/z : 528 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.03-2.23 (m, 4H), 3.28-3.34 (m, 1H), 3.50-3.92 (m, 4H), 4.13-4.32 (m, 4H), 4.84-4.93 (m, 1H), 6.81-6.90 (m, 2H), 7.50-7.53 (m, 2H), 7.72-7.92 (m, 4H).

Example 159



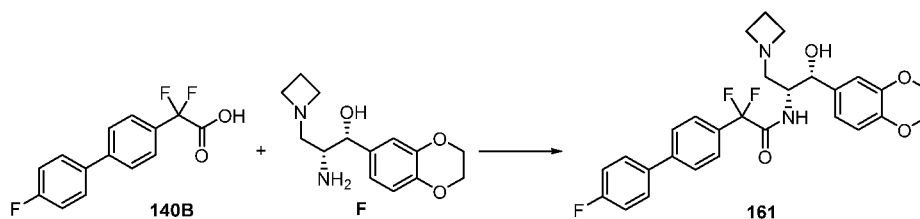
[000735] A mixture of Compound **140B** (172 mg, 0.64 mmol), EDCl.HCl (186 mg, 0.97 mmol), HOBT (132 mg, 0.97 mmol) and Intermediate **G** (200 mg, 0.64 mmol) in DCM (15 mL) was stirred at room temperature overnight. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to provide Compound **159**. LC-MS (ESI) m/z : 559.2 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.49-0.61 (m, 4H), 2.03-2.04 (m, 4H), 3.15-3.30 (m, 2H), 3.53-3.81 (m, 5H), 4.63 (d, $J = 10.4$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 7.11-7.13 (m, 1H), 7.21-7.25 (m, 2H), 7.34-7.36 (m, 3H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.71-7.75 (m, 2H).

Example 160



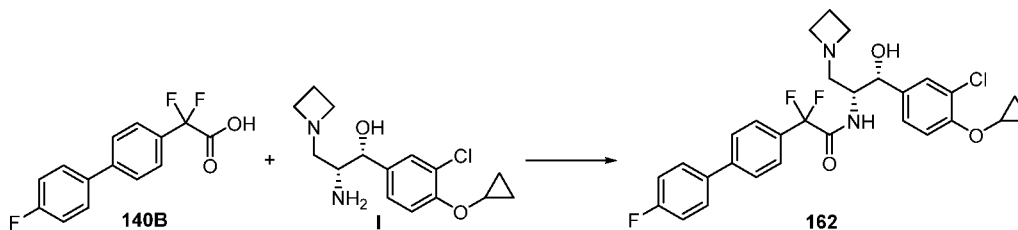
[000736] A mixture of Compound **140B** (0.10 g, 0.4 mmol), Intermediate **A** (0.10 g, 0.4 mmol), DIPEA (0.1 g, 0.8 mmol), EDCl.HCl (0.10 g, 0.6 mmol) and HOBT (0.08 g, 0.6 mmol) in DCM (2 mL) was stirred at 25 °C for 16 h. Then the mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **160**. LC-MS (ESI) m/z : 527 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.01-2.25 (m, 4H), 3.15-3.22 (m, 2H), 3.52-3.66 (m, 3H), 3.77-3.79 (m, 1H), 4.07 (s, 4H), 4.56-4.58 (m, 1H), 4.83 (d, $J = 3.2$ Hz, 1H), 6.63-6.65 (m, 1H), 6.72-6.77 (m, 2H), 7.20-7.25 (m, 2H), 7.43-7.45 (m, 2H), 7.65-7.73 (m, 4H).

Example 161



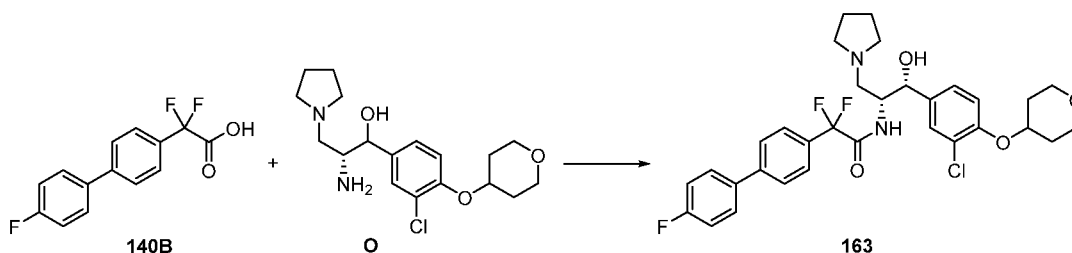
[000737] A mixture of Compound **140B** (0.10 g, 0.4 mmol), Intermediate **F** (0.10 g, 0.4 mmol), DIPEA (0.1 g, 0.8 mmol), EDCI.HCl (0.10 g, 0.6 mmol) and HOBt (0.08 g, 0.6 mmol) in DCM (2 mL) was stirred at 25 °C for 16 h. Then the mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **161**. LC-MS (ESI) m/z : 513 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 2.38-2.62 (m, 2H), 3.53-3.56 (m, 2H), 4.08 (s, 4H), 4.19-4.26 (m, 4H), 4.36-4.38 (m, 1H), 4.80 (d, $J = 3.2$ Hz, 1H), 6.64-6.77 (m, 3H), 7.21-7.25 (m, 2H), 7.41-7.43 (m, 2H), 7.65-7.73 (m, 4H).

Example 162



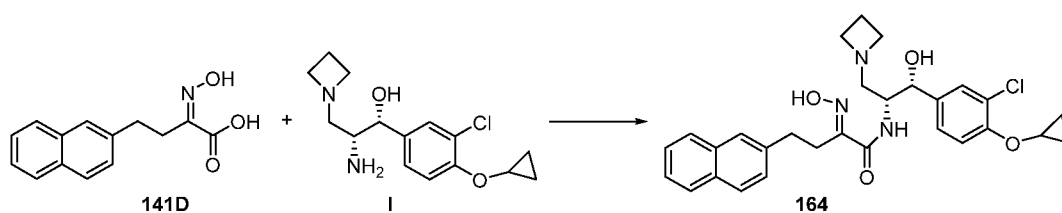
[000738] A mixture of Compound **140B** (172 mg, 0.64 mmol), EDCI.HCl (186 mg, 0.97 mmol), HOBt (132 mg, 0.97 mmol) and Intermediate **I** (191 mg, 0.64 mmol) in DCM (15 mL) was stirred at room temperature overnight. Then the reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to provide Compound **162**. LC-MS (ESI) m/z : 545.1 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.49-0.64 (m, 4H), 2.43-2.61 (m, 2H), 3.54-3.62 (m, 3H), 4.21-4.47 (m, 6H), 7.06 (d, $J = 8.4$ Hz, 1H), 7.11-7.13 (m, 1H), 7.21-7.25 (m, 2H), 7.32-7.36 (m, 3H), 7.61-7.64 (m, 3H), 7.71-7.74 (m, 2H).

Example 163



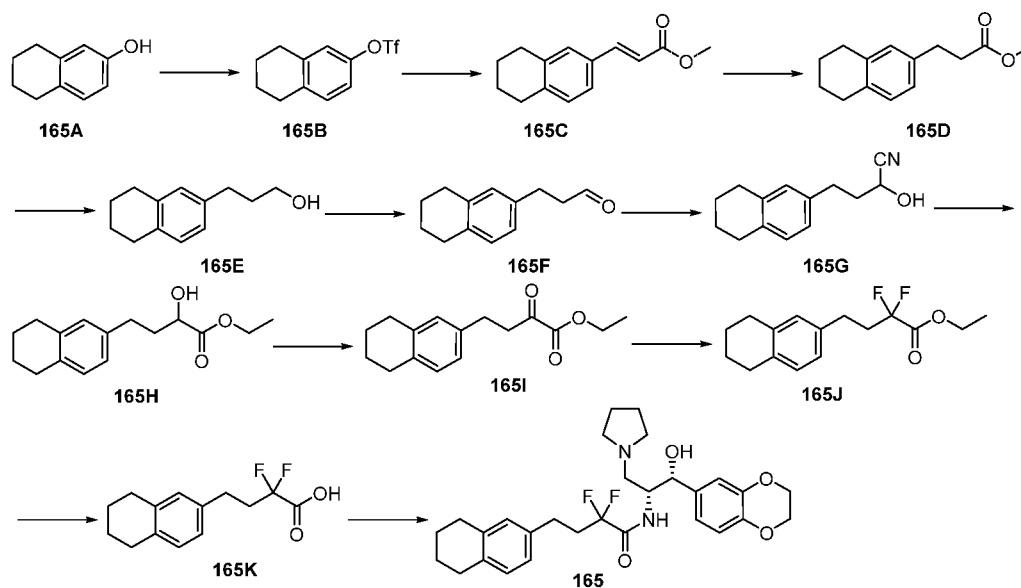
[000739] A mixture of Intermediate **O** (120 mg, 0.34 mmol), EDCl.HCl (98 mg, 0.51 mmol), HOBT (69 mg, 0.51 mmol) and Compound **140B** (90 mg, 0.34 mmol) in DCM (10 mL) was stirred for 12 h at 25 °C. Then the mixture was washed with saturated sodium bicarbonate (15 mL) and brine (15 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **163**. LC-MS (ESI) m/z : 603 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.65-1.75 (m, 2H), 1.85-1.89 (m, 2H), 2.13 (m, 4H), 2.91-3.03 (m, 2H), 3.49-3.54 (m, 4H), 3.76-3.94 (m, 4H), 4.40 (m, 2H), 5.16 (s, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 7.07-7.15 (m, 3H), 7.31-7.37 (m, 3H), 7.50-7.57 (m, 4H), 7.69 (d, $J = 4.8$ Hz, 1H), 11.80 (s, 1H).

Example 164



[000740] A solution of Compound **141D** (150 mg, 0.60 mmol), Intermediate **I** (182 mg, 0.6 mmol), EDCl.HCl (171 mg, 0.9 mmol), HOBT (121 mg, 0.9 mmol), and DIPEA (0.2 mL, 2.40 mmol) in DCM (10 mL) and DMF (10 mL) was stirred at room temperature overnight under nitrogen. Then it was evaporated and purified with prep-HPLC to furnish Compound **164**. LC-MS (ESI) m/z : 522 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.64-0.75 (m, 4H), 2.21-2.48 (m, 2H), 2.64-2.80 (m, 2H), 2.82-2.98 (m, 2H), 3.38-3.55 (m, 2H), 3.73-3.80 (m, 1H), 3.80-3.89 (m, 2H), 4.06-4.19 (m, 2H), 4.21-4.32 (m, 1H), 4.80-4.83 (m, 1H), 7.22-7.27 (m, 1H), 7.30-7.34 (m, 2H), 7.38-7.47 (m, 3H), 7.58-7.62 (m, 1H), 7.74-7.83 (m, 3H).

Example 165



[000741] To a cooled solution of Compound **165A** (10 g, 67 mmol), 2,6-dimethylpyridine (10.8 g, 101 mmol), and DMAP (1.65 mmol, 13 mmol) in DCM (100 mL) was added dropwise Tf_2O (30.5 g, 108 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight, diluted with DCM, and washed with diluted HCl. The mixture was extracted with DCM (50 mL x 2), washed with sat. sodium bicarbonate (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to afford Compound **165B**.

[000742] A mixture of Compound **165B** (18 g, 64 mmol), methyl acrylate (16.6 g, 193 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.26 g, 3.2 mmol), and K_2CO_3 (22 g, 161 mmol) in DMF (100 mL) was stirred at 100 °C for 12 h. The mixture was cooled to room temperature, and filtered. The filtrate was treated with water (50 mL), extracted with DCM (100 mL x 2), washed with water (100 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to afford Compound **165C**.

[000743] To a solution of Compound **165C** (11 g, 51 mmol) in methanol (150 mL) was added Pd/C (1.1 g). The resulting mixture was stirred at room temperature for 12 h under H_2 and filtered. The filtrate was concentrated to give a crude Compound **165D**.

[000744] To a solution of AlLiH_4 (1.2 g, 31 mmol) in THF (25 mL) was added Compound **165D** (6.76 g, 31 mmol) in THF (20 mL) dropwise under nitrogen at -78 °C. The mixture was stirred at -78 °C for 2 h and quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The filtrate was concentrated to afford the crude Compound **165E**.

[000745] To a solution of Compound **165E** (5.2 g, 27 mmol) in DCM (100 mL) was added Dess-Martin periodinane (13.9 g, 33 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h and filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to afford Compound **165F**.

[000746] Compound **165F** (4 g, 22 mmol) was added to a solution of $\text{Na}_2\text{S}_2\text{O}_5$ (4.11 g, 22 mmol) in water (150 mL). The resultant mixture was stirred for 2 h at room temperature, and NaCN (2.1 g, 43 mmol) was added. After stirring for 15 h, the mixture was diluted with ethyl acetate (50 mL), extracted with ethyl acetate (100 mL x 2), washed with sat. sodium bicarbonate (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **165G**.

[000747] To a solution of Compound **165G** (4.4 g, 20 mmol) in ethanol (50 mL) at 0 °C was bubbled a gentle stream of HCl gas (dried over con. H_2SO_4) for 5 h. The mixture was treated with water slowly at 0 °C and stirred at room temperature for 2 h. The mixture was extracted with DCM (100 mL x 2), washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **165H**.

[000748] To a solution of Compound **165H** (2 g, 7.6 mmol) in DCM (20 mL) was added Dess-Martin periodinane (3.88 g, 9.1 mmol). The mixture was stirred at room temperature for 2 h and filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **165I**.

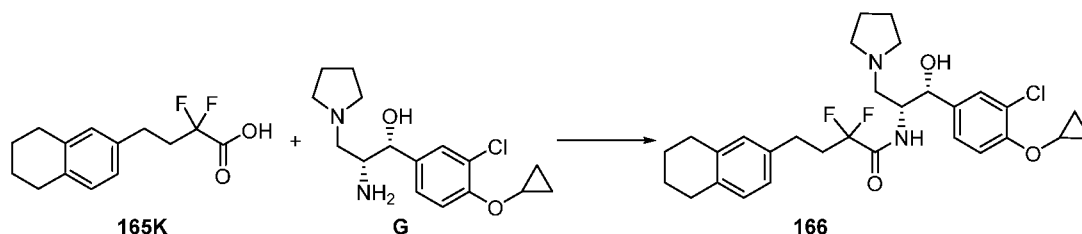
[000749] To a solution of Compound **165I** (1.7 g, 6.5 mmol) in DCM (20 mL) was added DAST (5.3 g, 33 mmol). The mixture was stirred at room temperature for 12 h and poured into ice water. The mixture was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **165J**.

[000750] To a solution of Compound **165J** (1.7 g, 6.0 mmol) in THF (50 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (758 mg, 18 mmol) in water (5 mL). The resulting mixture was stirred at room temperature for 2 h and evaporated to remove solvent. The mixture was treated with water (50 mL), adjusted to pH 2 with diluted HCl, extracted with ethyl acetate (50 mL x 2),

washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford the Compound **165K**.

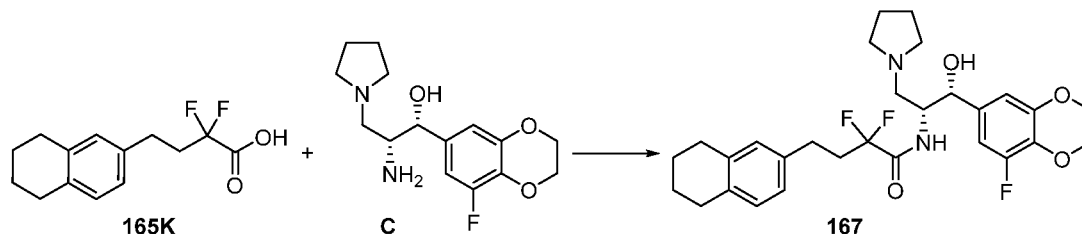
[000751] A mixture of Compound **165K** (164 mg, 0.65 mmol), Intermediate A (150 mg, 0.54 mmol), EDCL.HCl (155 mg, 0.81 mmol), and HOBt (110 mg, 0.81 mmol) in DCM (10 mL) was stirred at 25 °C overnight. Then the reaction mixture was concentrated to remove DCM. The residue was purified with prep-HPLC to provide Compound **165**. LC-MS (ESI) m/z : 515 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.77 (s, 4H), 2.11-2.13 (m, 5H), 2.20-2.29 (m, 1H), 2.72 (s, 4H), 2.87 (s, 3H), 3.03 (s, 1H), 3.44-3.46 (m, 2H), 3.83 (s, 2H), 3.98-4.05 (m, 4H), 4.42-4.44 (m, 1H), 5.08 (s, 1H), 6.78-6.82 (m, 4H), 6.87 (s, 1H), 6.96 (d, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 11.76 (s, 1H).

Example 166



[000752] A mixture of Intermediate **G** (200 mg, 0.64 mmol), Compound **165K** (164 mg, 0.64 mmol), EDCL.HCl (188 mg, 0.97 mmol), and HOBt (131 mg, 0.97 mmol) in DCM (10 mL) was stirred at 25 °C overnight. Then the reaction mixture was concentrated to remove DCM. The residue was purified with prep-HPLC to provide Compound **165**. LC-MS (ESI) m/z : 547 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.63-0.69 (m, 4H), 1.77 (s, 4H), 2.14-2.16 (m, 5H), 2.33-2.40 (m, 1H), 2.71 (s, 4H), 2.91-2.93 (m, 1H), 3.04 (s, 1H), 3.50 (s, 5H), 3.82 (s, 2H), 4.47-4.48 (m, 1H), 5.13 (s, 1H), 6.75-6.78 (m, 2H), 6.95 (d, $J = 7.6$ Hz, 1H), 7.16-7.21 (m, 2H), 7.36 (s, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 11.60 (s, 1H).

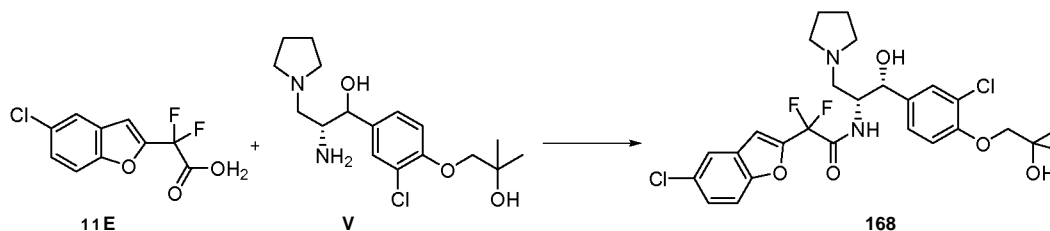
Example 167



[000753] A mixture of Intermediate **C** (200 mg, 0.67 mmol), Compound **165K** (172 mg, 0.67 mmol), EDCL.HCl (197 mg, 1.01 mmol), and HOBt (136 mg, 1.01 mmol) in DCM (10 mL) was stirred at 25 °C overnight. Then the reaction mixture was concentrated to remove DCM. The residue was purified with prep-HPLC to provide Compound **167**. LC-MS (ESI)

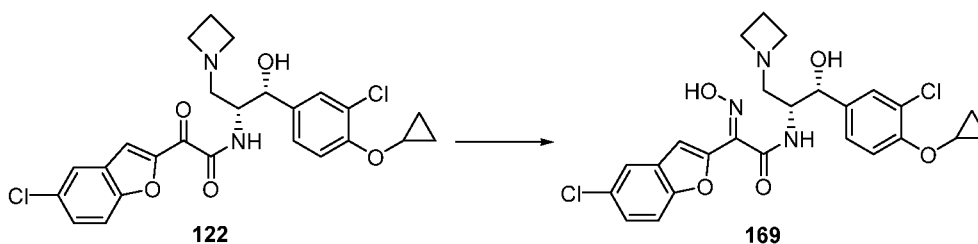
m/z: 533 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.75-1.78 (m, 4H), 2.15-2.21 (m, 6H), 2.38-2.44 (m, 1H), 2.71 (s, 4H), 2.91 (s, 1H), 3.05-3.13 (m, 3H), 3.48 (s, 2H), 3.83 (s, 2H), 4.00-4.06 (m, 3H), 4.44-4.45 (m, 1H), 5.07 (s, 1H), 6.67-6.72 (m, 2H), 6.78-6.82 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 11.70 (s, 1H).

Example 168



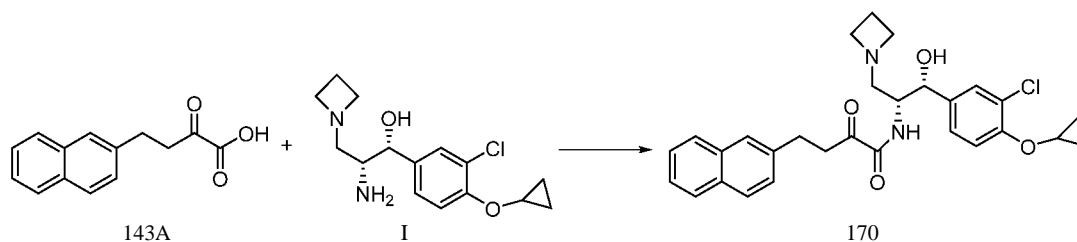
[000755] To a solution of Intermediate **V** (100 mg, 0.29 mmol) and Compound **HE** (72 mg, 0.29 mmol) in DMF (10 mL) was added EDCl.HCl (84 mg, 0.44 mmol) and HOBt (59 mg, 0.44 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. TLC and LC-MS showed the starting material was consumed completely, sat. sodium bicarbonate (5 mL) was added to the mixture and then extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), and dried over anhydrous sodium sulfate, and concentrated to provide the crude product. The crude product was purified with prep-HPLC to provide Compound **168**. LC-MS (ESI) m/z: 571 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 1.31 (s, 6H), 1.98-2.00 (m, 2H), 2.14-2.15 (m, 2H), 3.15-3.23 (m, 2H), 3.59-3.67 (m, 5H), 3.72-3.75 (m, 1H), 4.60-4.62 (m, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.74 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.39-7.41 (m, 2H), 7.53 (d, *J* = 9.2, 1H), 7.68 (d, *J* = 2.0 Hz, 1H).

Example 169



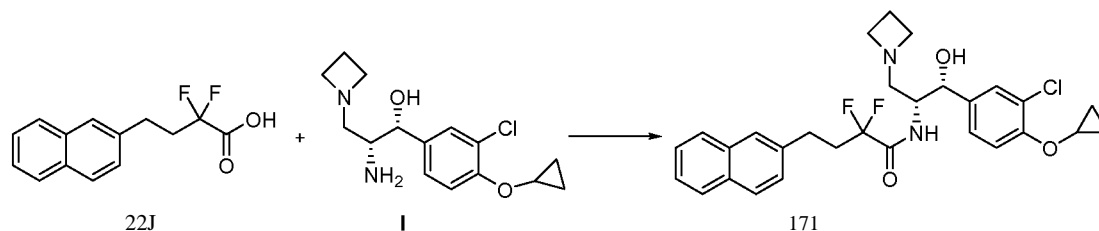
[000756] A mixture of **122** (40.8 mg, 0.08 mmol), hydroxylamine hydrochloride (76 mg, 1.1 mmol) and methanol (9 mL) was stirred at 50 °C for overnight. Then the mixture was purified with prep-HPLC to provide Compound **169**. LC-MS (ESI) m/z: 518.1 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 0.75-0.85 (m, 4H), 2.15-2.29 (m, 2H), 3.58-3.69 (m, 2H), 3.83-3.86 (m, 1H), 4.25-4.42 (m, 4H), 4.65-4.67 (m, 1H), 4.99 (d, *J* = 2.0 Hz, 1H), 5.86 (s, 1H), 7.32-7.35 (m, 1H), 7.38 (s, 2H), 7.44-7.46 (d, *J* = 8.8 Hz, 1H), 7.52-7.54 (m, 2H).

Example 170



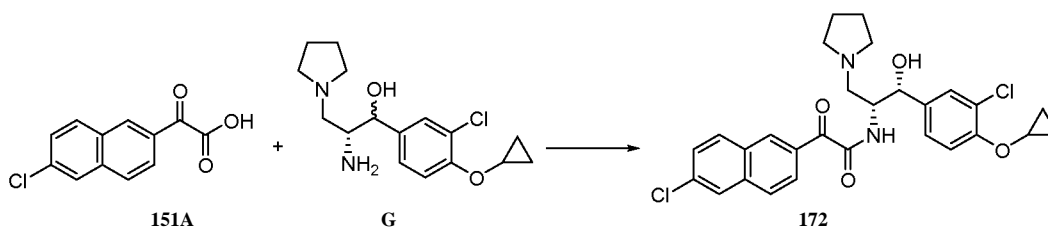
[000757] A solution of Compound **143A** (114 mg, 0.5 mmol), Intermediate **I** (148 mg, 0.5 mmol), and HATU (684 mg, 0.9 mmol) in DCM (16 mL) and DMF (6 mL) was stirred at room temperature overnight under nitrogen. Then it was evaporated and purified with prep-HPLC to furnish Compound **170**. LC-MS (ESI) m/z : 507 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.10-0.90 (m, 4H), 1.77-2.05 (m, 2H), 2.05-2.43 (m, 3H), 2.85-3.21 (m, 2H), 3.45-3.76 (m, 2H), 4.08-4.41 (m, 5H), 4.88 (m, 1H), 7.12-7.14 (m, 2H), 7.21-7.51 (m, 4H), 7.65-7.87 (m, 4H).

Example 171



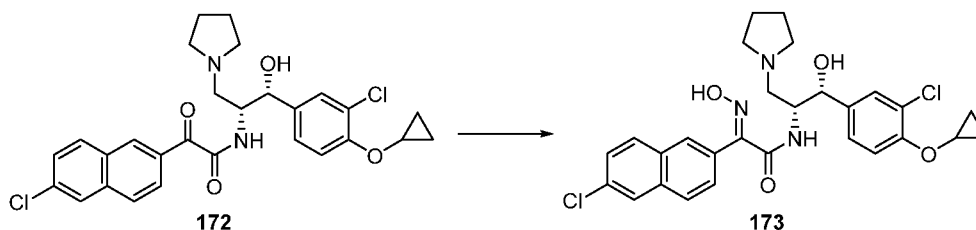
[000759] A solution of Intermediate **I** (150 mg, 0.60 mmol), Compound **22J** (148 mg, 0.5 mmol), EDCl.HCl (143 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol), and DIPEA (0.1 mL, 1.20 mmol) in DCM (20 mL) was stirred at room temperature overnight under nitrogen. Then it was evaporated, and purified with prep-HPLC to furnish a mixture (100 mg, yield 38%) as a white solid, then the mixture was further separated with chiral HPLC (co-solvent: MeOH (0.5% DEA), column OZ-H (250 * 4.6 mm 5 μ m)) and prep-HPLC to provide Compound **171**. LC-MS (ESI) m/z : 529 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.29-0.44 (m, 4H), 2.11-2.17 (m, 2H), 2.37-2.41 (m, 2H), 2.57-2.65 (m, 2H), 3.26-3.27 (m, 1H), 3.57-3.60 (m, 2H), 4.19-4.32 (m, 4H), 4.45-4.47 (m, 1H), 4.92-4.93 (m, 1H), 7.17-7.19 (m, 1H), 7.23-7.25 (m, 1H), 7.29-7.32 (m, 1H), 7.43-7.49 (m, 3H), 7.55 (s, 1H), 7.79-7.83 (m, 3H).

Example 172



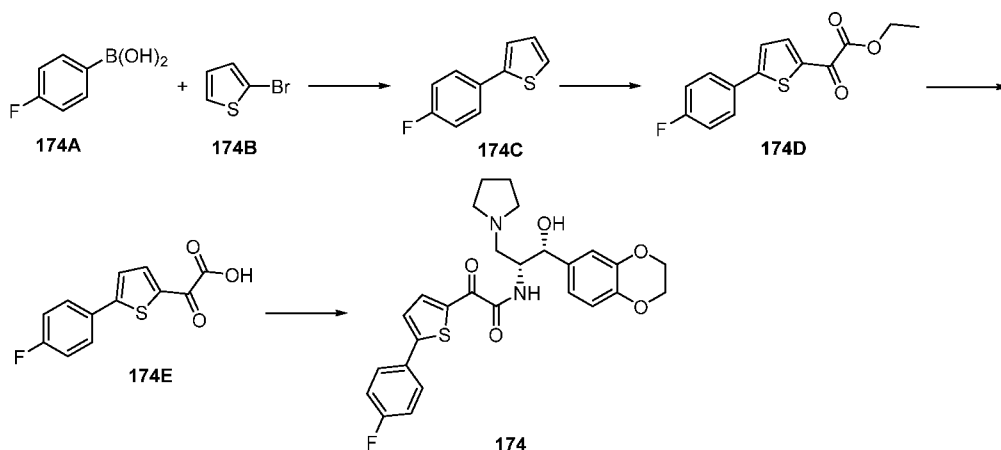
[000760] A mixture of Compound **151A** (137 mg, 0.59 mmol), HATU (445 mg, 1.17 mmol), DMF (4 mL), and Intermediate **G** (218 mg, 0.70 mmol) in DCM (16 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to afford Compound **172**. LC-MS (ESI) m/z : 527 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.54-0.79 (m, 4H), 2.04-2.22 (m, 5H), 3.23-3.26 (m, 1H), 3.58-3.82 (m, 6H), 4.70-4.73 (m, 1H), 4.99 (d, $J = 2.8$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.37-7.41 (m, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.57-7.59 (m, 1H), 7.88-7.93 (m, 3H), 7.99 (d, $J = 1.2$ Hz, 1H), 8.29 (s, 1H).

Example 173



[000761] A mixture of **172** (40.8 mg, 0.08 mmol), hydroxylamine hydrochloride (76 mg, 1.1 mmol) and methanol (9 mL) was stirred at 50 °C overnight. Then the mixture was purified with prep-HPLC to provide Compound **173**. LC-MS (ESI) m/z : 542.1 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 0.69-0.84 (m, 4H), 2.02-2.22 (m, 4H), 3.21-3.29 (m, 1H), 3.62-3.80 (m, 5H), 4.70-4.73 (m, 1H), 5.01 (d, $J = 2.8$ Hz, 1H), 7.32-7.34 (m, 1H), 7.39-7.43 (m, 1H), 7.45-7.49 (m, 1H), 7.51-7.53 (m, 1H), 7.63-7.85 (m, 3H), 7.88-7.90 (m, 1H).

Example 174



[000763] To a stirred solution of Compound **174A** (2.0 g, 15.4 mmol) in dioxane (60 mL) and water (20 mL) was added Pd(PPh₃)₂Cl₂ (1.08 g, 1.54 mmol), Compound **174B** (3.0 g, 18.5 mmol) and Na₂CO₃ (6.53 g, 61.6 mmol) under nitrogen. The mixture was stirred at 80 °C overnight. After the reaction was completed, it was evaporated to remove the solvent. The residue was diluted with EA (200 mL), washed with water (5 mL) and brine (5 mL), and dried over anhydrous sodium sulfate. The crude product was purified with flash column chromatography on silica gel (petroleum in ethyl acetate, 3% v/v) to furnish Compound **174C**.

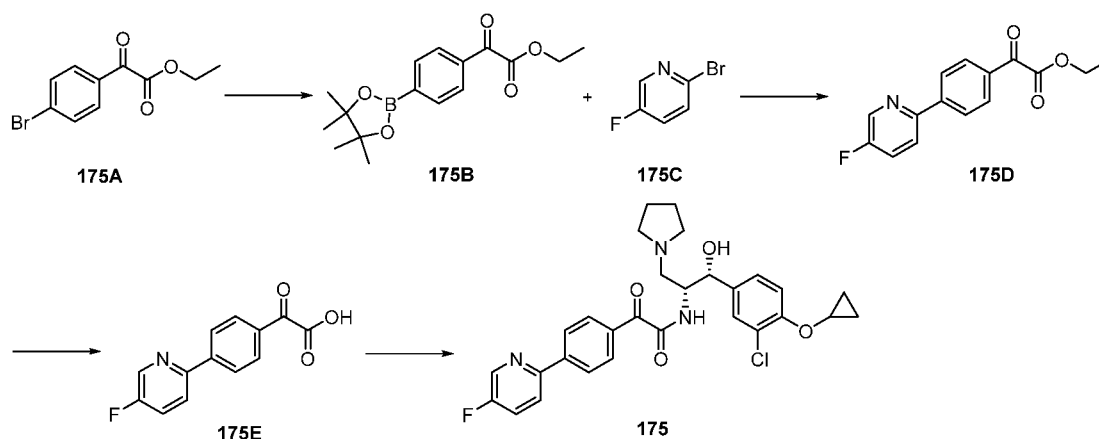
[000764] To a solution of Compound **174C** (890 mg, 5.0 mmol) in dry THF (50 mL) was added dropwise LDA (2.0 M, 3.0 mL, 6.0 mmol) under nitrogen at -70 °C. After stirring for 30 min., diethyl oxalate (2.19 g, 15.0 mmol) was added as soon as possible. Then the mixture was stirred at -70 °C for about 1 h. Then the mixture was quenched with sat. NH₄Cl (10 mL), extracted with ethyl acetate (50 mL x 3), washed with water (5 mL) and brine (5 mL), and dried over sodium sulfate. The crude product was purified with flash column chromatography on silica gel (petroleum in ethyl acetate, 10% v/v) to furnish Compound **174D**.

[000765] To a solution of Compound **174D** (500 mg, 1.8 mmol) in THF (6 mL) was added dropwise a solution of LiOH.H₂O (83 mg, 1.98 mmol) in water (1.5 mL) slowly at -30 °C. Then the mixture was stirred at -30 °C about 0.5 h. It was adjusted to pH 3 with HCl (1 N), and extracted with DCM (100 mL x 3). The organic phase was dried over sodium sulfate, filtered and concentrated to furnish the Compound **174E**.

[000766] To a solution of Compound **174E** (360 mg, 1.44 mmol) in DMF (15 mL) was added HATU (821 mg, 2.16 mmol). After stirring for two hours at 25 °C, Intermediate A (400 mg, 1.44 mmol) was added and the resultant mixture was stirred overnight at 25 °C.

TLC and LC-MS showed the starting material was consumed completely, and sat. sodium bicarbonate (5 mL) was added to the mixture and then extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), and dried over anhydrous sodium sulfate, and concentrated to provide the crude product. The crude product was purified with prep-HPLC to provide Compound **174**. LC-MS (ESI) m/z : 511 $[M+H]^+$; 1H -NMR (MeOD, 400 MHz) δ (ppm) 1.97-2.02 (m, 2H), 2.13-2.17 (m, 2H), 3.16-3.23 (m, 2H), 3.40-3.44 (m, 1H), 3.60-3.70 (m, 2H), 3.76-3.82 (m, 1H), 4.11-4.18 (m, 4H), 4.46-4.51 (m, 1H), 4.82 (d, $J = 3.6$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.85 (dd, $J = 2.0, 8.4$ Hz, 1H), 6.89 (d, $J = 1.6$ Hz, 1H), 7.21 (t, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 4.4$ Hz, 1H), 7.78-7.82 (m, 2H), 8.15 (d, $J = 4.4$ Hz, 1H).

Example 175



[000768] To a solution of Compound **175A** (5.12 g, 20 mmol) in dioxane (75 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.10 g, 24 mmol), Pd(dppf)Cl₂ (902 mg, 1 mmol) and KOAc (5.9 g, 60 mmol). The reaction mixture was heated to 90 °C for 2.5 h, then the solution was cooled to r.t and filtered. The filtrate was concentrated to offer the crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to offer Compound **175B**.

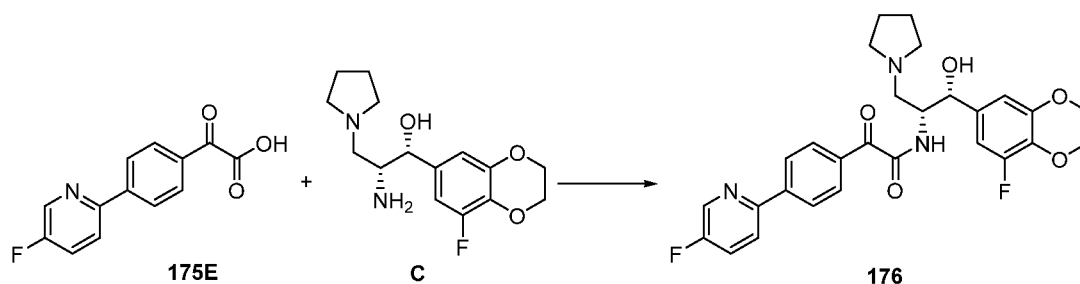
[000769] A mixture of Compound **175B** (730 mg, 2.4 mmol), Compound **175C** (350 mg, 2 mmol), Pd(PPh₃)₄ (116 mg, 0.1 mmol) and K₃P0₄ (1.27 g, 6 mmol) in toluene (20 mL) was heated to reflux, stirred for 3 h and filtered. The filtrate was concentrated to offer the crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to offer Compound **175D**.

[000770] To a solution of Compound **175D** (119 mg, 0.44 mmol) in THF/water (11 mL, 15 : 1, v/v) was added LiOH.H₂O (28 mg, 0.66 mmol). The mixture was stirred at -10 °C for

1 h. After the reaction, it was adjusted to pH 6 with 3 N HCl and extracted with ethyl acetate (20 mL x 3). The combined organic layers were concentrated in vacuum without dryness to offer the crude product Compound **175E**.

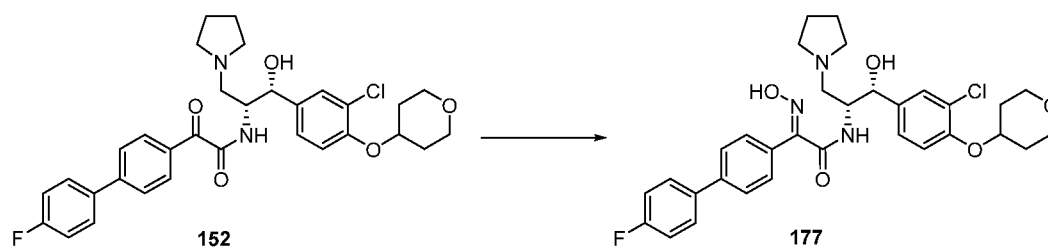
[000771] A mixture of Compound **175E** (100 mg, 0.408 mmol), Intermediate G (124 mg, 0.408 mmol) and HATU (233 mg, 0.612 mmol) in dichloromethane (2 mL) and DMF (2 mL) was stirred at 25 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **175**. LC-MS (m/z): 538 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 0.79-0.84 (m, 4H), 2.1 1-2.14 (m, 4H), 3.01-3.19 (m, 2H), 3.42-3.90 (m, 5H), 4.55-4.57 (m, 1H), 4.79 (m, 1H), 7.28-7.32 (m, 2H), 7.41-7.62 (m, 2H), 7.82-7.86 (m, 1H), 7.95-8.01 (m, 4H), 8.57 (d, *J* = 3.2 Hz, 1H).

Example 176



[000772] A mixture of Compound **175E** (98 mg, 0.4 mmol), Intermediate **C** (118 mg, 0.4 mmol), and HATU (228 mg, 0.6 mmol) in DMF (10 mL) was stirred at 30 °C for 8 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **176**. LC-MS (m/z): 524 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 2.04 (s, 2H), 2.19 (s, 2H), 3.18-3.30 (m, 2H), 3.48-3.57 (m, 1H), 3.65-3.74 (m, 2H), 3.78-3.84 (m, 1H), 4.19-4.34 (m, 5H), 4.65 (d, *J* = 8 Hz, 1H), 6.81 (d, *J* = 12 Hz, 1H), 7.69-7.76 (m, 1H), 7.90 (d, *J* = 8 Hz, 2H), 8.02-8.05 (m, 1H), 8.1 1 (d, *J* = 8 Hz, 2H), 8.60 (s, 1H).

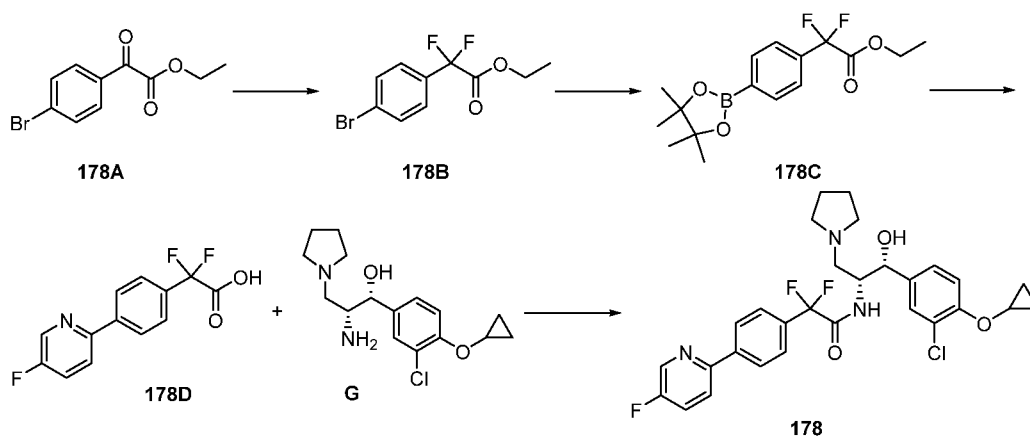
Example 177



[000773] A mixture of **152** (30 mg, 0.04 mmol) and NH₂OH.HCl (27.6 mg, 0.4 mmol) in MeOH (3 mL) was stirred for 4 h at 55 °C. After filtration, the filtrate was purified with

prep-HPLC to furnish Compound **177**. LC-MS (m/z): 596 $[M+1]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) major characteristic peaks: δ (ppm) 172-1.81 (m, 2H), 1.98-2.08 (m, 2H), 3.30 (m, 1H), 3.51-3.74 (m, 4H), 3.88-3.99 (m, 4H), 4.65-4.70 (m, 1H), 5.03 (s, 1H), 7.09-7.11 (m, 2H), 7.15-7.23 (m, 3H), 7.35 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.66-7.70 (m, 2H).

Example 178



[000775] To a solution of Compound **178A** (2.56 g, 10 mmol) in dry dichloromethane (50 mL) was added DAST (3.30 mL, 25 mmol). Then the mixture was stirred at 25 °C for 14 h. After the reaction, dichloromethane (25 mL) was added, then the organic layer was washed with water (50 mL), followed by addition of aq. sodium bicarbonate (30 mL) and brine (50 mL), dried over sodium sulfate and concentrated to offer the crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to offer Compound **178B**.

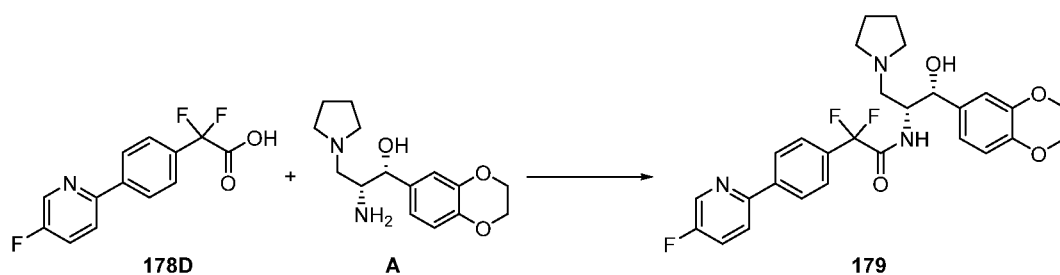
[000776] To a solution of Compound **178B** (2.58 g, 9.3 mmol) in dioxane (45 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.82 g, 11.1 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (409 mg, 0.5 mmol) and KOAc (2.72 g, 27.8 mmol). The reaction mixture was heated to 90 °C for 2.5 h, then the solution was cooled to r.t and filtered. The filtrate was concentrated to offer the crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to offer Compound **178C**.

[000777] To a solution of Compound **178C** (717 mg, 2.2 mmol), 2-bromo-5-fluoropyridine (350 mg, 2 mmol), and K_3CO_3 (828 mg, 6 mmol) in dioxane (20 mL) and water (2 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (82 mg, 0.1 mmol) at 25 °C under nitrogen. Then the mixture was heated to reflux, stirred for 3 h and filtered. The filtrate was concentrated to offer the crude product. Water (10 mL) was added, and the mixture was extracted with ethyl

acetate (100 mL). Then 2 N HCl was added to the aqueous layer, adjusted to pH = 6-7, then extracted with THF in ethyl acetate (20% v/v, 35 mL x 3). The organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to obtain Compound **178D**.

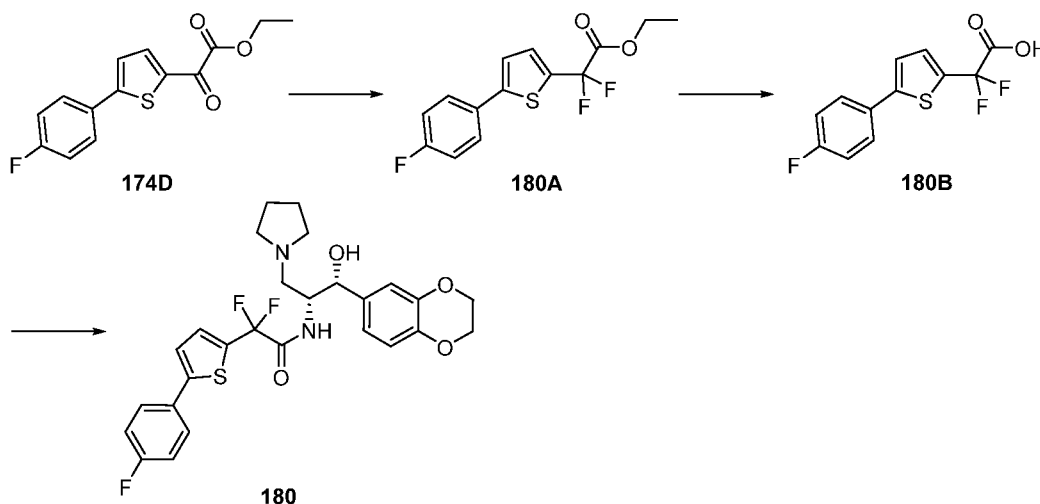
[000778] A mixture of Compound **178D** (88 mg, 0.33 mmol), Intermediate **G** (105 mg, 0.34 mmol), EDCI.HCl (96 mg, 0.49 mmol), and HOBt (67 mg, 0.49 mmol) in dichloromethane (2 mL) and DMF (2 mL) was stirred at 25 °C for 5 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **178**. LC-MS (m/z): 560 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.63-0.69 (m, 4H), 2.13 (br, 2H), 3.03-3.05 (br, 2H), 3.36-3.61 (m, 5H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.95 (d, *J* = 3.2 Hz, 1H), 7.08 (s, 2H), 7.34 (s, 1H), 7.41-7.44 (m, 2H), 7.58-7.62 (m, 1H), 7.83-7.95 (m, 3H), 8.54 (d, *J* = 3.2 Hz, 1H).

Example 179



[000779] A mixture of Compound **178D** (88 mg, 0.33 mmol), Intermediate **A** (100 mg, 0.35 mmol), EDCI.HCl (96 mg, 0.49 mmol), and HOBt (67 mg, 0.49 mmol) in dichloromethane (15 mL) and DMF (2 mL) was stirred at 25 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **179**. LC-MS (m/z): 528 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 2.09-2.14 (m, 4H), 2.81-2.84 (m, 2H), 3.41-3.45 (m, 2H), 3.72-3.88 (m, 2H), 4.15 (s, 4H), 4.41 (m, 1H), 5.06 (d, *J* = 2.0 Hz, 1H), 6.73-6.80 (m, 3H), 7.43-7.52 (m, 3H), 7.72-7.76 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 8.56 (d, *J* = 2.8 Hz, 1H), 11.79 (brs, 1H).

Example 180

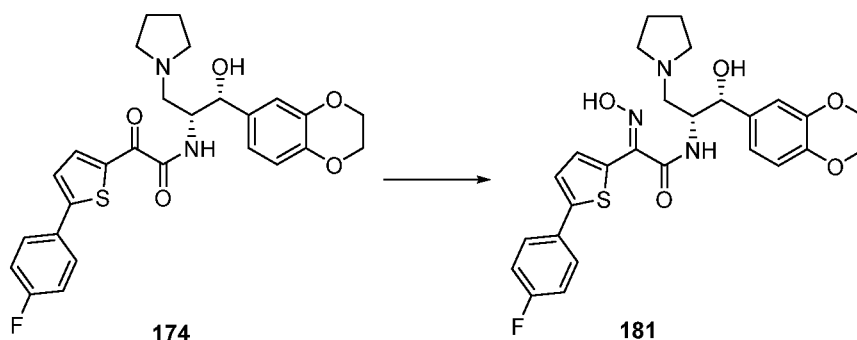


[000780] To a solution of Compound **174D** (290 mg, 1.07 mmol) in DCM (5 mL) was added DAST (1 mL, excess) at room temperature and the resultant mixture was stirred at 30 °C overnight. Poured into ice-water (100 mL) and extracted with DCM (50 mL x 3). The combined organic phase was washed with water (5 mL) and brine (5 mL), and dried over anhydrous sodium sulfate. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to obtain Compound **180A**.

[000781] To a solution of Compound **180A** (130 mg, 0.43 mmol) in THF/water (6 mL, 4:1, v/v) was added LiOH.H₂O (73 mg, 1.73 mmol). The mixture was stirred at 25 °C for 2 h. After the reaction, it was adjusted to pH 3 with HCl (1 N) and separated. The organic phase was dried over sodium sulfate. Filtered and concentrated to furnish the Compound **180C**.

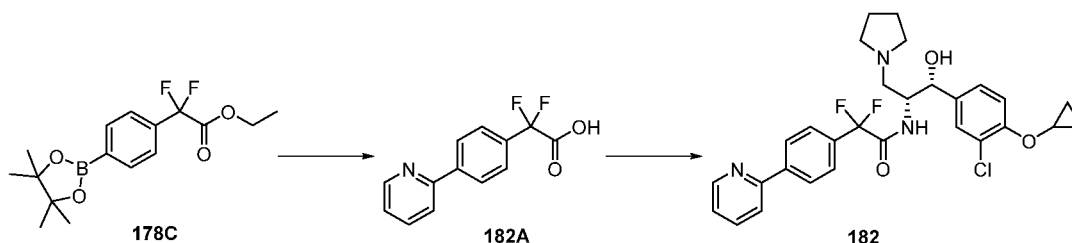
[000782] To a mixture of Compound **180C** (98 mg, 0.36 mmol) in DMF (10 mL) was added EDCl.HCl (104 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol) and Compound (A) (100 mg, 0.36 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. TLC and LC-MS showed the starting material was consumed completely. Then sat. sodium bicarbonate (5 mL) was added to the mixture which was extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), dried over anhydrous sodium sulfate, and concentrated to offer the crude product. The crude product was purified with prep-HPLC to offer Compound **180**. LC-MS (m/z): 533 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 1.96-2.00 (m, 2H), 2.11-2.14 (m, 2H), 3.11-3.20 (m, 2H), 3.46-3.50 (m, 1H), 3.56-3.62 (m, 2H), 3.71-3.77 (m, 1H), 4.01 (s, 4H), 4.50-4.53 (m, 1H), 4.79 (d, *J* = 3.2 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 3.6 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 4.0 Hz, 1H), 7.63-7.67 (m, 2H).

Example 181



[000783] To a solution of **174** (50 mg, 0.08 mmol) in MeOH (10 mL) was added hydroxylamine hydrochloride (112 mg, 1.6 mmol). The mixture was stirred overnight at 25 °C. LC-MS showed the starting material was consumed completely, and the solvent was evaporated. The crude product was purified with prep-HPLC to offer Compound **181**. LC-MS (m/z): 526 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 1.97-2.00 (m, 2H), 2.13-2.15 (m, 2H), 3.14-3.23 (m, 2H), 3.42-3.46 (m, 1H), 3.57-3.63 (m, 2H), 3.74-3.81 (m, 1H), 4.15-4.20 (m, 4H), 4.57-4.69 (m, 1H), 4.70 (d, *J* = 2.8 Hz, 1H), 6.74-6.86 (m, 2H), 6.90-6.94 (m, 1H), 7.10-7.15 (m, 2H), 7.27 (d, *J* = 4.0 Hz, 1H), 7.51 (d, *J* = 4.0 Hz, 1H), 7.61-7.69 (m, 2H).

Example 182

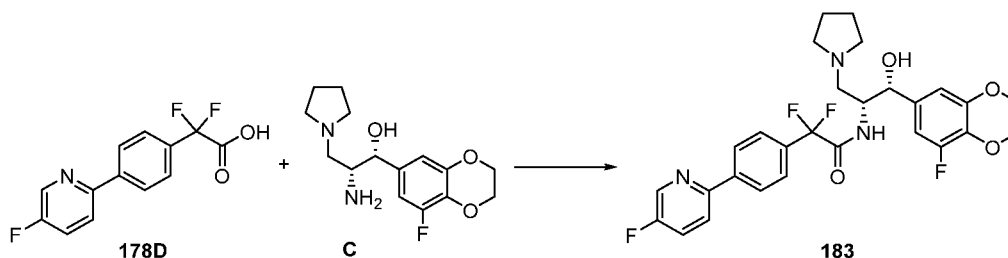


[000784] A mixture of Compound **178C** (1.3 g, 4 mmol), 2-bromopyridine (628 mg, 4 mmol), Pd(dppf)₂Cl₂ (160 mg, 0.2 mmol), and Na₂CO₃ (1.27 g, 12 mmol) in dioxane (30 mL) and water (4 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). The mixture was filtered and the filtrate was treated with water (50 mL), extracted with ethyl acetate (50 mL x 2), then the water layer was adjusted to pH 3 by aqueous HCl solution (3 N), and extracted with ethyl acetate (50 mL x 2). The ethyl acetate layer was washed with water (50 mL x 2), dried over sodium sulfate, filtered, and concentrated to furnish the Compound **182A**.

[000785] A mixture of Compound **182A** (90 mg, 0.36 mmol), EDCI.HCl (103 mg, 0.54 mmol), HOBT (73 mg, 0.54 mmol), and Intermediate **G** (111 mg, 0.36 mmol) in DCM (5 mL) was stirred at 10 °C for 18 h. Then the mixture was diluted by ethyl acetate (50 mL),

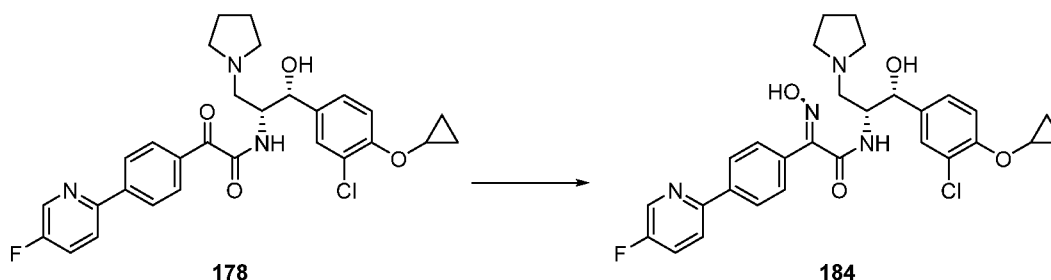
washed with sat. sodium bicarbonate solution (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **182**. LC-MS (m/z): 542 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 0.48-0.59 (m, 4H), 2.03-2.24 (m, 4H), 3.17-3.26 (m, 2H), 3.54-3.81 (m, 5H), 4.62 (d, *J* = 9.2 Hz, 1H), 4.94-4.96 (m, 1H), 7.00-7.03 (m, 1H), 7.09-7.11 (m, 1H), 7.34-7.36 (m, 1H), 7.47-7.59 (m, 3H), 8.02-8.14 (m, 4H), 8.71-8.74 (m, 1H).

Example 183



[000786] A mixture of Compound **178D** (88 mg, 0.33 mmol), Intermediate C (105 mg, 0.34 mmol), EDCI.HCl (96 mg, 0.49 mmol), and HOBt (67 mg, 0.49 mmol) in dichloromethane (15 mL) was stirred at 25 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **183**. LC-MS (m/z): 546 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 2.02-2.19 (m, 4H), 3.15-3.31 (m, 2H), 3.52-3.56 (m, 3H), 3.79-3.80 (m, 1H), 4.04-4.08 (m, 4H), 4.56 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 2.8 Hz, 1H), 6.57-6.68 (m, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.71-7.76 (m, 1H), 8.01-8.07 (m, 3H), 8.59 (d, *J* = 3.2 Hz, 1H).

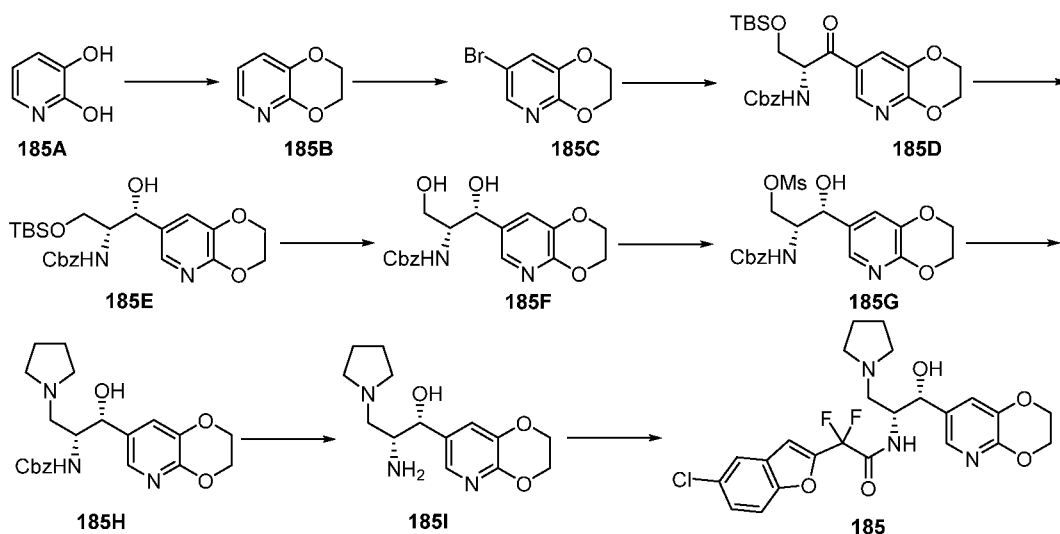
Example 184



[000787] To a solution of Compound **178** (56 mg, 0.086 mmol) in MeOH (20 mL) was added hydroxylamine hydrochloride (120 mg, 1.72 mmol) at 25 °C, then the reaction was stirred at 55 °C for 14 h. Then it was purified with prep-HPLC to obtain Compound **184**. LC-MS (m/z): 553 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 0.77-0.85 (m, 4H), 2.03-2.06 (m, 2H), 2.20-2.22 (m, 2H), 3.19-3.26 (m, 1H), 3.62-3.92 (m,

5H), 4.60-4.89 (m, 2H), 5.02 (d, $J = 2.8$ Hz, 1H), 7.16-7.51 (m, 5H), 7.51-7.74 (m, 1H), 7.86-7.98 (m, 3H), 8.51-8.54 (m, 1H).

Example 185



[000788] A mixture of Compound **185A** (22.2 g, 200 mmol), 1,2-dibromoethane (55.8 g, 300 mmol), and K_2CO_3 (55.2 g, 600 mmol) in DMSO (270 mL) was stirred at 100 °C for 10 h under nitrogen protection. Then it was cooled to room temperature and extracted with ethyl acetate (100 mL x 3). The ethyl acetate layers were combined and washed with water (50 mL x 3) and brine (50 mL), dried over sodium sulfate, and concentrated to offer the title Compound **185B**.

[000789] A mixture of Compound **185B** (1.37 g, 10 mmol) and Br_2 (1.6 g, 10 mmol) in DCM (27 mL) was stirred at 25 °C for 24 h, cooled to room temperature, quenched by NH_4Cl (20 mL), and extracted with DCM (100 mL x 3). The DCM layers were combined and washed with water (50 mL x 3) and brine (50 mL), dried over sodium sulfate, concentrated and recrystallized from methanol to offer the title Compound **185C**.

[000790] To a mixture of Compound **185C** (3.23 g, 15 mmol) in THF (27 mL) at -65 °C was added by n-BuLi solution (6.45 mL), and the mixture was stirred at -65 °C for 1 h. Then a solution of Compound **A4** (1.98 g, 5 mmol) in THF (10 mL) was added. The resultant mixture was stirred for 1 h, quenched by NH_4Cl (20 mL), and extracted with EA (100 mL x 3). The EA layers were combined and washed with water (50 mL x 3) and brine (50 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel with EA in PE (1/20 to 1/5 v/v) to offer the title Compound **185D**.

[000791] To a mixture of Compound **185D** (1.4 g, 3 mmol) in THF (17 mL) at -90 °C was added L-Selectride (1 M in THF, 6 mL), then it was stirred at -90 °C for 0.5 h, quenched by NH_4Cl (20 mL), and extracted with EA (100 mL x 3). The EA layers were combined and

washed with water (50 mL x 3) and brine (50 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel with EA in PE (1/2 v/v) to offer the title Compound **185E**.

[000792] A mixture of Compound **185E** (1.4 g, 3 mmol) and TBAF.3H₂O (945 mg, 3 mmol) in THF (17 mL) at 20 °C was stirred for 15 h. Then it was diluted by EA (50 mL), washed with water (10 mL x 3) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel with methanol in DCM (1/100 to 1/20 v/v) to offer the title Compound **185F**.

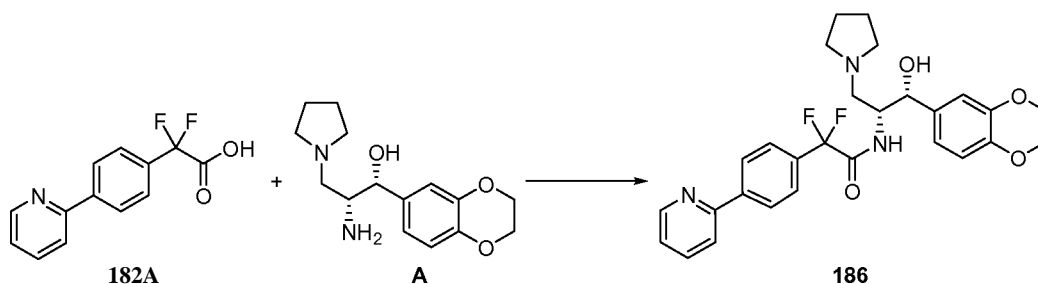
[000793] To a mixture of Compound **185F** (800 mg, 2.2 mmol) and TEA (404 mg, 4.4 mmol) in DCM (8 mL) at 20 °C was added MsCl (1.77 mL, 2.2 mmol). The mixture was stirred for 30 min, quenched by water (5 mL), and extracted with DCM (10 mL x 3). The combined DCM layers were washed with water (10 mL x 3) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel with methanol in DCM (1/100 to 1/50 v/v) to offer the title Compound **185G**.

[000794] A mixture of Compound **185G** (390 mg, 0.9 mmol) and pyrrolidine (632 mg, 9 mmol) in THF (8 mL) at 50 °C was stirred for 13 h then concentrated. The residue was dissolved into EA (50 mL), washed with water (10 mL x 3) and brine (10 mL), dried over sodium sulfate, and concentrated to offer the title Compound **185H**.

[000795] A mixture of Compound **185H** (380 mg, 0.9 mmol) and LiOH.H₂O (77 mg, 1.8 mmol) in EtOH (4 mL) was stirred at 100 °C for 13 h then concentrated. The residue was dissolved into DCM (50 mL), washed with water (10 mL x 3) and brine (10 mL), dried over sodium sulfate, and concentrated to offer the title Compound **185I**.

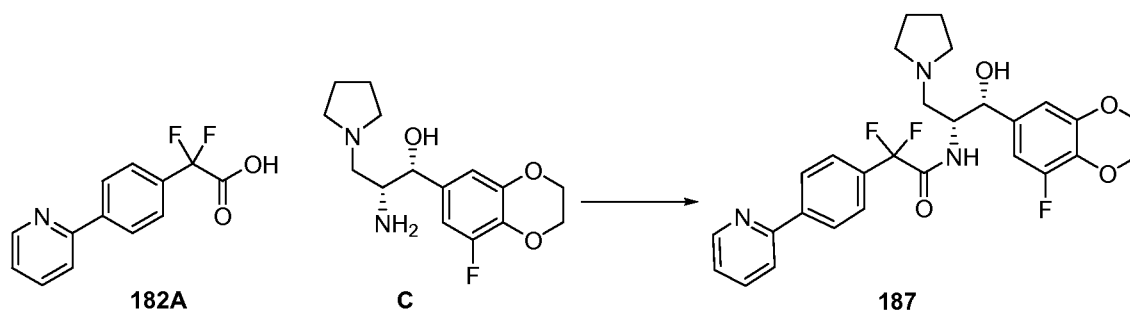
[000796] A mixture of Compound **185I** (180 mg, 0.644 mmol), Compound **HE** (159 mg, 0.644 mmol), HATU (294 mg, 0.773 mmol) and DIPEA (125 mg, 0.966 mmol) in DCM (4 mL) was stirred at r.t. overnight then concentrated. The residue was dissolved into DCM (50 mL), washed with water (10 mL x 3) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with chiral HPLC to offer Compound **185**. LC-MS (m/z): 508 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.75 (m, 4H), 2.61-2.69 (m, 4H), 2.77-2.81 (m, 1H), 2.92-2.97 (m, 1H), 4.03-4.10 (m, 1H), 4.18-4.36 (m, 4H), 5.19 (d, *J* = 7.6 Hz, 1H), 5.27-5.29 (m, 1H), 6.91 (s, 1H), 7.12 (d, *J* = 5.2 Hz, 1H), 7.27-7.30 (m, 1H), 7.37-7.39 (m, 1H), 7.40-7.42 (m, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.83 (d, *J* = 5.2 Hz, 1H).

Example 186



[000797] A mixture of Compound **182A** (90 mg, 0.36 mmol), EDCI.HCl (103 mg, 0.54 mmol), HOBT (73 mg, 0.54 mmol), and Intermediate **A** (100 mg, 0.36 mmol) in DCM (5 mL) was stirred for 18 h at 10 °C. Then the mixture was diluted by ethyl acetate (50 mL), washed with sat. sodium bicarbonate solution (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **186**. LC-MS (m/z): 510 $[M+1]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) major characteristic peaks: δ (ppm) 2.02-2.04 (m, 4H), 3.13-3.20 (m, 2H), 3.49-3.67 (m, 4H), 4.06-4.09 (m, 4H), 4.55-4.57 (m, 1H), 4.81 (d, $J = 3.2$ Hz, 1H), 6.61 (d, $J = 8.0$ Hz, 1H), 6.73 (dd, $J = 8.4, 2.0$ Hz, 1H), 6.77 (d, $J = 2.0$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.75 (t, $J = 6.4$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 2H), 8.18 (d, $J = 8.4$ Hz, 1H), 8.30-8.32 (m, 1H), 8.80 (d, $J = 5.2$ Hz, 1H).

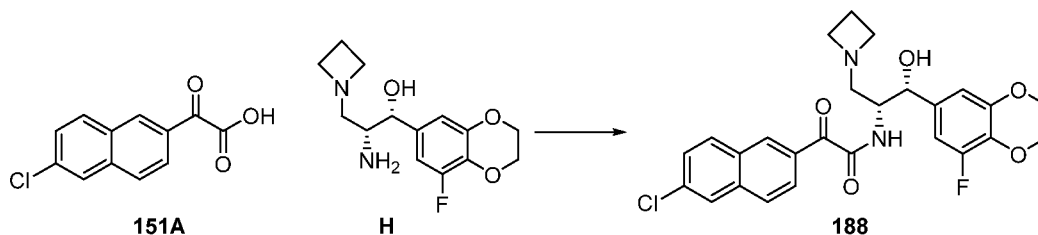
Example 187



[000798] A mixture of Compound **182A** (90 mg, 0.36 mmol), EDCI.HCl (103 mg, 0.54 mmol), HOBT (73 mg, 0.54 mmol), and Intermediate **C** (107 mg, 0.36 mmol) in DCM (5 mL) was stirred for 18 h at 10 °C. Then the mixture was diluted by ethyl acetate (50 mL), washed with sat. sodium bicarbonate solution (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **187**. LC-MS (m/z): 528 $[M+1]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) major characteristic peaks: δ (ppm) 2.04-2.16 (m, 4H), 3.31-3.32 (m, 2H), 3.52-3.19 (m, 4H), 4.05-4.11 (m, 4H), 4.56-4.59 (m, 1H), 4.81 (d, $J = 3.2$ Hz, 1H), 6.58 (s, 1H), 6.64 (dd, $J = 11.2, 2.0$

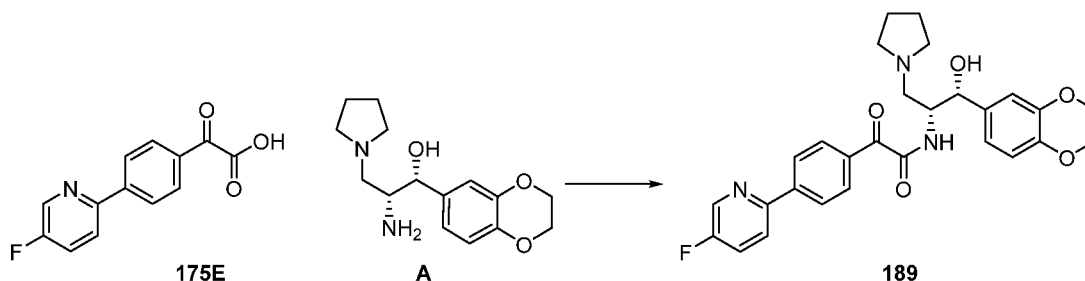
Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.64-7.67 (m, 1H), 8.04 (d, $J = 8.0$ Hz, 2H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.20-8.23 (m, 1H), 8.76 (d, $J = 9.0$ Hz, 1H).

Example 188



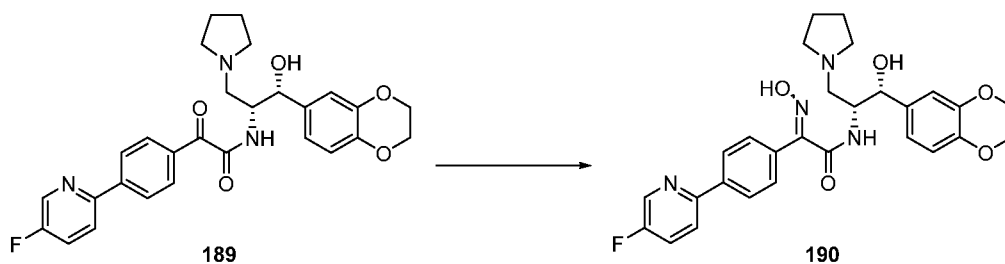
[000799] To a solution of Compound **151A** (85 mg, 0.37 mmol) and Intermediate **H** (104 mg, 0.37 mmol) in dichloromethane (6 mL) and DMF (2 mL) was added HATU (208 mg, 0.55 mmol) at 25 °C. Then the reaction was stirred at 28 °C for 15 hours. Then the reaction mixture was treated with water (40 mL), extracted with DCM (20 mL x 2), washed with brine (10 mL), dried over sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to obtain Compound **188**. LC-MS (m/z): 499 $[M+1]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz) δ (ppm) 2.08-2.40 (m, 2H), 2.70-3.35 (m, 2H), 3.50-4.10 (m, 3H), 4.24-4.29 (m, 6H), 4.78 (s, 1H), 6.76-6.85 (m, 2H), 7.67-7.70 (m, 1H), 7.87 (d, $J = 1.6$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 8.20 (d, $J = 2.0$ Hz, 1H), 8.48 (s, 1H), 8.76 (br, 1H).

Example 189



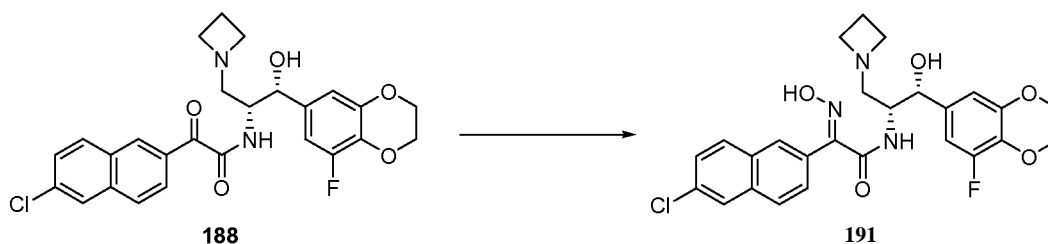
[000800] A mixture of Compound **175E** (100 mg, 0.408 mmol) and Intermediate **A** (114 mg, 0.408 mmol) and HATU (155 mg, 0.612 mmol) in dichloromethane (4 mL) and DMF (2 mL) was stirred at 25 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum and purified with prep-HPLC to obtain Compound **189**. LC-MS (m/z): 506 $[M+1]^+$; 1H -NMR (CD_3OD , 400 MHz) δ (ppm) 2.03-2.24 (m, 6H), 3.12-3.25 (m, 3H), 3.60-3.71 (m, 2H), 3.82-3.95 (m, 1H), 4.19-4.28 (m, 2H), 4.55-4.58 (m, 1H), 4.93 (d, $J = 2.8$ Hz, 1H), 6.85-6.92 (m, 3H), 7.61-7.90 (m, 2H), 8.00 (s, 4H), 8.59 (d, $J = 2.8$ Hz, 1H).

Example 190



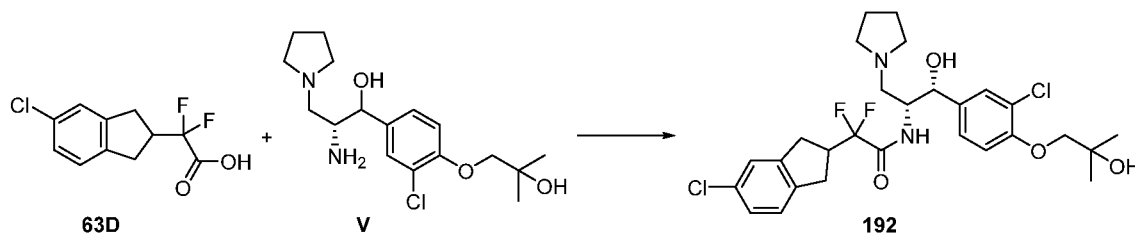
[000801] To a solution of **189** (40 mg, 0.065 mmol) in MeOH (18 mL) was added hydroxylamine hydrochloride (90 mg, 1.29 mmol) at 25 °C, then the reaction was stirred at 55 °C for 14 h. Then it was purified with prep-HPLC to obtain Compound **190**. LC-MS (m/z): 521 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 1.91-2.10 (m, 4H), 2.56-3.17 (m, 1H), 3.17-3.77 (m, 4H), 4.12-4.19 (m, 4H), 4.46-4.71 (m, 2H), 4.83-4.84 (m, 1H), 6.70-6.90 (m, 3H), 7.19-7.34 (m, 2H), 7.57-7.63 (m, 1H), 7.82-7.85 (m, 3H), 8.47-8.50 (m, 1H).

Example 191



[000802] To a solution of **188** (30 mg, 0.049 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (80 mg, 0.98 mmol) at 30 °C, then the reaction was stirred at 55 °C for 4 h. Then it was purified with prep-HPLC to obtain Compound **191**. LC-MS (m/z): 514 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 2.40-2.71 (m, 2H), 3.55-3.64 (m, 2H), 4.02-4.50 (m, 9H), 4.63-4.83 (m, 1H), 6.78-6.85 (m, 2H), 7.47-7.51 (m, 2H), 7.68-7.90 (m, 4H).

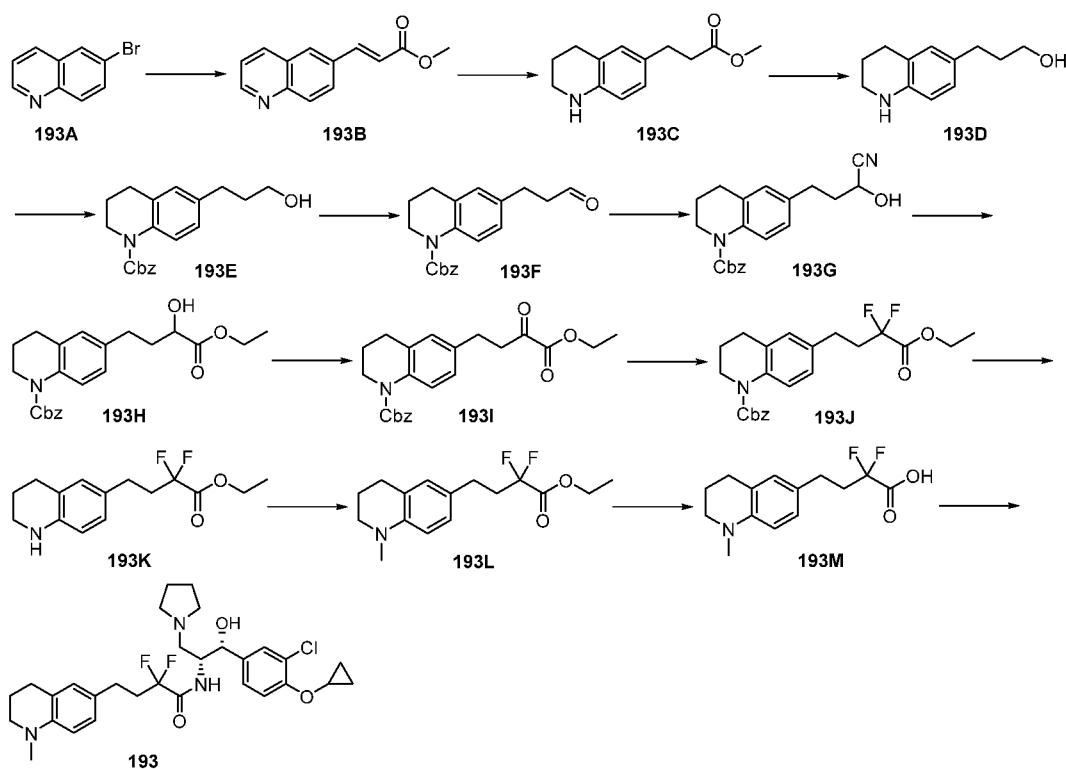
Example 192



[000803] To a solution of Intermediate **V** (100 mg, 0.29 mmol) and Compound **63D** (72 mg, 0.29 mmol) in DMF (10 mL) was added EDCI.HCl (84 mg, 0.44 mmol), and HOBT (59 mg, 0.44 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. TLC and LC-MS

showed the starting material was consumed completely, sat. sodium bicarbonate (5 mL) was added to the mixture and then extracted with EA (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), dried over anhydrous sodium sulfate, and concentrated to offer the crude product. The crude product was purified with prep-HPLC to offer Compound **192**. LC-MS (m/z): 571 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 1.31-1.34 (m, 6H), 2.00-2.03 (m, 3H), 2.14-2.17 (m, 2H), 2.55-2.61 (m, 2H), 2.64-2.72 (m, 1H), 2.78-2.98 (m, 2H), 3.15-3.25 (m, 2H), 3.51-3.55 (m, 1H), 3.60-3.66 (m, 2H), 3.74-3.79 (m, 3H), 4.62-4.65 (m, 1H), 4.92 (d, *J* = 2.8 Hz, 1H), 7.02 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.08-7.15 (m, 3H), 7.29 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H).

Example 193



[000804] A mixture of Compound **193A** (13 g, 62 mmol), methyl acrylate (16.0 g, 187 mmol), Pd(PPh₃)₂Cl₂ (2.0 g, 3.0 mmol), and K₂CO₃ (22 g, 156 mmol) in DMF (100 mL) was stirred at 100 °C for 12 h, then cooled to room temperature and filtered. The filtrate was treated with water (50 mL), extracted with DCM (100 mL x 2), washed with water (100 mL x 3) and brine (100 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193B**.

[000805] To a solution of Compound **193B** (11.5 g, 54 mmol) in MeOH (100 mL) was added Pd/C (1.1 g), then the mixture was stirred at room temperature for 12 h under H₂, then filtered. The filtrate was concentrated to furnish the crude Compound **193C**.

[000806] To a solution of AlLiH₄ (1.56 g, 4.1 mmol) in THF (100 mL) was added Compound **193C** (9.0 g, 4.1 mmol) in THF (20 mL) dropwise at -78 °C under nitrogen, then the mixture was stirred at -78 °C for 2 h and quenched with Na₂SO₄·10H₂O. Silica gel was added and the resultant mixture was filtered. The filtrate was concentrated to furnish the crude Compound **193D**.

[000807] To a solution of Compound **193D** (8 g, 42 mmol) in THF (80 mL) was added K₂CO₃ (5.8 g, 42 mmol), water (25 mL), and CbzCl (7.1 mL) under ice-cooling, and the resulting mixture was stirred at 25 °C for 12 h. EA (200 mL) was added. The organic layer was separated, dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193E**.

[000808] To a solution of Compound **193E** (12.2 g, 37.5 mmol) in DCM (100 mL) was added DMP (16.0 g, 37.5 mmol) at 0 °C, then the mixture was stirred at room temperature for 2 h, then filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193F**.

[000809] Compound **193F** (9.8 g, 30 mmol) was added to a solution of Na₂S₂O₅ (5.8 g, 30 mmol) in water (150 mL), then the mixture was stirred for 2 h at room temperature. And after the addition of NaCN (3 g, 6.1 mmol) the mixture was stirred for 15 h, diluted with EA (50 mL), extracted with EA (100 mL x 2), washed with sat. sodium bicarbonate (100 mL x 2) and brine (100 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193G**.

[000810] To a solution of Compound **193G** (10 g, 28 mmol) in EtOH (150 mL) cooled to 0 °C was bubbled a gentle stream of HCl gas (dried over con. H₂SO₄) for 5 h. Then the mixture was treated with water slowly at 0 °C, stirred at room temperature for 2 h, then extracted with DCM (100 mL x 2), washed with brine (100 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193H**.

[000811] To a solution of Compound **193H** (845 mg, 2.13 mmol) in DCM (20 mL) was added DMP (1.1 g, 2.55 mmol) at 0 °C, then the mixture was stirred at room temperature for 2 h, then filtered. The filtrate was concentrated and the resulting residue was purified with

flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193I**.

[000812] To a solution of Compound **193I** (730 mg, 1.84 mmol) in DCM (20 mL) was added DAST (1.5 g, 9.24 mmol), then the mixture was stirred at room temperature for 12 h, poured into ice water, extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193J**.

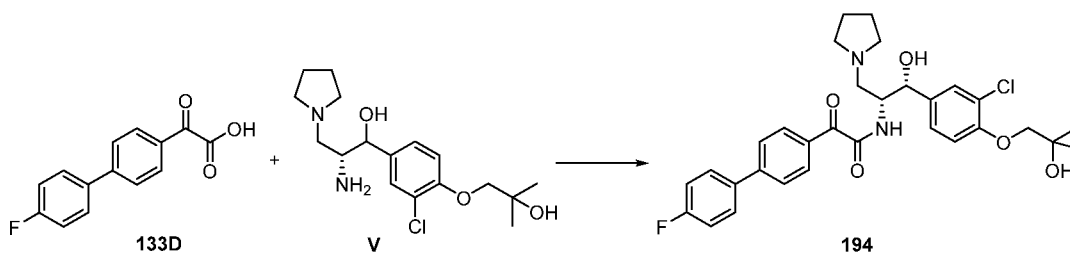
[000813] Compound **193J** (730 mg, 1.75 mmol) was dissolved in ethanol (20 mL), then Pd(OH)₂ (100 mg) was added, then the mixture was stirred at room temperature under H₂ overnight, then filtered and evaporated to furnish the product Compound **193K**.

[000814] To a solution of Compound **193K** (350 mg, 1.24 mmol) in CH₃CN (5 mL) was added CH₃I (526 mg, 3.71 mmol), then the mixture was stirred at 70 °C for 2 h, then cooled to room temperature, evaporated and purified with flash column chromatography on silica gel (20% ethyl acetate in petroleum) to furnish Compound **193L**.

[000815] To a solution of Compound **193L** (200 mg, 0.67 mmol) in THF (10 mL) was added LiOH (85 mg, 2.02 mmol) in water (2 mL), then the mixture was stirred at room temperature for 2 h, then evaporated to remove solvent. The mixture was treated with water (50 mL), adjusted to pH 2 with diluted HCl, then extracted with EA (50 mL x 2), washed with brine (50 mL), dried over sodium sulfate, and concentrated to furnish the Compound **193M**.

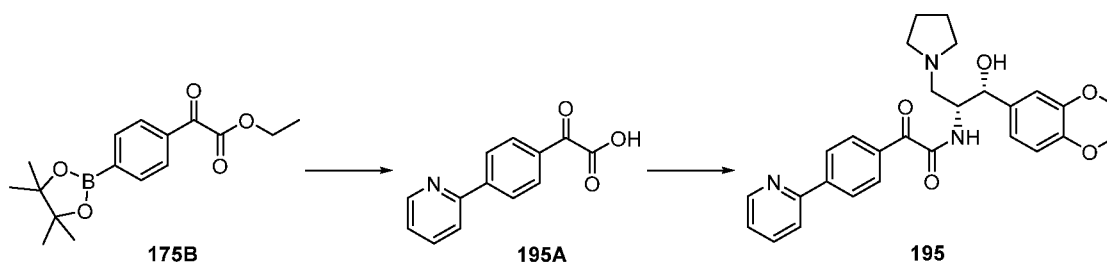
[000816] A mixture of Compound **193M** (96 mg, 0.36 mmol), Intermediate **G** (111 mg, 0.36 mmol), EDCI.HCl (103 mg, 0.54 mmol), and HOBt (73 mg, 0.54 mmol) in DCM (10 mL) was stirred at room temperature overnight. The mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), washed with water (50 mL x 2) and brine (50 mL), dried over sodium sulfate, concentrated, and purified with prep-HPLC to offer Compound **193**. LC-MS (m/z): 562 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.66-0.75 (m, 4H), 2.13 (s, 8H), 2.24-2.31 (m, 1H), 2.41-2.49 (m, 1H), 2.87-2.90 (m, 4H), 3.13 (s, 3H), 3.39-3.64 (m, 5H), 3.76 (s, 2H), 4.50 (s, 1H), 5.05 (s, 1H), 6.90 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 2H), 7.27 (s, 1H), 7.29 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 11.62 (s, 1H).

Example 194



[000817] To a solution of Intermediate V (100 mg, 0.29 mmol) in DMF (10 mL) was added HATU (167 mg, 0.44 mmol). After stirring for two hours at 25 °C, Compound **133D** (71 mg, 0.29 mmol) was added and the resultant mixture was stirred overnight at 25 °C. TLC and LC-MS showed the starting material was consumed completely, and sat. sodium bicarbonate (5 mL) was added to the mixture which was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (5 mL x 3) and brine (5 mL), dried over anhydrous sodium sulfate, and concentrated to offer the crude product. The crude product was purified with prep-HPLC to offer Compound **194**. LC-MS (m/z): 569 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 1.27-1.31 (m, 6H), 2.02-2.07 (m, 2H), 2.20-2.23 (m, 2H), 3.19-3.24 (m, 1H), 3.46-3.56 (m, 1H), 3.60-3.83 (m, 5H), 4.56-4.57 (m, 1H), 4.69-4.72 (m, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.64-7.67 (m, 3H), 7.71-7.74 (m, 3H).

Example 195

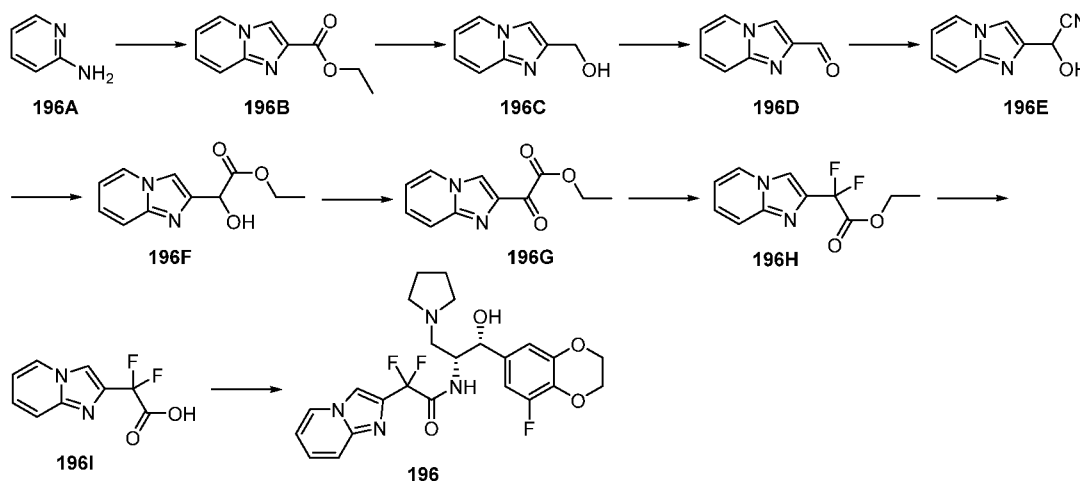


[000818] A mixture of Compound **175B** (608 mg, 2 mmol), 2-bromopyridine (314 mg, 2 mmol), Pd(dppf)Cl₂ (82 mg, 0.1 mmol), and Na₂CO₃ (636 mg, 6 mmol) in dioxane (15 mL) and water (2 mL) was stirred at 100 °C for 3 h and concentrated. The mixture was treated with water (50 mL) and extracted with DCM (50 mL x 3). The aqueous layer was acidified with 1 M HCl and extracted with DCM (50 mL x 3). The aqueous layer was purified with prep-HPLC to offer Compound **195A**.

[000819] A solution of Compound **195A** (100 mg, 0.44 mmol), Intermediate A (122 mg, 0.44 mmol), and HATU (335 mg, 0.88 mmol) in DMF (10 mL) was stirred at 25 °C for 16 h. Then it was treated with EA (50 mL), washed with water (20 mL x 3) and brine (20 mL x 1),

dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to obtain Compound **195**. LC-MS (m/z): 488 $[M+1]^+$; 1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.75 (s, 4H), 2.64 (m, 4H), 2.81-2.94 (m, 2H), 4.15 (s, 4H), 4.27 (s, 1H), 4.99 (s, 1H), 6.77 (m, 3H), 7.31 (m, 1H), 7.72 (s, 2H), 8.00 (m, 2H), 8.26 (m, 2H), 8.66 (m, 1H).

Example 196



[000820] A mixture of Compound **196A** (10 g, 106 mmol) and ethyl 3-bromo-2-oxopropanoate (22.8 g, 117 mmol) in THF (300 mL) was stirred at r.t. for 1 h, then heated to 80 °C overnight, cooled to room temperature, diluted with water (50 mL), adjusted to pH > 9 with Na_2CO_3 , and extracted with ethyl acetate (100 mL x 3). The ethyl acetate layers were combined and washed with brine (100 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to offer Compound **196B**.

[000821] To a suspension of $AlLiH_4$ (4.2 g, 111.3 mmol) in THF (200 mL) was added Compound **196B** (10.7 g, 55.6 mmol) in THF (50 mL) dropwise at 0 °C under nitrogen. Then the mixture was stirred at 0 °C for 30 min, quenched with $Na_2SO_4 \cdot 10H_2O$ and filtered. The filtrate was concentrated to furnish the crude Compound **196C**.

[000822] To a solution of Compound **196C** (6.9 g, 46.6 mmol) in DCM (140 mL) was added DMP (23.7 g, 55.9 mmol) at 0 °C, then the mixture was stirred at room temperature for 2 h, then filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to furnish Compound **196D**.

[000823] Compound **196D** (2.5 g, 17.1 mmol) was added to a solution of $Na_2S_2O_5$ (3.25 g, 17.1 mol) in water (300 mL), then the mixture was stirred for 2 h at room temperature. And

after the addition of NaCN (1.68 g, 34.2 mol), it was stirred again for 15 h, diluted with water (50 mL), stirred for 30 min, and filtered. The solid was collected, washed with water (50 mL), and dried to offer Compound **196E**.

[000824] To a solution of Compound **196E** (2.8 g, 16.2 mmol) in EtOH (80 mL) at 0 °C was bubbled a gentle stream of HCl gas (dried over con. H₂SO₄) for 5 h. Then the mixture was treated with ice-water slowly at 0 °C, stirred at room temperature for 2 h, adjusted to pH > 7 with sodium bicarbonate, extracted with DCM (100 mL x 2), washed with brine (100 mL), dried over sodium sulfate, and concentrated to furnish Compound **196F**.

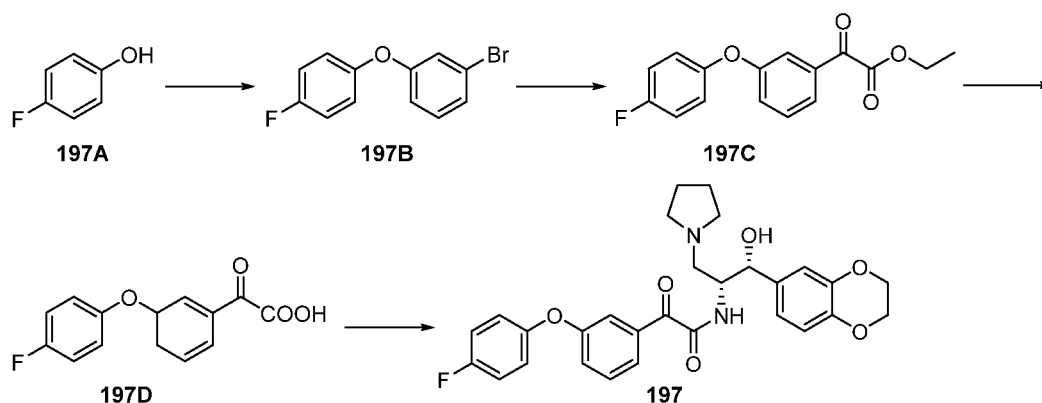
[000825] To a solution of Compound **196F** (1.7 g, 7.72 mmol) in DCM (30 mL) was added DMP (3.93 g, 9.26 mmol), then the mixture was stirred at 0 °C for 2 h, then filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to furnish Compound **196G**.

[000826] To a solution of Compound **196G** (1.68 g, 7.72 mmol) in DCM (60 mL) was added DAST (6.22 g, 38.6 mmol), then the mixture was stirred at room temperature overnight, poured into ice water, extracted with DCM (100 mL x 2), washed with brine (50 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to furnish Compound **196H**.

[000827] To a solution of Compound **196H** (960 mg, 4.0 mmol) in THF (20 mL) and water (2 mL) was added LiOH (252 mg, 6.0 mmol), then the mixture was stirred at room temperature overnight, then evaporated to remove solvent. The mixture was treated with water (50 mL), adjusted to pH 2 with diluted HCl, and purified with prep-HPLC to furnish the Compound **196I**.

[000828] A mixture of Compound **196I** (100 mg, 0.471 mmol), Intermediate **C** (140 mg, 0.471 mmol), and HATU (215 mg, 0.565 mmol) in DCM (2 mL) was stirred at room temperature overnight and concentrated. The residue was dissolved into DCM (50 mL), washed with water (50 mL) and brine (10 mL), dried over sodium sulfate, concentrated, and purified with chiral HPLC to offer Compound **196J**. LC-MS (m/z): 490 [M+]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.82-2.01 (m, 4H), 3.05-3.11 (m, 2H), 3.31-3.38 (m, 1H), 3.44-3.52 (m, 3H), 4.19-4.23 (m, 4H), 4.35-4.41 (m, 1H), 4.66-4.67 (m, 1H), 6.62 (s, 1H), 6.69-6.73 (m, 1H), 7.03-7.07 (m, 1H), 7.39-7.43 (m, 1H), 7.59-7.61 (m, 1H), 8.26 (s, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.68-8.70 (m, 1H), 9.41 (brs, 1H).

Example 197



[000829] An aqueous solution of KOH (4.9 g, 87.5 mmol) in water (10 mL) was added to a stirred solution of 4-fluorophenol **197A** (8.4 g, 75 mmol) in methanol (25 mL). When the addition was complete, the mixture was evaporated in vacuum and the residual solid was dissolved in 1-methyl-2-pyrrolidinone (30 mL) and 3-fluorobromobenzene (13 g, 75 mmol) was added and the mixture was refluxed for 24 hours, then cooled to room temperature, poured into water (150 mL) and extracted with ether (30 mL x 2). The combined extracts were dried over sodium sulfate and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **197B**.

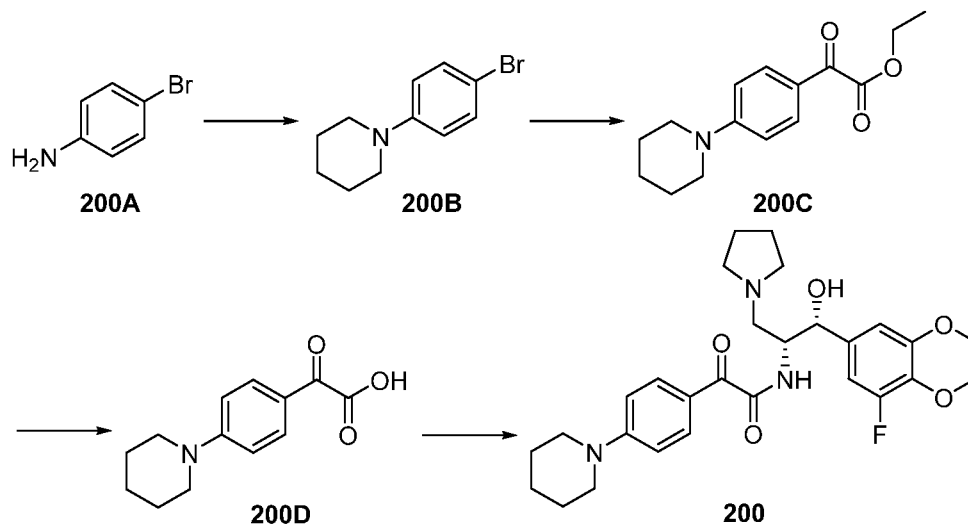
[000830] To a solution of Compound **197B** (2.66 g, 10 mmol) in THF (30 mL) was added dropwise n-BuLi solution (2.5 M, 4 mL, 10 mmol) at -78 °C under nitrogen. The mixture was stirred at -78 °C for 0.5 h, and then the mixture was added to a solution of diethyl oxalate (3 g, 20 mmol) in THF (20 mL) at -78 °C. The mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous NH₄Cl solution (40 mL). The reaction mixture was extracted with EA (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **197C**.

[000831] Lithium hydroxide (420 mg, 10 mmol) was added to a solution of Compound **197C** (1.44 g, 5 mmol) in EtOH (20 mL) and water (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was added 1 N HCl to adjust to pH 7 and concentrated in vacuum. The residue was extracted with EA (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **197D**.

[000832] A mixture of Compound **197D** (262 mg, 1 mmol), Intermediate A (278 mg, 1 mmol), and HATU (760 mg, 2 mmol) in DMF (20 mL) was stirred at 25 °C for 16 h. Then it

(m, 1H), 4.38-4.45 (m, 1H), 4.75-4.76 (m, 1H), 7.04-7.08 (m, 1H), 7.15-7.21 (m, 2H), 7.30 (d, $J = 1.6$ Hz, 1H), 7.39-7.44 (m, 1H), 7.62-7.64 (m, 1H), 8.23 (s, 1H), 8.59 (d, $J = 7.2$ Hz, 1H), 8.69-8.71 (m, 1H), 9.52 (brs, 1H).

Example 200



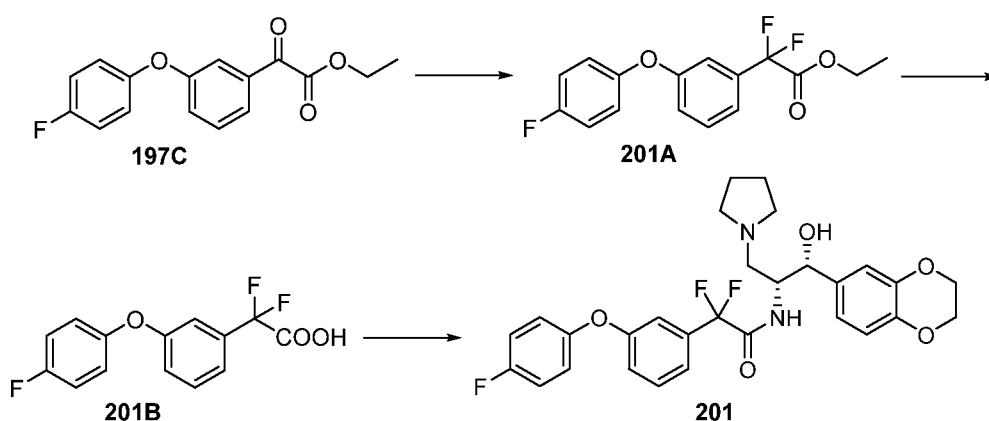
[000835] Compound **200A** (1.72 g, 10.0 mmol), 1,5-dibromopentane (2.52 g, 11.0 mmol), and K_2CO_3 (1.51 g, 11.0 mmol) were taken in water (5 mL) and heated at 100 °C for 20 min. in a microwave oven. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (30 mL x 2). The combined organic extracts were dried over sodium sulfate, evaporated, and purified with flash column chromatography on silica gel (petroleum ether in ethyl acetate, 10% v/v) to offer Compound **200B**.

[000836] To a solution of Compound **200B** (240 mg, 1.0 mmol) in THF (25 mL) was added dropwise n-BuLi (2.5 M in hexane, 0.48 mL) at -60 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min. at the same temperature. The resulting mixture was added to the solution of diethyl oxalate (292 mg, 2.0 mmol) in THF (25 mL) at -60 °C. The reaction mixture was stirred for 2 hours at -60 °C, quenched with sat NH_4Cl , and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with brine (50 mL), dried over sodium sulfate, evaporated, and purified with prep-TLC (petroleum ether in ethyl acetate, 20% v/v) to yield Compound **200C**.

[000837] To a solution of Compound **200C** (97 mg, 0.37 mmol) in MeOH (5 mL) was added $LiOH \cdot H_2O$ (18 mg, 0.42 mmol) and water (0.5 mL). The reaction mixture was stirred overnight at 15 °C, neutralized with 1 N HCl, and evaporated. The residue was dissolved in water (5 mL), extracted with ethyl acetate (10 mL x 2), dried over sodium sulfate, filtered, and evaporated to offer Compound **200D**.

[000838] To a solution of Compound **200D** (58 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added Intermediate **C** (74 mg, 0.25 mmol) and HATU (142 mg, 0.375 mmol). The reaction mixture was stirred overnight at 15 °C, evaporated and purified with prep-HPLC to offer Compound **200**. LC-MS: (m/z) 512 [M+]⁺; ¹H-NMR (CD_3OD , 400 MHz) major characteristic peaks: δ (ppm) 1.71 (br, 6H), 1.95-2.07 (m, 4H), 2.18-2.21 (m, 2H), 3.52-3.53 (m, 4H), 3.64-3.71 (m, 4H), 4.21-4.30 (m, 5H), 4.88-4.89 (m, 2H), 6.76-6.82 (m, 2H), 6.91-6.93 (m, 2H), 7.57-7.63 (m, 2H).

Example 201

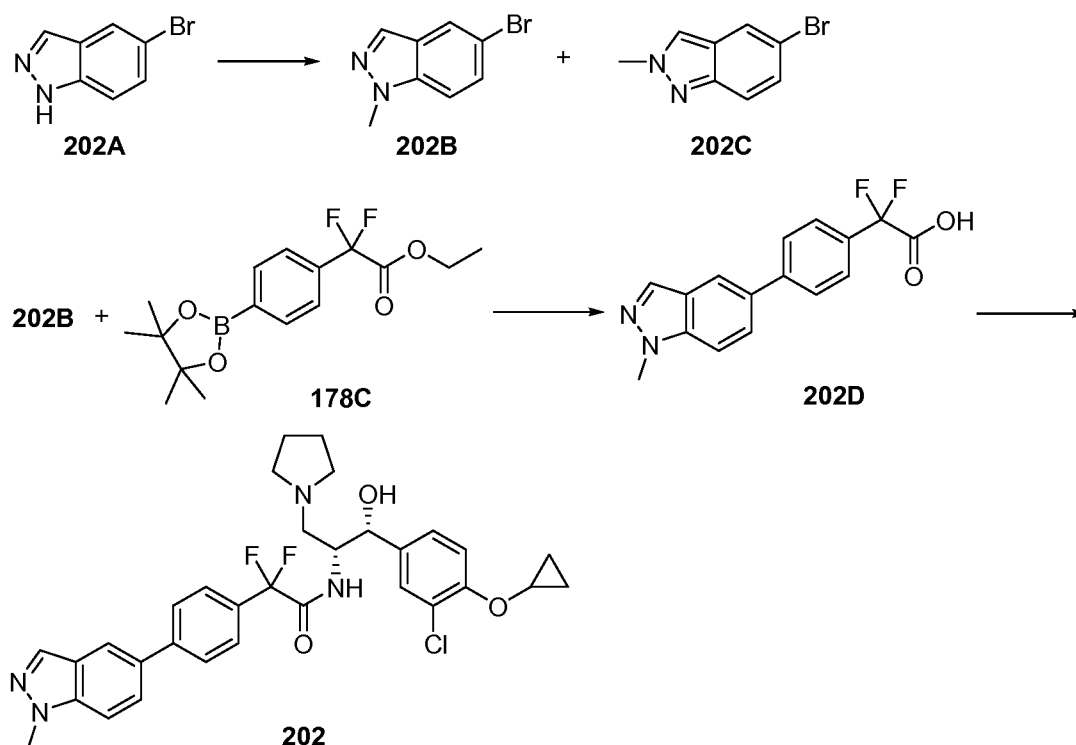


[000839] To a solution of Compound **197C** (2.89 g, 10 mmol) in DCM (120 mL) was added dropwise DAST (4 mL) at room temperature. The mixture was stirred at room temperature overnight. Then it was quenched with ice, extracted with DCM (30 mL x 3), washed with water (50 mL x 3) and brine (50 x 2 mL), dried over anhydrous sodium sulfate, and evaporated to obtain Compound **201A**.

[000840] Lithium hydroxide (420 mg, 10 mmol) was added to a solution of Compound **201A** (1.55 g, 5 mmol) in EtOH (20 mL) and water (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was added 1 N HCl to adjust to pH 7 and concentrated in vacuum. The residue was extracted with EA (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **201B**.

[000841] A mixture of Compound **201B** (141 mg, 0.5 mmol), Intermediate A (139 mg, 0.5 mmol), HATU (380 mg, 1 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. Then it was diluted with DCM (70 mL), washed with water (50 mL x 3) and brine (50 x 2 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to obtain Compound **201**. LC-MS (m/z): 543 [M+]⁺; ¹H-NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.71-1.80 (m, 4H), 2.64-2.69 (m, 4H), 2.94 (d, $J = 4.4$ Hz, 2H), 4.14 (m, 1H), 4.22 (m, 4H), 5.02 (s, 1H), 6.71-6.73 (m, 1H), 6.78-6.82 (m, 3H), 6.98-7.07 (m, 7H), 7.30-7.32 (m, 1H).

Example 202



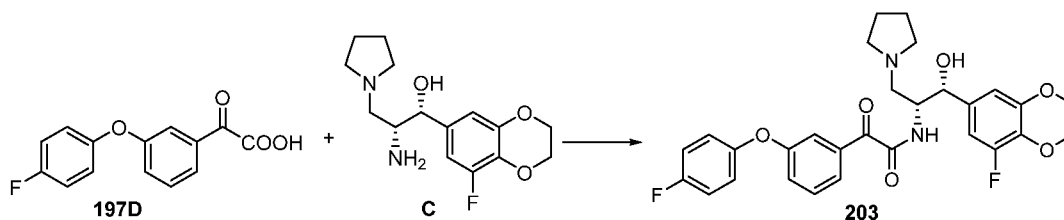
[000842] To a solution of 5-bromo-1H-indazole, **202A**, (4.92 g, 25.0 mmol) in THF (300 mL) at 0 °C was added NaH (1.10 g, 27.5 mmol). The reaction solution was stirred at this temperature for 1 hour before methyl iodide (5.32 g, 37.5 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature slowly, stirred for 2 hours, and quenched with water and concentrated in *vacuo*. The residue was diluted with water and extracted with dichloromethane (80 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **202B** and Compound **202C**.

[000843] A mixture of Compound **178C** (153 mg, 0.47 mmol), **202B** (100 mg, 0.47 mmol), Pd(dppf)₂Cl₂ (20 mg, 0.02 mmol), and K₂CO₃ (195 mg, 1.41 mmol) in dioxane (3 mL) and water (3 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (50 mL). The mixture was filtered through celite, then the filtrate was treated with water (40 mL), extracted with ethyl acetate (50 mL x 2). The water layer was purified with flash chromatography to furnish the Compound **202D**.

[000844] A mixture of Compound **202D** (90 mg, 0.30 mmol), EDCI.HCl (86 mg, 0.45 mmol), HOBT (61 mg, 0.45 mmol), and Intermediate **G** (93 mg, 0.30 mmol) in DCM (5 mL) was stirred for 18 h at 10 °C. Then the mixture was diluted by ethyl acetate (50 mL), washed

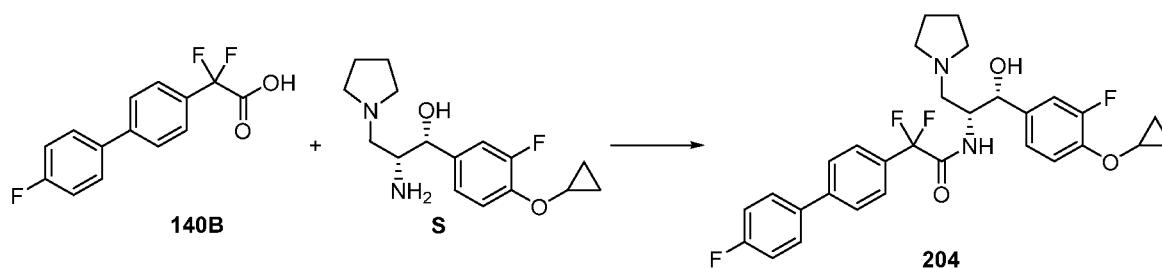
with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **202**. LC-MS (m/z): 595 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 0.49-0.51 (m, 4H), 2.03-2.17 (m, 4H), 3.16-3.31 (m, 2H), 3.51-3.74 (m, 5H), 4.11 (s, 3H), 4.64 (d, *J* = 10.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.36-7.38 (m, 3H), 7.65-7.71 (m, 3H), 7.79 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.08-8.09 (m, 2H).

Example 203



[000845] A mixture of Compound **197D** (131 mg, 0.5 mmol), Intermediate **C** (154 mg, 0.5 mmol), HATU (380 mg, 1 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. Then it was diluted with DCM (20 mL), washed with water (50 mL x 3) and brine (50 x 2 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to obtain Compound **203**. LC-MS (m/z): 539 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.08-2.19 (m, 4H), 2.87-3.04 (m, 4H), 3.45-3.56 (m, 2H), 3.87 (m, 1H) 4.20-4.28 (m, 4H), 4.47 (m, 1H), 5.05 (s, 1H), 6.71-6.76 (m, 2H), 6.87-6.98 (m, 4H), 6.98-7.05 (m, 1H), 7.27 (m, 1H), 7.35-7.42 (m, 1H), 7.65 (s, 1H), 7.90-7.93 (m, 1H), 11.77 s, 1H).

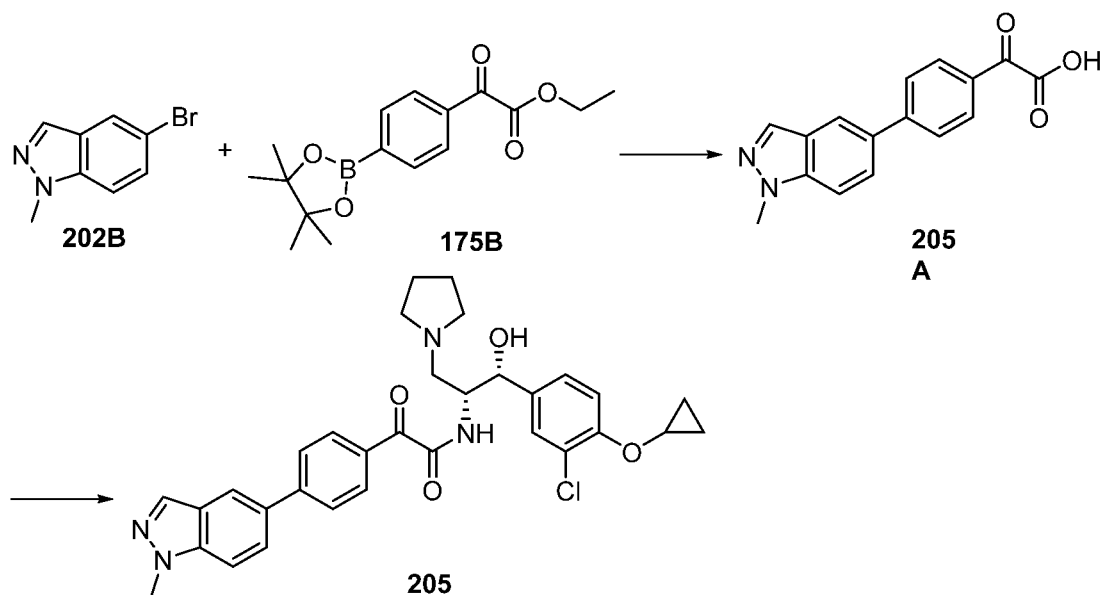
Example 204



[000846] A mixture of Intermediate **S** (88 mg, 0.30 mmol), Compound **140B** (78 mg, 0.30 mmol), EDCl.HCl (86 mg, 0.45 mmol), and HOBT (60 mg, 0.45 mmol) in dichloromethane (10 mL) was stirred at 10 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum, and purified with prep-HPLC to obtain Compound **204**. LC-MS (m/z): 543 [M+]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.49-0.62 (m, 4H), 2.04 (s, 2H), 2.18 (s, 2H), 3.17 (s, 1H), 3.27 (s, 1H), 3.54-3.71 (m, 4H), 3.78 (s, 1H), 4.58 (d, *J* = 12 Hz,

1H), 4.89 (s, 1H), 6.95 (d, $J = 8$ Hz, 1H), 7.04 (t, $J = 8$ Hz, 2H), 7.22 (t, $J = 8$ Hz, 2H), 7.39 (d, $J = 8$ Hz, 2H), 7.63 (d, $J = 8$ Hz, 2H), 7.72 (t, $J = 8$ Hz, 2H).

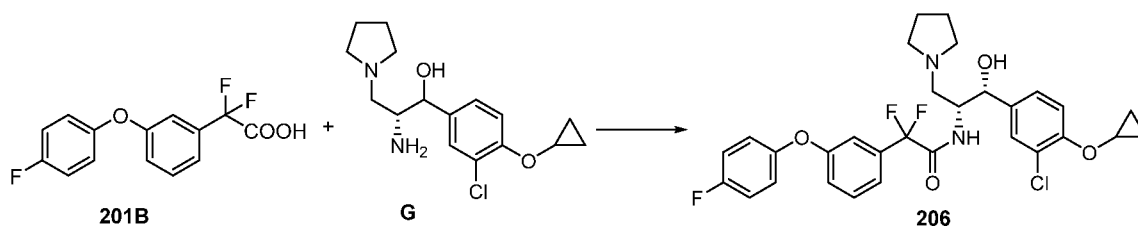
Example 205



[000848] A mixture of Compound **175B** (288 mg, 0.95 mmol), **202B** (200 mg, 0.95 mmol), Pd(dppf)Cl₂ (40 mg, 0.05 mmol), and K₂CO₃ (393 mg, 2.85 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 90 °C for 3 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (50 mL). The mixture was filtered through celite, then the filtrate was treated with water (40 mL), extracted with ethyl acetate (50 mL x 2). The water layer was adjusted to pH 3 by aqueous HCl solution (3 N), extracted with ethyl acetate (50 mL x 2) and the ethyl acetate layer was washed with water (50 mL x 2), dried over sodium sulfate, filtered, and concentrated to furnish the Compound **205A**.

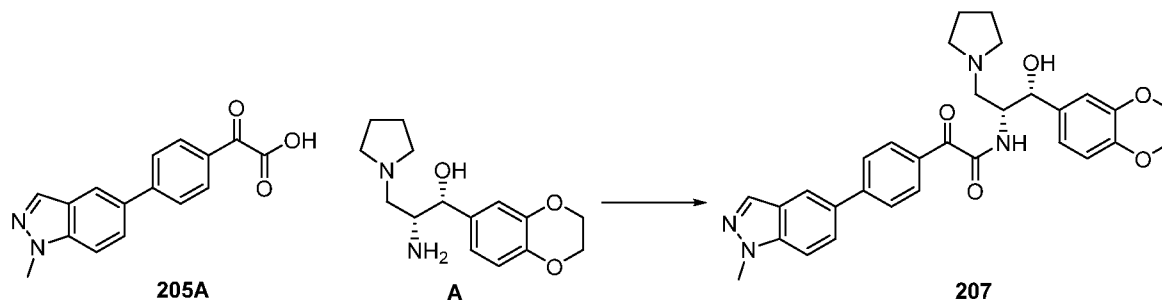
[000849] A mixture of Compound **205A** (120 mg, 0.43 mmol), HATU (247 mg, 0.65 mmol), and Intermediate **G** (133 mg, 0.43 mmol) in DMF (5 mL) was stirred for 18 h at 10 °C. Then the mixture was purified with prep-HPLC to furnish Compound **205**. LC-MS (m/z): 573 [M+]⁺; ¹H-NMR (CD₃OD, 400 MHz) major characteristic peaks: δ (ppm) 0.71-0.83 (m, 4H), 2.05-2.23 (m, 4H), 3.24-3.34 (m, 2H), 3.59-3.88 (m, 5H), 4.12 (s, 3H), 4.72-4.75 (m, 1H), 5.02 (d, $J = 2.4$ Hz, 1H), 7.40 (s, 2H), 7.50 (s, 1H), 7.67-7.75 (m, 5H), 7.81 (dd, $J = 8.8, 1.2$ Hz, 1H), 8.12-8.13 (m, 2H).

Example 206



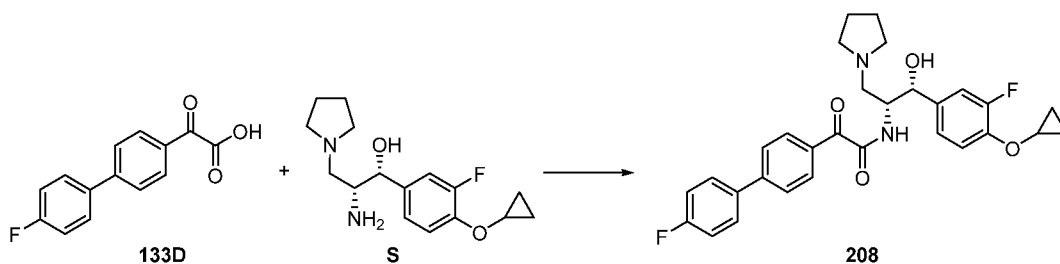
[000850] A mixture of Compound **133D** (141 mg, 0.5 mmol), Intermediate **G** (155 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in DMF (5 mL) was stirred at 25 °C overnight. The reaction mixture was diluted with DCM (70 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified with prep-HPLC to furnish Compound **206**. LC-MS (ESI) m/z : 575 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.66-0.81 (m, 4H), 2.00-2.15 (m, 4H), 3.12-3.23 (m, 2H), 3.51-3.65 (m, 3H), 3.73-3.77 (m, 2H), 4.54 (m, 1H), 4.87 (s, 1H), 7.02-7.07 (m, 5H), 7.10-7.15 (m, 4H), 7.30 (s, 1H), 7.38 (m, 1H).

Example 207



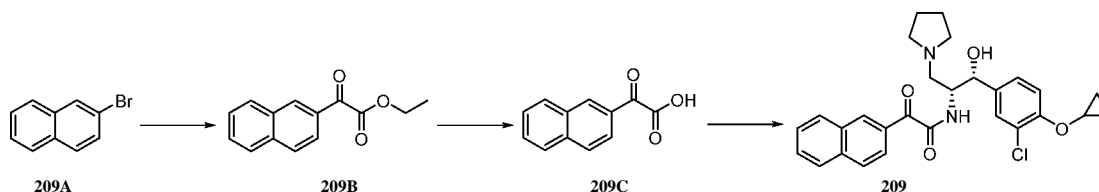
[000851] A mixture of Compound **205A** (144 mg, 0.51 mmol), HATU (293 mg, 0.77 mmol), and Intermediate **A** (142 mg, 0.51 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, evaporated, and purified with prep-HPLC to yield Compound **207**. LC-MS (ESI) m/z : 541 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.01-2.24 (m, 4H), 3.19-3.31 (m, 2H), 3.52-3.56 (m, 1H), 3.68-3.72 (m, 2H), 3.81-3.88 (m, 1H), 4.10-4.21 (m, 7H), 4.65-4.69 (m, 1H), 4.87 (s, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.91-6.94 (m, 1H), 6.97 (d, $J = 2.0$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.79-7.83 (m, 3H), 7.87-7.89 (m, 2H), 8.12-8.13 (m, 2H).

Example 208



[000852] A mixture of Intermediate **S** (118 mg, 0.40 mmol), Compound **133D** (97 mg, 0.40 mmol), and HATU (228 mg, 0.60 mmol) in dichloromethane (10 mL) was stirred at 30 °C for 15 h. Then it was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in vacuum, and purified with prep-HPLC to obtain Compound **208**. LC-MS (*m/z*): 521 [*M*+]⁺; ¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 0.67-0.82 (m, 4H), 2.05 (s, 2H), 2.21 (s, 2H), 3.10-3.27 (m, 2H), 3.56-3.60 (m, 1H), 3.68-3.74 (m, 2H), 3.80-3.88 (m, 2H), 4.70 (d, *J* = 8 Hz, 1H), 4.98 (s, 1H), 7.19-7.27 (m, 4H), 7.37 (t, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.72-7.78 (m, 4H).

Example 209

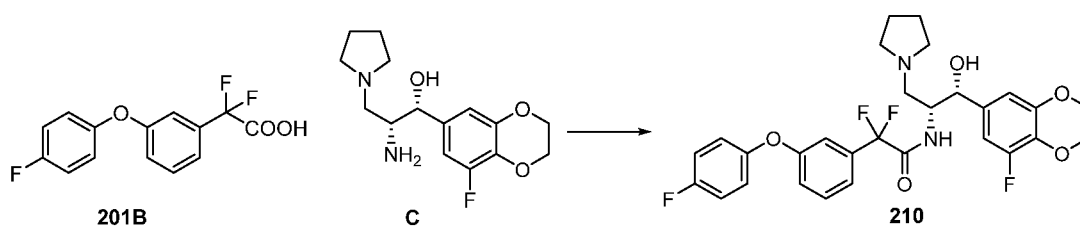


[000853] A mixture of Compound **209A** (1.0 g, 4.85 mmol), magnesium chips (0.17 g, 7.0 mmol) and THF (15 mL) was stirred at 50 °C for 1 h, and diethyl oxalate (3 mL) was added. The mixture was stirred at 60 °C for 3 h, and saturated NH₄Cl solution (10 mL) was added. It was extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified flash with column chromatography on silica gel (10% ethyl acetate in petroleum ether) to afford Compound **209B**.

[000854] To a solution of Compound **209B** (1.4 g, 6.1 mmol) in THF (15 mL) was added LiOH (390 mg, 9.0 mmol) in water (15 mL) at -10 °C, and the mixture was stirred at this temperature for 5 h. The reaction mixture was treated with ice water (20 mL) and extracted with ethyl acetate (50 mL). The water layer was adjusted to pH 2 with 1 M HCl and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resulting solid was washed with petroleum ether and filtered to furnish the crude Compound **209C**.

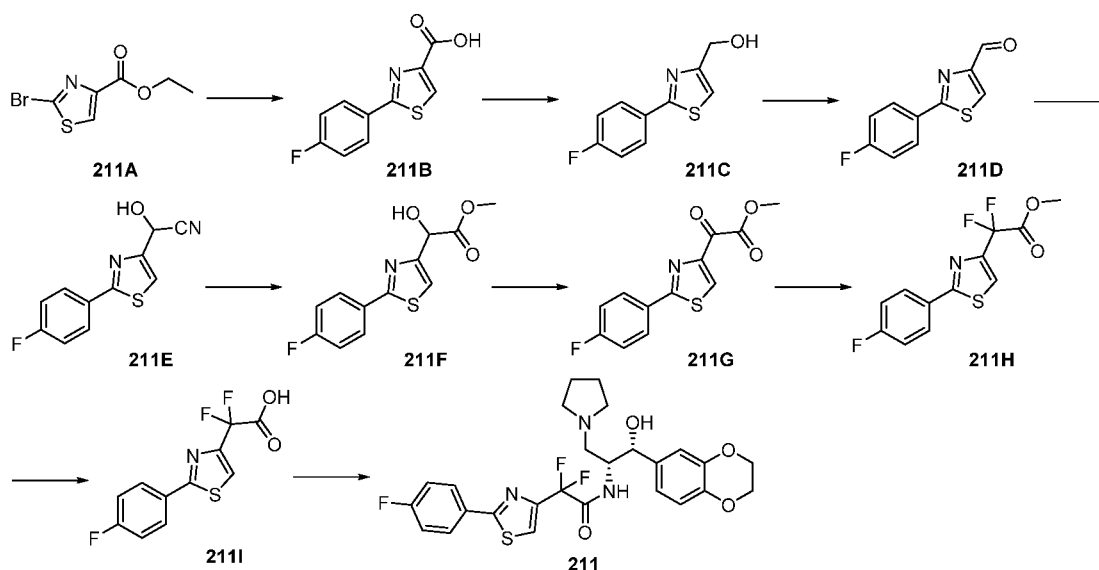
[000855] A mixture of Compound **209C** (160 mg, 0.8 mmol), HATU (608 mg, 1.6 mmol), DMF (6.5 mL), and Intermediate **G** (298 mg, 0.96 mmol) in DCM (8 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to afford Compound **209**. LC-MS (ESI) m/z : 493 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.5-0.75 (m, 4H), 2.06-2.21 (m, 4H), 3.26-3.30 (m, 1H), 3.58-3.82 (m, 6H), 4.73 (d, $J = 8.0$ Hz, 1H), 5.0 (s, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.40 (d, $J = 8.8$ Hz, 1H), 7.51 (s, 1H), 7.57-7.71 (m, 2H), 7.84-7.95 (m, 4H), 8.26 (s, 1H).

Example 210



[000856] A mixture of Compound **201B** (141 mg, 0.5 mmol), Intermediate **C** (148 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with DCM (70 mL), and washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified with prep-HPLC to yield Compound **210**. LC-MS (ESI) m/z : 561 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.00-2.15 (m, 4H), 3.14-3.26 (m, 2H), 3.50-3.64 (m, 3H), 3.75 (m, 1H), 4.21-4.23 (m, 4H), 4.54 (m, 1H), 4.79 (s, 1H), 6.60-6.63 (m, 2H), 7.05-7.09 (m, 5H), 7.15-7.17 (m, 2H), 7.34 (t, $J = 8.0$ Hz, 1H).

Example 211



[000857] A mixture of Compound **211A** (10.00 g, 42.37 mmol), 4-fluorophenylboronic acid (5.51 g, 42.37 mol), $\text{PdCl}_2(\text{PPh}_3)_2$ (1.49 g, 2.12 mmol), and sodium bicarbonate (10.68 g, 127.1 mmol) in dioxane (150 mL) and water (30 mL) was stirred at 90 °C for 16 h. It was adjusted to pH 1 with aqueous HCl solution (6 N, 10 mL). The mixture was extracted with dichloromethane (100 mL x 3). The combined organic phases were washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 0% to 8% v/v) to yield Compound **211B**.

[000858] To a solution of Compound **211B** (2.00 g, 7.97 mmol) in THF (50 mL) was added LiAlH_4 (303 mg, 7.97 mmol) carefully. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched slowly with ice water (4 mL), filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 50% v/v) to afford Compound **211C**.

[000859] To a solution of Compound **211C** (4.30 g, 20.57 mmol) in DCM (100 mL) was added Dess-Martin periodinane (9.60 g, 22.63 mmol) carefully. The mixture was stirred at 25 °C for 16 h. The mixture was filtered to remove the solid and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to afford Compound **211D**.

[000860] To a solution of Compound **211D** (1.80 g, 3.69 mmol) and NaCN (352 mg, 17.39 mmol) in methanol (20 mL) was added AcOH (222 mg, 3.69 mmol) carefully. The mixture was stirred at 25 °C for 16 h, quenched with ice water to form a solid, filtered, and dried to afford Compound **211E**.

[000861] A mixture of Compound **211E** (1.20 g, 5.13 mmol) in methanol (20 mL) under HCl gas was stirred at 20 °C for 16 h. The reaction mixture was quenched with ice water and extracted with dichloromethane (50 mL x 3). The combined organic phases were washed with water (150 mL) and brine (150 mL), dried over anhydrous sodium sulfate, and evaporated to furnish Compound **211F**.

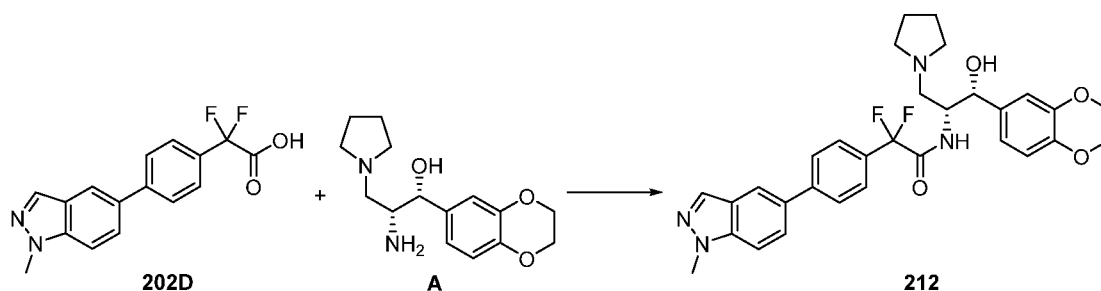
[000862] To a solution of Compound **211F** (1.20 g, 4.49 mmol) in DCM (20 mL) was added Dess-Martin periodinane (1.91 g, 4.49 mmol) carefully. The mixture was stirred at 25 °C for 16 h. The mixture was filtered to remove the solid. The filtrate was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30% v/v) to yield Compound **211G**.

[000863] To a solution of Compound **211G** (1.00 g, 3.80 mmol) in DCM (10 mL) was added dropwise DAST (3.06 g, 19.00 mmol). The mixture was stirred at 25 °C for 16 h and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 15% v/v) to furnish Compound **211H**.

[000864] A solution of Compound **211H** (900 mg, 3.14 mmol) and aqueous LiOH·H₂O solution (1 N, 4.7 mL, 4.70 mmol) in THF (10 mL) was stirred at 25 °C for 2 h. The mixture was adjusted to pH 1 with aqueous HCl solution (6 N, 5 mL), diluted with ice water (50 mL) to form a solid, filtered, and dried to yield Compound **211I**.

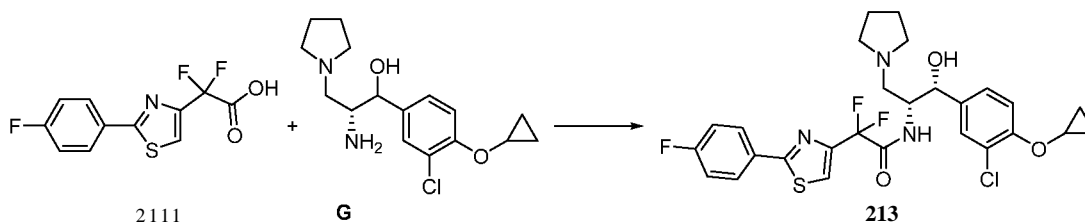
[000865] A mixture of Compound **211I** (100 mg, 0.37 mmol), Intermediate A (102 mg, 0.37 mmol), EDCI (106 mg, 0.56 mmol), and HOBt (76 mg, 0.56 mmol) in dichloromethane (5 mL) and triethylamine (0.2 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **211**. LC-MS (ESI) m/z: 534 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 1.92-2.13 (m, 4H), 3.12-3.22 (m, 2H), 3.55-3.65 (m, 3H), 3.72-3.78 (m, 1H), 4.12 (s, 4H), 4.50-4.55 (m, 1H), 4.80 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.75-6.81 (m, 2H), 7.26 (t, *J* = 8.8 Hz, 2H), 7.85 (s, 1H), 8.04-8.08 (m, 2H).

Example 212



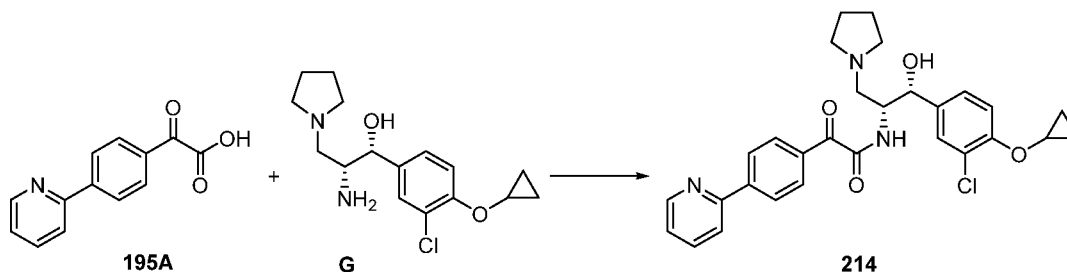
[000866] A mixture of Compound **202D** (50 mg, 0.16 mmol), EDCI (48 mg, 0.25 mmol), HOBt (34 mg, 0.25 mmol), and Intermediate **A** (28 mg, 0.26 mmol) in DCM (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to afford Compound **212**. LC-MS (ESI) *m/z*: 563 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 2.02-2.18 (m, 4H), 3.14-3.24 (m, 2H), 3.53-3.65 (m, 3H), 3.77-3.84 (m, 1H), 4.06 (s, 4H), 4.12 (s, 3H), 4.55-4.57 (m, 1H), 4.82 (d, *J* = 3.2 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.77 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.80 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.08-8.09 (m, 1H), 8.10 (d, *J* = 1.2 Hz, 1H).

Example 213



[000867] A mixture of Compound **2111** (100 mg, 0.37 mmol), Intermediate **G** (115 mg, 0.37 mmol), HOBt (76 mg, 0.56 mmol), and EDCI (106 mg, 0.56 mmol) in dichloromethane (5 mL) and triethylamine (0.2 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to afford Compound **213**. LC-MS (ESI) *m/z*: 566 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.62-0.75 (m, 4H), 1.96-2.14 (m, 4H), 3.13-3.26 (m, 2H), 3.60-3.67 (m, 4H), 3.73-3.78 (m, 1H), 4.54-4.58 (m, 1H), 4.88 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.24-7.29 (m, 3H), 7.34 (s, 1H), 7.85 (s, 1H), 8.04-8.08 (m, 2H).

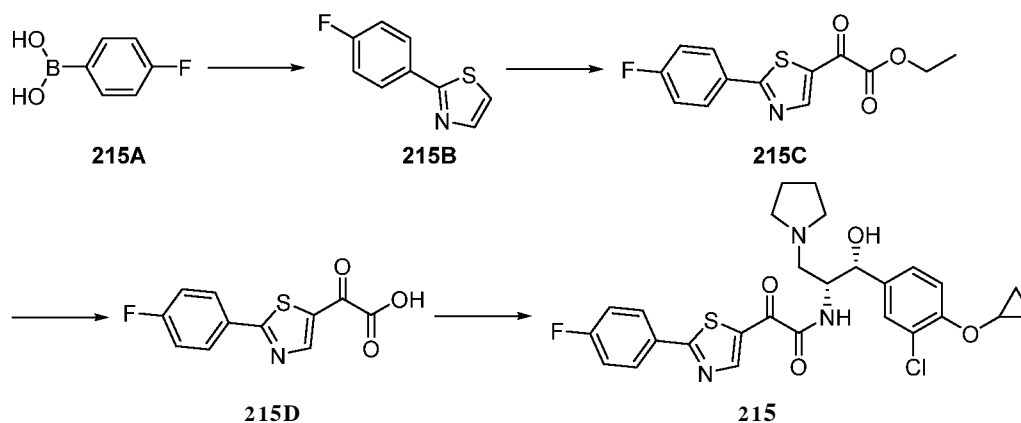
Example 214



[000868] A mixture of Compound **195A** (150 mg, 0.66 mmol), Intermediate **G** (205 mg, 0.66 mmol), HATU (500 mg, 1.32 mmol), and DIPEA (0.2 mL) in DMF (20 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with

water (20 mL x 3) and brine (20 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC and chiral HPLC to furnish the desired product, which was further purified with prep-HPLC to yield Compound **214**. LC-MS (ESI) m/z : 520 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.62-0.81 (m, 4H), 2.05-2.23 (m, 4H), 3.15-3.28 (m, 2H), 3.58-3.85 (m, 5H), 4.69-4.72 (m, 1H), 4.99 (m, 1H), 7.09-8.06 (m, 10H), 8.72 (m, 1H).

Example 215



[000869] A mixture of Compound **215A** (2.05 g, 14.6 mmol), 2-bromothiazole (2 g, 12.2 mmol), K_2CO_3 (3.12 g, 24.4 mmol) and $Pd(PPh_3)_2Cl_2$ (856 mg, 1.22 mmol) in dioxane (40 mL) and water (4 mL) was stirred at 80 °C for 2 h. The mixture was cooled to room temperature, diluted with water (50 mL), extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water (100 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **215B**.

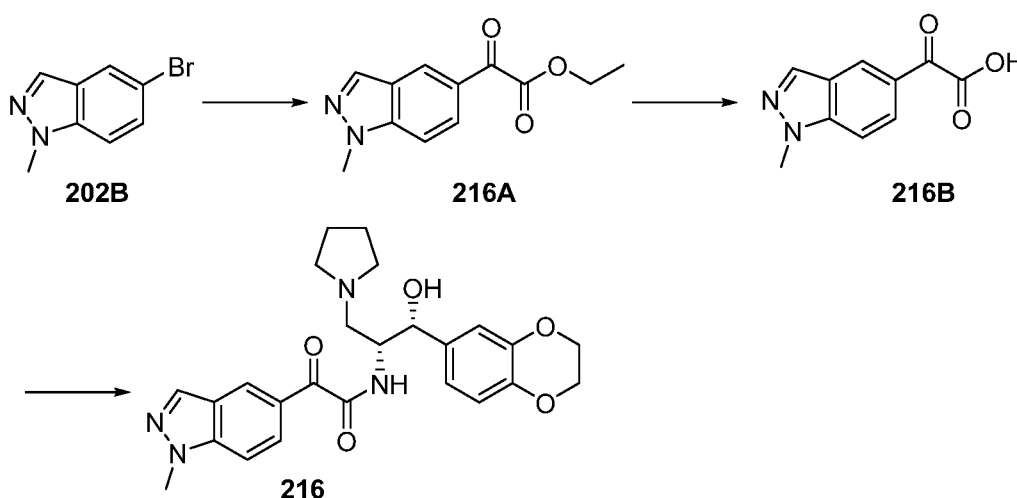
[000870] To a solution of Compound **215B** (1.4 g, 7.8 mmol) in THF (30 mL) was added *n*-BuLi (3.4 mL, 8.6 mmol) dropwise at -78 °C. The mixture was stirred for 15 min and diethyl oxalate (2.28 g, 15.6 mmol) was added at -78 °C. The mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford Compound **215C**.

[000871] To a solution of Compound **215C** (400 mg, 1.43 mmol) in THF (10 mL) and water (1 mL) was added LiOH (90 mg, 2.15 mmol). The mixture was stirred at room temperature overnight, diluted with water (50 mL), and extracted with ethyl acetate (50 mL). The aqueous layer was adjusted to pH 2 with 1 M HCl. The precipitate was collected with filtration and dried to furnish Compound **215D**.

[000872] To a mixture of Compound **215D** (97 mg, 0.386 mmol) in DCM (2 mL) was added HATU (176 mg, 0.463 mmol) and Intermediate **G** (120 mg, 0.386 mmol). The mixture

was stirred at room temperature overnight. The mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to afford Compound **215**. LC-MS (ESI) m/z : 544 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.61-0.66 (m, 2H), 0.76-0.82 (m, 2H), 1.80-1.88 (m, 2H), 1.96-2.03 (m, 2H), 3.09-3.17 (m, 2H), 3.30-3.37 (m, 1H), 3.47-3.60 (m, 3H), 3.87-3.91 (m, 1H), 4.41-4.47 (m, 1H), 4.79-4.80 (m, 1H), 6.02-6.07 (m, 1H), 7.28-7.45 (m, 5H), 8.14-8.18 (m, 2H), 8.63 (d, $J = 9.2$ Hz, 1H), 8.81 (s, 1H), 9.10-9.18 (m, 1H).

Example 216



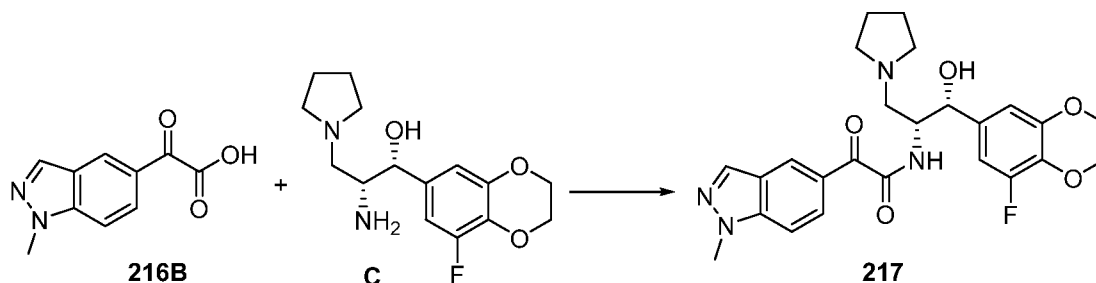
[000874] To a solution of Compound **202B** (400 mg, 1.89 mmol) in THF (10 mL) was added *n*-BuLi (2.5 *N*, 0.76 mL) under nitrogen at -78 °C, and the resultant mixture was stirred for 30 min. And then diethyl oxalate (0.65 mL, 4.73 mmol) was added to above mixture, and the resultant mixture was stirred at -78 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), and extracted with ethyl acetate (50 mL x 2), washed with saturated aqueous sodium bicarbonate solution (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **216A**.

[000875] To a solution of Compound **216A** (490 mg, 2.11 mmol) in methanol (5 mL) was added a solution of $LiOH \cdot H_2O$ (177 mg, 4.22 mmol) in water (5 mL), and the mixture was stirred at room temperature overnight. The crude product was purified with reverse phase chromatography using eluent (methanol in water, from 0% to 7% v/v) to furnish Compound **216B**.

[000876] A mixture of Compound **216B** (100 mg, 0.49 mmol), HATU (279 mg, 0.74 mmol), and Intermediate **A** (136 mg, 0.49 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to afford Compound **216**. LC-MS (ESI) m/z : 465 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.03-2.07 (m, 2H), 2.18-2.22 (m, 2H),

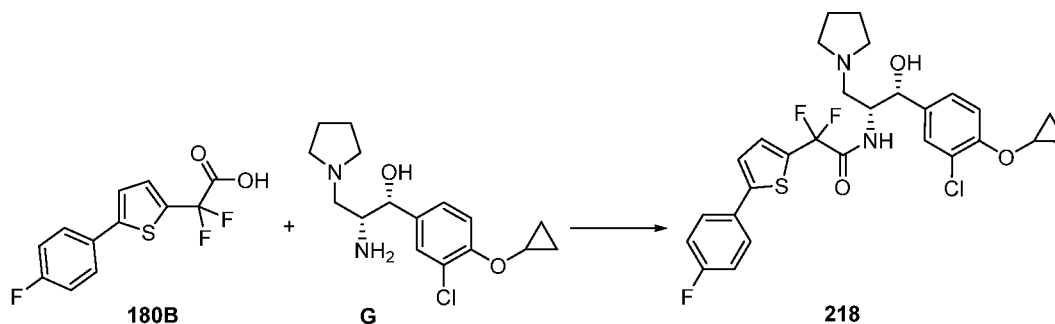
3.22-3.27 (m, 2H), 3.54-3.58 (m, 1H), 3.67-3.73 (m, 2H), 3.79-3.85 (m, 1H), 4.03-4.24 (m, 7H), 4.68-4.71 (m, 1H), 4.92 (s, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.93 (dd, $J = 8.4, 2.0$ Hz, 1H), 6.97 (d, $J = 1.6$ Hz, 1H), 7.63 (d, $J = 9.2$ Hz, 1H), 7.96 (dd, $J = 8.8, 1.6$ Hz, 1H), 8.11 (s, 1H), 8.20 (s, 1H).

Example 217



[000877] A mixture of Compound **216B** (100 mg, 0.49 mmol), HATU (279 mg, 0.74 mmol), and Intermediate C (138 mg, 0.49 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to afford Compound **217**. LC-MS (ESI) m/z : 483 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.03-2.07 (m, 2H), 2.20-2.22 (m, 2H), 3.20-3.29 (m, 2H), 3.55-3.59 (m, 1H), 3.67-3.73 (m, 2H), 3.78-3.84 (m, 1H), 4.08-4.13 (m, 4H), 4.20-4.31 (m, 3H), 4.68-4.71 (m, 1H), 4.90 (d, $J = 2.4$ Hz, 1H), 6.82-6.86 (m, 2H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.96 (dd, $J = 8.8, 1.6$ Hz, 1H), 8.17 (s, 1H), 8.19 (s, 1H).

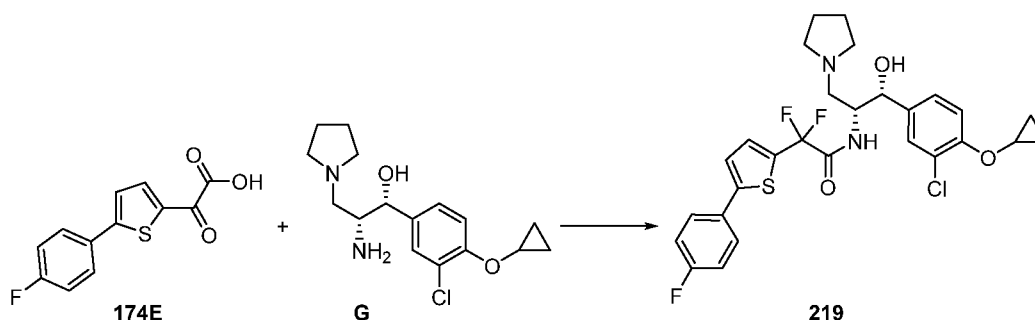
Example 218



[000878] To a solution of Compound **180B** (88 mg, 0.32 mmol) in DMF (10 mL) was added EDCI (93 mg, 0.48 mmol), HOBt (65 mg, 0.48 mmol) and Intermediate **G** (100 mg, 0.32 mmol). The mixture was stirred at 25 °C overnight. The reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **218**. LC-MS (ESI) m/z : 565 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.54-0.56 (m, 2H), 0.63-0.64 (m, 2H), 2.03-2.05 (m, 2H), 2.16-2.18 (m, 2H), 3.18-3.26 (m, 2H), 3.54-3.59 (m, 2H), 3.66-3.72 (m, 2H), 3.78-3.79 (m, 1H),

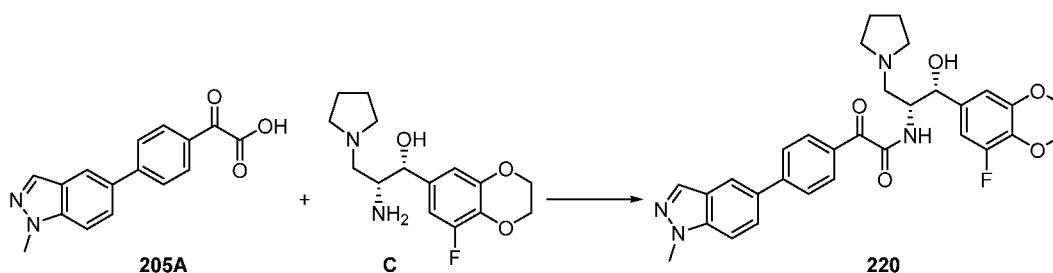
4.61-4.64 (m, 1H), 4.91 (s, 1H), 7.05 (d, $J = 3.2$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.17-7.21 (m, 3H), 7.24 (d, $J = 3.6$ Hz, 1H), 7.34 (d, $J = 1.2$ Hz, 1H), 7.67-7.70 (m, 2H).

Example 219



[000879] To a solution of Intermediate **G** (136 mg, 0.44 mmol) in DMF (10 mL) was added Compound **174E** (110 mg, 0.44 mmol), HATU (251 mg, 0.66 mmol), and DIPEA (114 mg, 0.88 mmol). The mixture was stirred at 25 °C overnight. The reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with prep-HPLC to afford Compound **219**. LC-MS (ESI) m/z : 543 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.62-0.66 (m, 2H), 0.73-0.78 (m, 2H), 2.00-2.04 (m, 2H), 2.16-2.19 (m, 2H), 3.19-3.28 (m, 2H), 3.48-3.52 (m, 1H), 3.65-3.79 (m, 4H), 4.52-4.54 (m, 1H), 4.91 (s, 1H), 7.22 (t, $J = 8.8$ Hz, 2H), 7.32 (s, 2H), 7.41 (s, 1H), 7.48 (t, $J = 2.4$ Hz, 1H), 7.78-7.82 (m, 2H), 8.11 (d, $J = 4.4$ Hz, 1H).

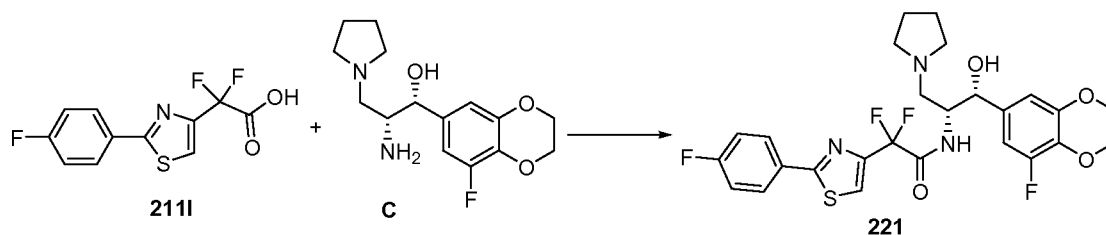
Example 220



[000880] A mixture of Compound **205A** (56 mg, 0.20 mmol), Intermediate **C** (59 mg, 0.20 mmol), and HATU (119 mg, 0.30 mmol) in DMF (10 mL) was stirred at 10 °C for 2 h. The reaction mixture was treated with water (10 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to yield Compound **220**. LC-MS (ESI) m/z : 559 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.88 (s, 2H), 2.03 (s, 2H), 3.09-3.21 (m, 2H), 3.45 (d, $J = 8$ Hz, 2H), 3.56 (s,

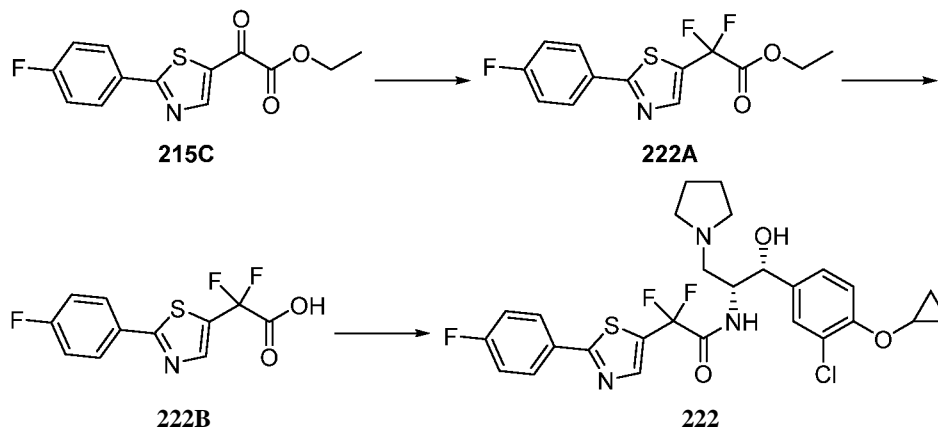
2H), 4.09 (s, 3H), 4.28 (s, 4H), 4.51 (s, 1H), 4.78 (s, 1H), 6.81 (t, $J = 16$ Hz, 2H), 7.80 (q, $J = 12$ Hz, 2H), 7.91 (dd, $J = 12, 4$ Hz, 4H), 8.17 (s, 2H), 8.74 (d, $J = 8$ Hz, 1H).

Example 221



[000881] A mixture of Compound **2111** (100 mg, 0.37 mmol), Intermediate **C** (110 mg, 0.37 mmol), HOBT (76 mg, 0.56 mmol), and EDCI (106 mg, 0.56 mmol) in dichloromethane (5 mL) and triethylamine (0.2 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to afford Compound **221**. LC-MS (ESI) m/z : 552 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.95-2.14 (m, 4H), 3.14-3.31 (m, 2H), 3.58-3.64 (m, 3H), 3.72-3.78 (m, 1H), 4.17 (s, 4H), 4.52-4.56 (m, 1H), 4.82 (s, 1H), 6.85-6.70 (m, 2H), 7.24-7.29 (m, 2H), 7.91 (s, 1H), 8.05-8.09 (m, 2H).

Example 222



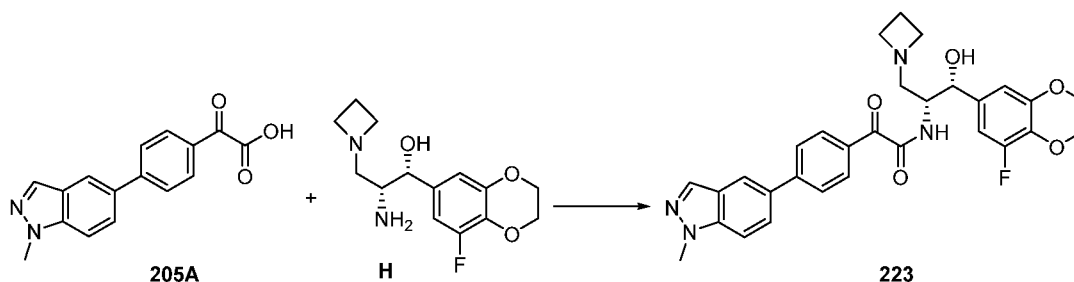
[000882] To a solution of Compound **215C** (1.0 g, 3.58 mmol) in DCM (20 mL) was added DAST (2.89 g, 17.9 mmol) and the mixture was stirred at 30 °C overnight. The mixture was diluted with DCM (100 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **222A**.

[000883] To a solution of Compound **222A** (1.04 g, 3.45 mmol) in THF (20 mL) and water (2 mL) was added LiOH (217 mg, 5.18 mmol). The mixture was stirred at room

temperature overnight, diluted with water (50 mL), and adjusted to pH 2 with 1M HCl. The precipitate was collected with filtration and dried to furnish Compound **222B**.

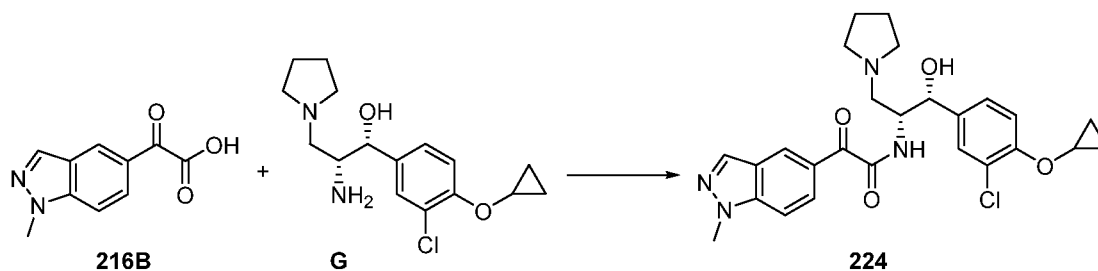
[000884] To a mixture of Compound **222B** (100 mg, 0.366 mmol) in DCM (2 mL) was added HATU (167 mg, 0.44 mmol) and Intermediate **G** (114 mg, 0.366 mmol). The mixture was stirred at room temperature overnight. The mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to afford Compound **222**. LC-MS (ESI) m/z : 566 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.51-0.53 (m, 2H), 0.66-0.67 (m, 2H), 1.85-1.90 (m, 2H), 1.98-2.02 (m, 2H), 3.10-3.21 (m, 2H), 3.42-3.53 (m, 4H), 3.63-3.67 (m, 1H), 4.45-4.51 (m, 1H), 4.80 (s, 1H), 5.98-6.01 (m, 1H), 7.14-7.18 (m, 2H), 7.26 (s, 1H), 7.39-7.43 (m, 2H), 7.94 (s, 1H), 8.02-8.05 (m, 2H), 8.89 (d, $J = 9.2$ Hz, 1H), 9.38-9.47 (m, 1H).

Example 223



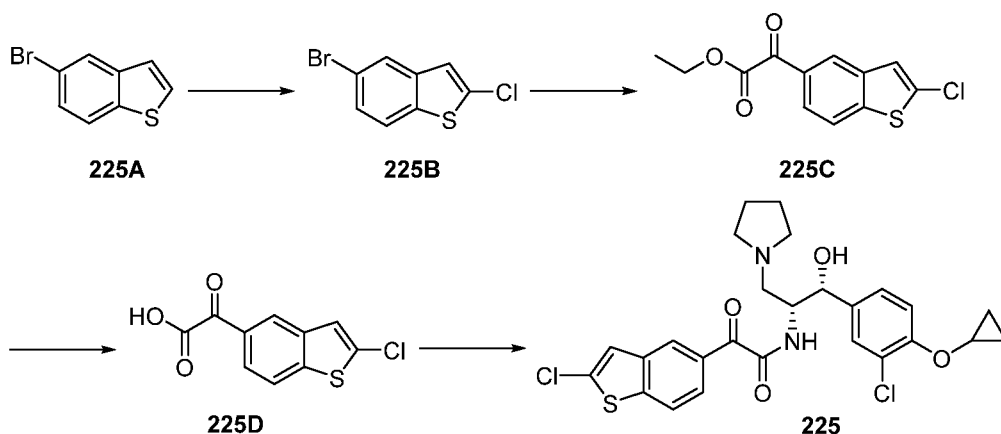
[000885] A mixture of Compound **205A** (56 mg, 0.20 mmol), Intermediate **H** (56 mg, 0.20 mmol), and HATU (119 mg, 0.30 mmol) in DMF (10 mL) was stirred at 10 °C for 2 h. The reaction mixture was treated with water (10 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to yield Compound **223**. LC-MS (ESI) m/z : 545 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 2.26 (s, 1H), 2.42 (t, $J = 8$ Hz, 1H), 3.44-3.48 (m, 2H), 4.09 (s, 3H), 4.19-4.43 (m, 9H), 4.74 (s, 1H), 6.80 (t, $J = 16$ Hz, 2H), 7.81-7.87 (m, 6H), 8.17 (s, 2H), 8.74 (d, 2H), 9.63 (brs, 2H).

Example 224



[000886] A mixture of Compound **216B** (100 mg, 0.49 mmol), HATU (279 mg, 0.74 mmol), and Intermediate **G** (152 mg, 0.49 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to afford Compound **224**. LC-MS (ESI) *m/z*: 497 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.59-0.83 (m, 4H), 2.04-2.23 (m, 4H), 3.24-3.27 (m, 1H), 3.34-3.35 (m, 1H), 3.59-3.82 (m, 5H), 4.11 (s, 3H), 4.73-4.77 (m, 1H), 5.01 (s, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.99 (s, 1H), 8.15 (s, 1H).

Example 225



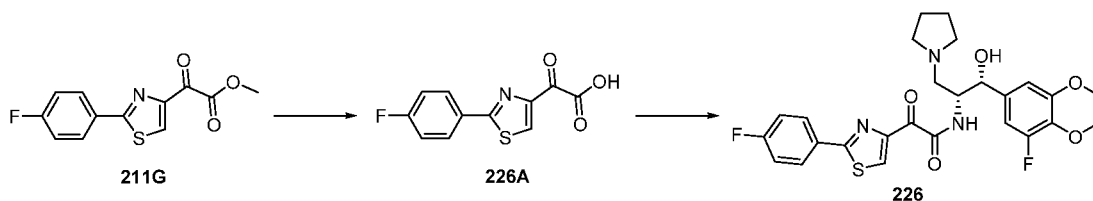
[000887] To a mixture of LDA (2 N, 8.3 mL, 16.5 mmol) in tetrahydrofuran (10 mL) under nitrogen was added Compound **225A** (3.2 g, 15.0 mmol) in tetrahydrofuran (5 mL) slowly at -78 °C. It was stirred at -78 °C for 1 h, and the mixture was added to a solution of carbon tetrachloride (5.5 mL, 56.6 mmol) in tetrahydrofuran (15 mL) at -78 °C. The resultant mixture was stirred at -78 °C for 1.5 h, quenched with ammonium chloride solution (50 mL), warmed to room temperature, and extracted with DCM (100 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to furnish Compound **225B**.

[000888] A solution of Compound **225B** (1.2 g, 5 mmol) in THF (10 mL) under nitrogen was added *n*-BuLi (2.4 N, 2.5 mL, 6 mmol) at -78 °C. The mixture was stirred at -78 °C for 30 min. To the above mixture was added diethyl oxalate (5 mL). The resultant solution was stirred at -78 °C for 15 min, quenched with saturated aqueous NH₄Cl solution (10 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to afford Compound **225C**.

[000889] To a solution of Compound **225C** (268 mg, 1 mmol) in MeOH (5 mL) was added a solution of LiOH·H₂O (126 mg, 3 mmol) in water (2 mL). The mixture was stirred at room temperature overnight. The solution was concentrated to remove methanol, adjusted to pH 2 with HCl (6 N, 2 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 20% v/v) to furnish Compound **225D**.

[000890] A mixture of Compound **225D** (125 mg, 0.5 mmol), HATU (342 mg, 0.9 mmol), and Intermediate **G** (162 mg, 0.5 mmol) in DMF (2 mL) and DCM (5 mL) was stirred at 25 °C overnight. The mixture was concentrated, and purified with prep-HPLC to yield Compound **225**. LC-MS (ESI) m/z: 533 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.65-0.90 (m, 4H), 1.97-2.23 (m, 4H), 3.12-3.27 (m, 1H), 3.58-3.62 (m, 1H), 3.69-3.85 (m, 5H), 4.60-4.63 (m, 1H), 5.01 (s, 1H), 7.37-7.52 (m, 4H), 7.52 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H).

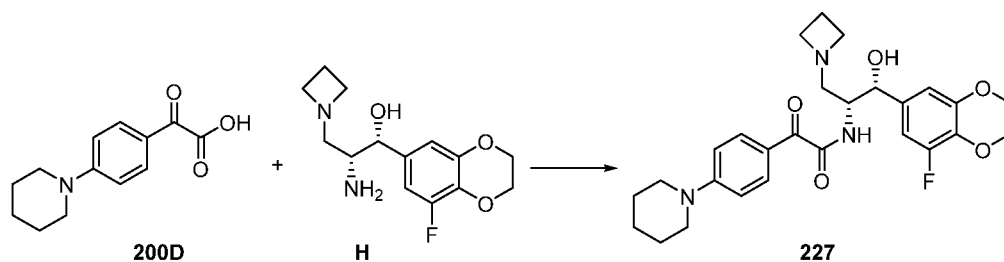
Example 226



[000891] A solution of Compound **211G** (500 mg, 1.89 mmol) and LiOH·H₂O (119 mg, 2.83 mmol) in THF (10 mL) and water (2 mL) was stirred at -10 °C for 1 h. It was diluted with ice water (20 mL) and adjusted to pH 1 with diluted hydrochloric acid (6 M) to form a solid. The mixture was filtered and the resulting solid was dried to yield Compound **226A**.

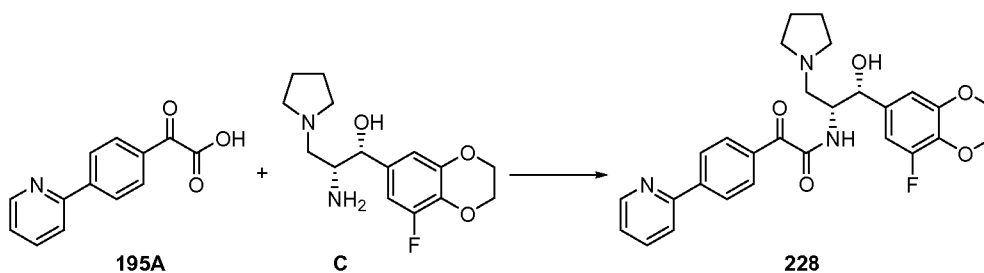
[000892] A mixture of Compound **226A** (100 mg, 0.40 mmol), Intermediate **C** (118 mg, 0.40 mmol), and HATU (228 mg, 0.60 mmol) in DMF (3 mL) was stirred at room temperature for 16 h. It was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to afford Compound **226**. LC-MS (ESI) m/z: 530 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.84 (brs, 2H), 1.99 (brs, 2H), 3.08-3.16 (m, 2H), 3.38-3.54 (m, 4H), 4.25 (s, 4H), 4.45 (t, *J* = 6.0 Hz, 1H), 4.76 (s, 1H), 6.14 (brs, 1H), 6.74 (s, 1H), 6.81 (d, *J* = 11.6 Hz, 1H), 7.40 (t, *J* = 8.8 Hz, 2H), 8.08-8.12 (m, 2H), 8.80 (d, *J* = 9.6 Hz, 1H), 8.96 (s, 1H), 9.37 (brs, 1H).

Example 227



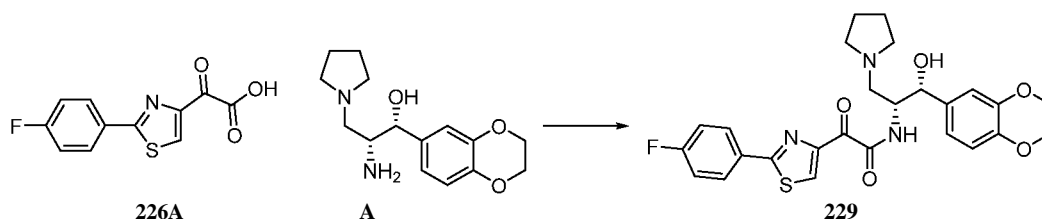
[000893] A mixture of Compound **200D** (46 mg, 0.20 mmol), Intermediate **H** (63 mg, 0.20 mmol), and HATU (119 mg, 0.30 mmol) in DMF (10 mL) was stirred at 10 °C for 3 h. The reaction mixture was treated with water (10 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to yield Compound **227**. LC-MS (ESI) *m/z*: 498 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.22 (s, 2H), 1.66 (s, 6H), 3.44-3.48 (m, 5H), 3.67 (d, *J* = 12 Hz, 1H), 4.15-4.33 (m, 9H), 4.90 (s, 1H), 6.69 (d, *J* = 12 Hz, 2H), 6.76 (d, *J* = 8 Hz, 2H), 7.67 (d, *J* = 8 Hz, 2H).

Example 228



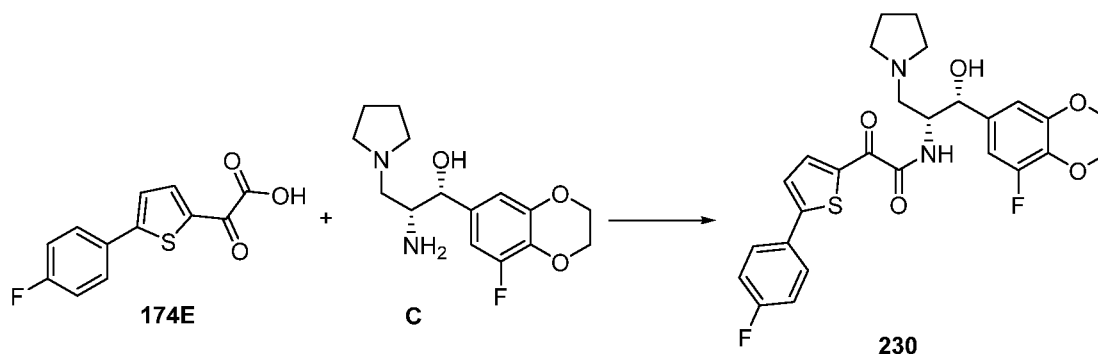
[000894] A mixture of Compound **195A** (100 mg, 0.44 mmol), Intermediate **C** (130 mg, 0.44 mmol), and HATU (335 mg, 0.88 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (20 mL x 3) and brine (20 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to yield Compound **228**. LC-MS (ESI) *m/z*: 506 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.73-1.75 (m, 4H), 2.54-2.68 (m, 6H), 4.31-4.33 (m, 5H), 4.76-4.77 (s, 1H), 5.69 (s, 1H), 6.75 (s, 1H), 6.81 (d, *J* = 10.4 Hz, 1H), 7.45-7.46 (m, 1H), 7.83-7.98 (m, 3H), 8.07-8.08 (m, 1H), 8.19-8.20 (m, 2H), 8.63-8.64 (m, 1H), 8.74-8.75 (m, 1H).

Example 229



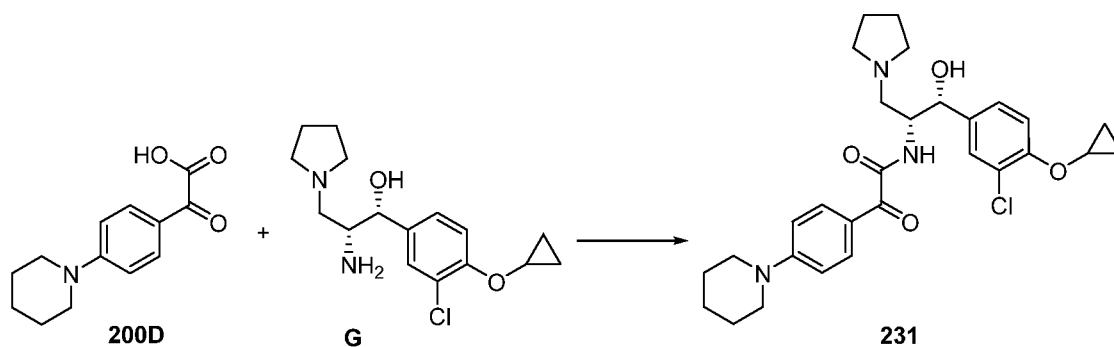
[000895] A mixture of Compound **226A** (100 mg, 0.40 mmol), Intermediate **A** (111 mg, 0.40 mmol), and HATU (228 mg, 0.60 mmol) in DMF (3 mL) was stirred at room temperature for 16 h. It was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to afford Compound **229**. LC-MS (ESI) m/z : 512 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 1.83 (brs, 2H), 1.99 (brs, 2H), 3.06-3.17 (m, 2H), 3.37-3.53 (m, 4H), 4.18 (s, 4H), 4.43 (t, $J = 11.2$ Hz, 1H), 4.74 (s, 1H), 5.99 (brs, 1H), 6.77-6.87 (m, 3H), 7.40 (t, $J = 8.8$ Hz, 2H), 8.08-8.12 (m, 2H), 8.80 (d, $J = 9.6$ Hz, 1H), 8.95 (s, 1H), 9.24 (brs, 1H).

Example 230



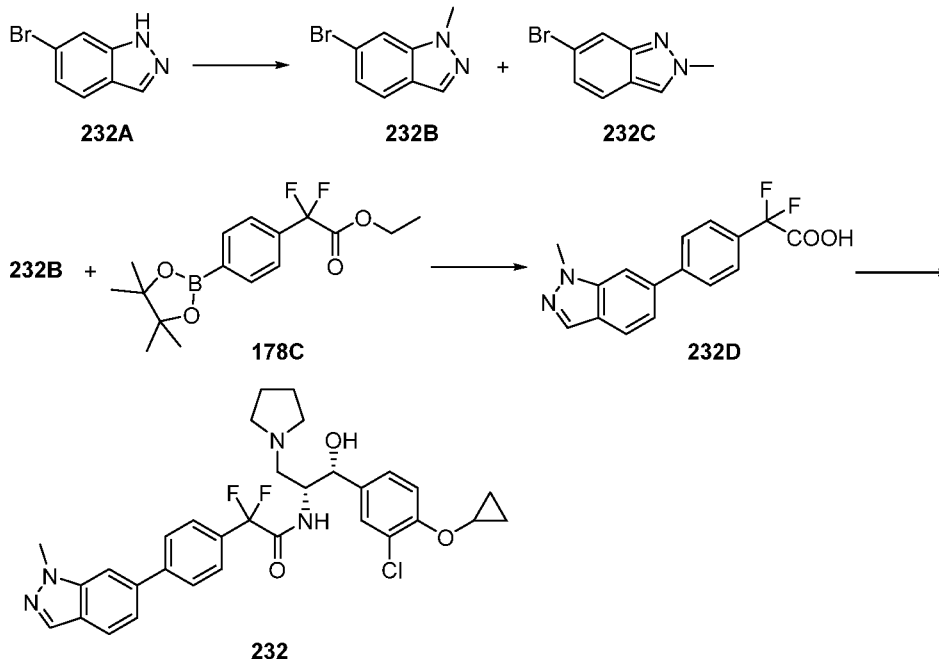
[000896] To a solution of Compound **174E** (62 mg, 0.25 mmol) in DMF (5 mL) was added Intermediate **C** (74 mg, 0.25 mmol) and HATU (141 mg, 0.37 mmol). The reaction mixture was stirred at 25 °C for 16 h. The mixture was purified with prep-HPLC to yield Compound **230**. LC-MS (m/z) 529 $[M+H]^+$; 1H -NMR (CDC_3 , 400 MHz): δ (ppm) 2.14-2.17 (m, 4H), 2.77-2.87 (m, 2H), 3.11-3.14 (m, 2H), 3.49-3.51 (m, 1H), 3.82-3.92 (m, 3H), 4.15-4.19 (m, 3H), 4.89 (brs, 1H), 5.16 (s, 1H), 6.70-6.74 (m, 2H), 7.07-7.11 (m, 2H), 7.24-7.25 (m, 1H), 7.59-7.63 (m, 2H), 8.03-8.06 (m, 1H), 8.16-8.17 (m, 1H), 9.70 (brs, 1H).

Example 231



[000897] To a solution of Compound **200D** (100 mg, 0.43 mmol) in DMF (5 mL) was added Intermediate **G** (151 mg, 0.43 mmol) and HATU (151 mg, 0.43 mmol). The reaction mixture was stirred at 15 °C overnight. The mixture was purified with prep-HPLC to give Compound **231**. LC-MS (m/z) 526 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.77-0.79 (m, 4H), 1.66 (s, 6H), 2.04-2.08 (m, 4H), 3.34-3.51 (m, 10H), 3.72-3.74 (m, 1H), 4.49-4.51 (m, 1H), 5.15 (s, 1H), 6.70-6.73 (m, 2H), 7.20-7.24 (m, 1H), 7.36 (s, 1H), 7.75-7.77 (m, 1H), 7.89-7.91 (m, 2H).

Example 232



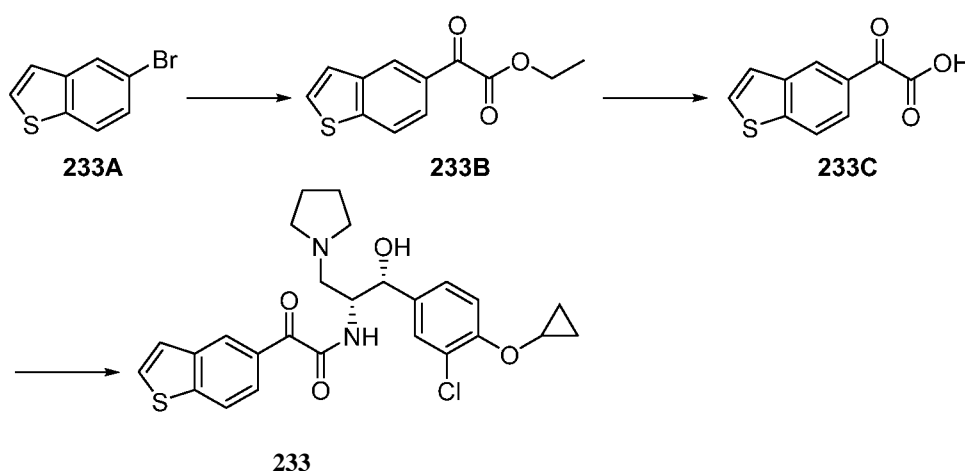
[000898] To Compound **232A** (10 g, 50.8 mmol) in THF (50 mL) was added sodium hydride (60% in mineral, 2.2 g, 55.8 mmol) with ice bath cooling. The mixture was stirred at room temperature for 30 min. Methyl iodide (4.74 mL, 76.1 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over

anhydrous sodium sulfate, and concentrated. Purification with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% to 30% v/v) gave Compound **232B** and Compound **232C**.

[000899] A mixture of Compound **232B** (600 mg, 2.84 mmol), Compound **178B** (926 mg, 2.84 mmol), Pd(dppf)Cl₂ (116 mg, 0.14 mmol), and K₂CO₃ (1.18 g, 8.52 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 2), and then the organic layer was discarded off. The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **232D**.

[000900] A mixture of Compound **232D** (100 mg, 0.33 mmol), EDCI (95 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol), and Intermediate **G** (102 mg, 0.33 mmol) in dichloromethane (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **232**. LC-MS (ESI) m/z: 595 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.33-0.41 (m, 4H), 1.95-2.08 (m, 4H), 3.08-3.17 (m, 2H), 3.38-3.64 (m, 4H), 3.70-3.72 (m, 1H), 4.05 (s, 3H), 4.54-4.56 (m, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.02 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.28-7.30 (m, 3H), 7.42 (d, *J* = 9.2 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.75-7.77 (m, 2H), 7.95 (s, 1H).

Example 233



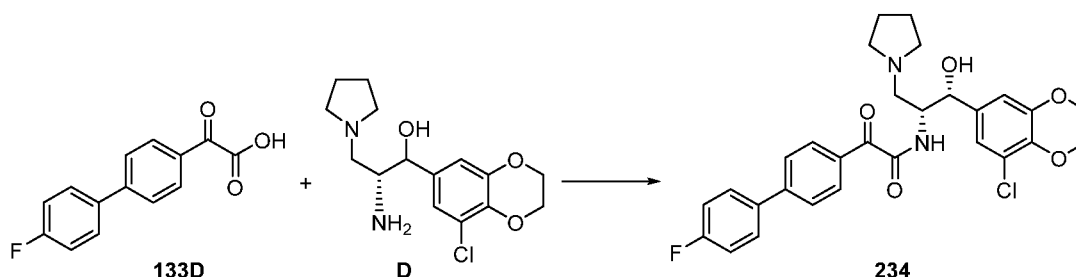
[000901] To a solution of Compound **233A** (1.0 g, 4.7 mmol) in THF (30 mL) was added magnesium chips (0.23 g, 9.4 mmol) at room temperature. The mixture was stirred at

50 °C for 2 h, and then diethyl oxalate (3 mL) was added in one portion. The mixture was stirred at 60 °C for 3 h. The solution was quenched with saturated NH₄Cl solution and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **233B**.

[000902] To a solution of Compound **233B** (1.4 g, 6.1 mmol) in THF (15 mL) was added LiOH·H₂O (390 mg, 9.0 mmol) in water (15 mL) at -10 °C, and the mixture was stirred at this temperature for 5 hours. The reaction mixture was treated with ice water (20 mL) and extracted with ethyl acetate (50 mL). The water layer was adjusted to pH 2 with diluted HCl and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resulting solid was washed with petroleum ether and filtered off to furnish the crude Compound **233C**.

[000903] A mixture of Compound **233C** (160 mg, 0.8 mmol), HATU (608 mg, 1.6 mmol), DMF (6.5 mL) and Intermediate **G** (298 mg, 0.96 mmol) in DCM (8 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (20 mL), extracted with DCM 50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **233**. LC-MS (ESI) m/z: 499.1 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.61-0.79 (m, 4H), 2.01-2.23 (m, 4H), 3.21-3.30 (m, 1H), 3.58-3.86 (m, 6H), 4.73 (d, *J* = 10.8 Hz, 1H), 5.00 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 5.2 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.73-7.75 (m, 2H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H).

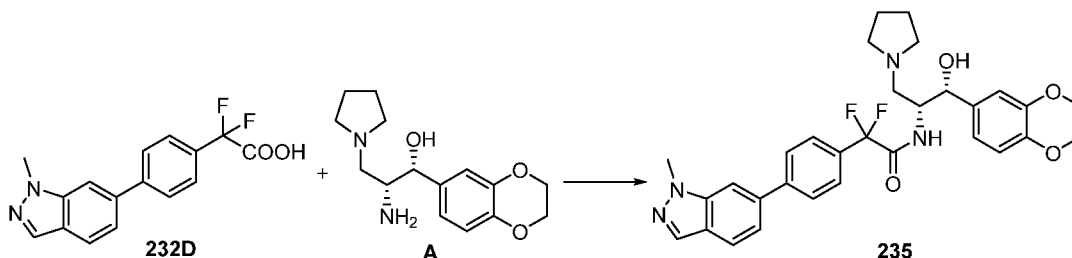
Example 234



[000904] A mixture of Compound **133D** (156 mg, 0.50 mmol), Intermediate **D** (100 mg, 0.45 mmol), and HATU (285 mg, 0.75 mmol) in dichloromethane (10 mL) was stirred at 10 °C for 15 h. And then it was treated with water (10 mL) and extracted with dichloromethane (10 mL x 3mL). The organic layers were washed with water (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to furnish

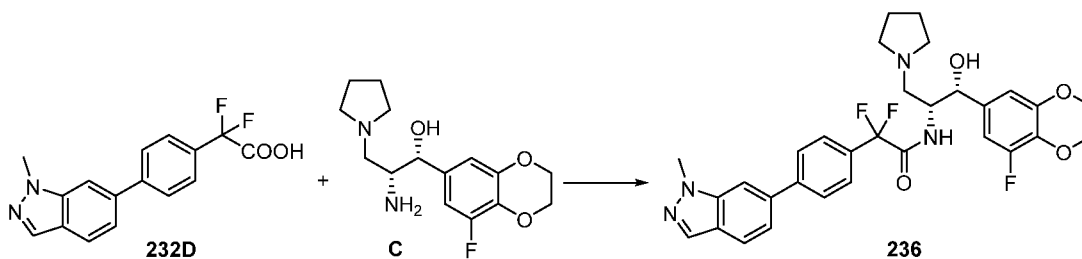
Compound **234**. LC-MS (ESI) m/z : 539 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.09 (s, 4H), 3.06 (s, 2H), 3.46 (s, 1H), 3.73 (t, $J = 12$ Hz, 1H), 3.89 (s, 2H), 4.10-4.19 (m, 4H), 4.43 (s, 1H), 4.99 (s, 1H), 6.76 (s, 1H), 6.92 (s, 1H), 7.08 (t, $J = 8$ Hz, 2H), 7.50 (t, $J = 8$ Hz, 4H), 7.67 (d, $J = 8$ Hz, 2H), 7.80 (d, $J = 8$ Hz, 2H), 8.50 (s, 1H).

Example 235



[000905] A mixture of Compound **232D** (100 mg, 0.33 mmol), EDCI (95 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol), and Intermediate A (92 mg, 0.33 mmol) in dichloromethane (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **235**. LC-MS (ESI) m/z : 563 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.03-2.17 (m, 4H), 3.15-3.24 (m, 2H), 3.53-3.67 (m, 3H), 3.80-3.82 (m, 1H), 4.07 (s, 4H), 4.15 (s, 3H), 4.56-4.58 (m, 1H), 4.83 (d, $J = 3.2$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 6.72-6.79 (m, 2H), 7.47-7.53 (m, 3H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.86-7.88 (m, 2H), 8.05 (s, 1H).

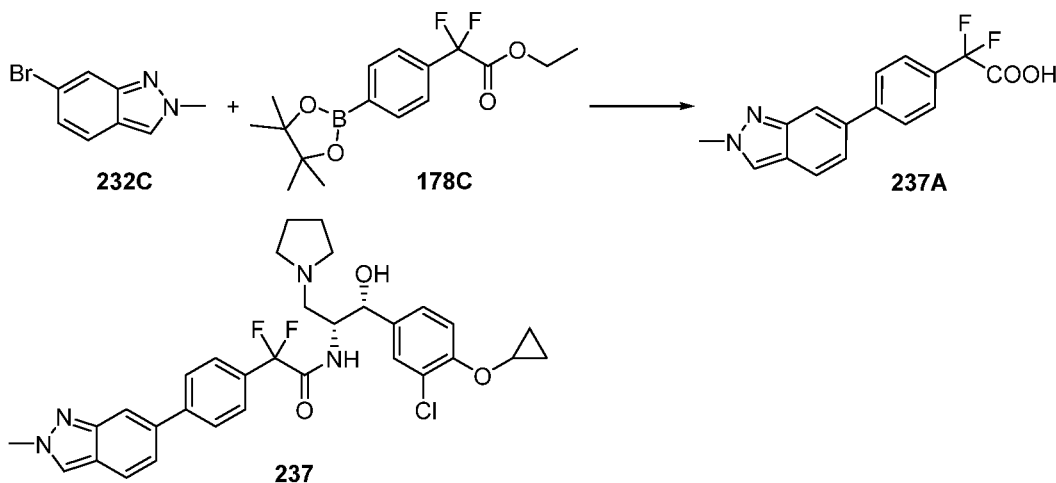
Example 236



[000906] A mixture of Compound **232D** (100 mg, 0.33 mmol), EDCI (95 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol), and Intermediate C (98 mg, 0.33 mmol) in dichloromethane (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **236**. LC-MS (ESI) m/z : 581 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.03-2.18 (m, 4H), 3.17-3.27 (m, 2H), 3.53-3.81 (m, 4H), 4.01-4.07 (m, 4H), 4.15 (s, 3H), 4.59-4.62 (m, 1H), 4.84 (d, $J = 2.8$ Hz, 1H), 6.59 (s, 1H), 6.68 (dd, $J = 11.6, 2.0$ Hz,

1H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.86-7.88 (m, 2H), 8.05 (s, 1H).

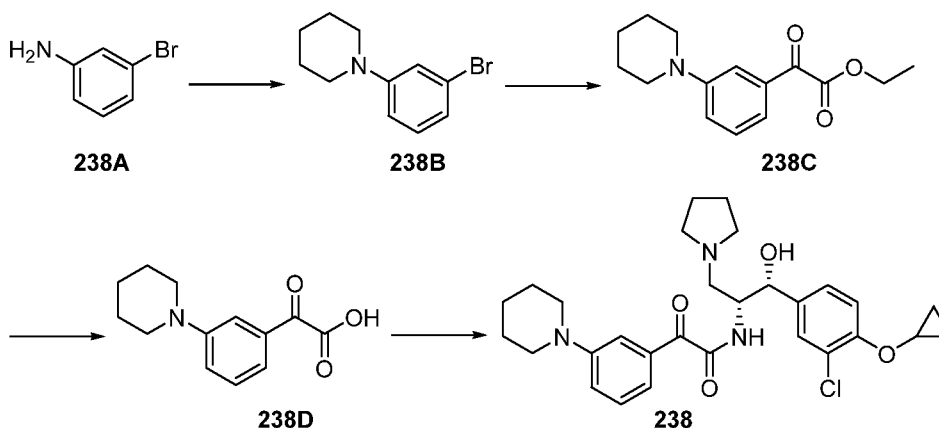
Example 237



[000907] A mixture of Compound **232C** (200 mg, 0.95 mmol), Compound **178C** (310 mg, 0.95 mmol), Pd(dppf)Cl₂ (39 mg, 0.05 mmol), and K₂CO₃ (393 mg, 2.85 mmol) in dioxane (3 mL) and water (3 mL) was stirred under nitrogen at 100 °C for 4 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was treated with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **237A**.

[000908] A mixture of Compound **237A** (100 mg, 0.33 mmol), EDCI (95 mg, 0.5 mmol), HOBT (68 mg, 0.5 mmol), and Intermediate **G** (102 mg, 0.33 mmol) in dichloromethane (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **237**. LC-MS (ESI) m/z : 595 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.45-0.54 (m, 4H), 2.04-2.18 (m, 4H), 3.17-3.32 (m, 2H), 3.49-3.81 (m, 5H), 4.26 (s, 3H), 4.62-4.64 (m, 1H), 4.90 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 7.11 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.37-7.40 (m, 3H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 8.8$ Hz, 1H), 7.90 (s, 1H), 8.25 (s, 1H).

Example 238



[000909] A mixture of Compound 238A (1.72 g, 10 mmol), 1,5-dibromopentane (2.75 g, 12 mmol), sodium dodecyl sulfate (SDS, cat. 40 mg), and sodium bicarbonate (1 g, 12 mmol) in water (20 mL) was heated at 100 °C for 1.5 hours. The reaction mixture was treated with water (20 mL) and extracted with ethyl acetate (50 mL x 3). The extraction was washed with water (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 1% v/v) to give Compound 238B.

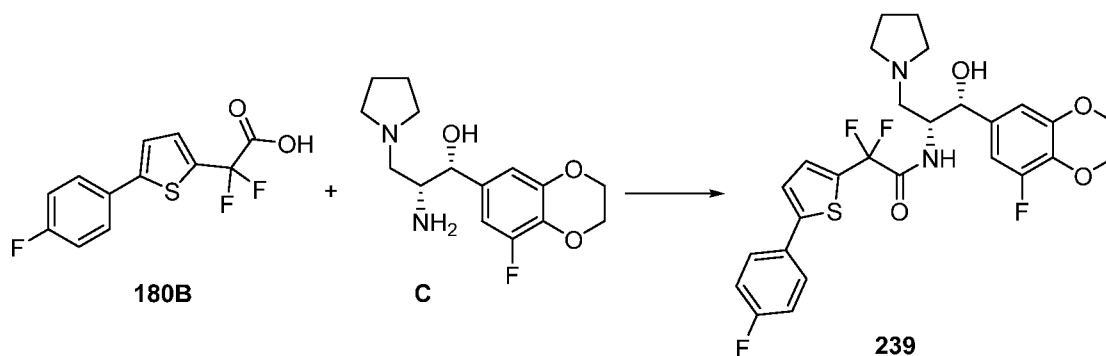
[000910] To a solution of Compound 238B (2.4 g, 10 mmol) in dry THF (50 mL) was added dropwise LDA (2.0 M, 5.0 mL, 12.0 mmol) under nitrogen at -70 °C. After stirring for 30 min., diethyl oxalate (2.19 g, 15.0 mmol) was added quickly. The mixture was stirred at -70 °C for about an hour. It was quenched with saturated ammonium chloride (10 mL) solution and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound 238C.

[000911] To a solution of Compound 238C (261 mg, 1 mmol) in methanol (5 mL) was added dropwise lithium hydroxide (1 N, 2 mL, 2 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction mixture was concentrated, HCl (2 N, 1 mL) was added to adjust pH 7, followed by extraction with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound 238D.

[000912] To a solution of Compound 238D (100 mg, 0.429 mmol) in dichloromethane (3 mL) was added Intermediate G (130 mg, 0.429 mmol) and HATU (196 mg, 0.515 mmol).

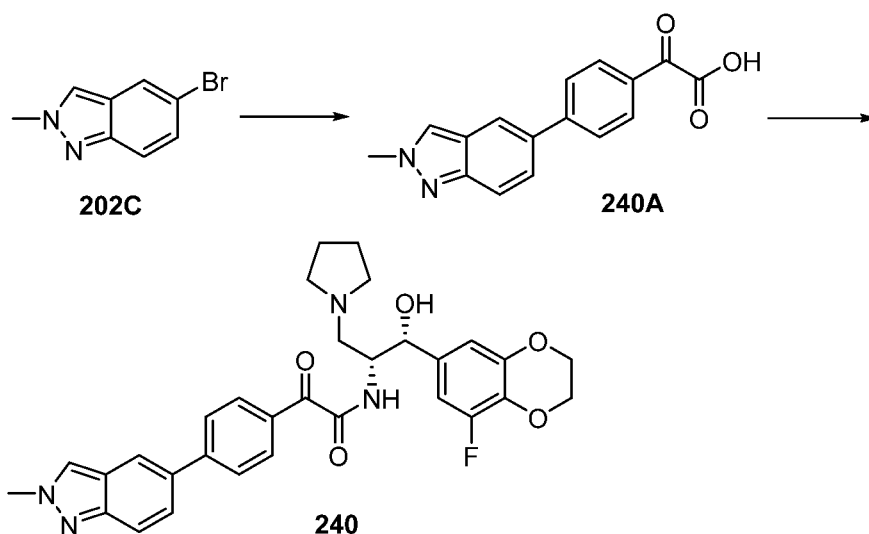
The mixture was stirred at room temperature for 2 h. It was concentrated and the resulting residue was purified with prep-HPLC to furnish Compound **238**. LC-MS (ESI) m/z : 526 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.79-0.83 (m, 4H), 1.57-1.61 (m, 2H), 1.67-1.72 (m, 5H), 1.85-1.87 (m, 4H), 2.71-2.92 (m, 4H), 2.96-3.07 (m, 2H), 3.17-3.19 (m, 4H), 3.75-3.78 (m, 1H), 4.31-4.32 (m, 1H), 5.14 (d, $J = 1.6$ Hz, 1H), 7.16-7.23 (m, 2H), 7.24-7.37 (m, 3H), 7.58-7.60 (m, 1H), 7.76-7.78 (m, 1H).

Example 239



[000913] To a solution of Compound **180B** (68 mg, 0.25 mmol) in DMF (5 mL) was added Intermediate **C** (74 mg, 0.25 mmol) and HATU (142 mg, 0.37 mmol). The reaction mixture was stirred at 25 °C for 16 h. The mixture was purified with prep-HPLC to yield Compound **239**. LC-MS (m/z) 551 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.15-2.18 (m, 4H), 2.94-2.97 (m, 1H), 3.06-3.10 (m, 1H), 3.50-3.53 (m, 2H), 3.82-3.88 (m, 2H), 4.08-4.10 (m, 3H), 4.16-4.23 (m, 1H), 4.39-4.42 (m, 1H), 5.08 (brs, 1H), 6.59-6.67 (m, 2H), 7.08-7.11 (m, 3H), 7.51-7.55 (m, 3H).

Example 240

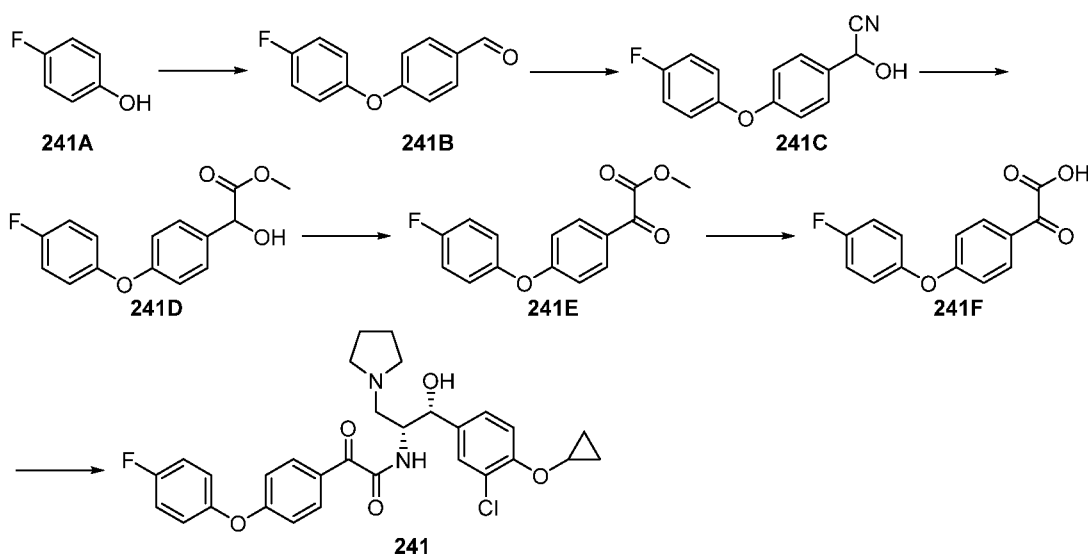


[000914] To a solution of Compound **202C** (158 mg, 0.75 mmol) in 1,4-dioxane (15 mL) was added ethyl **178C** (250 mg, 0.825 mmol), $Pd(dppf)Cl_2$ (30 mg, 0.0375 mmol),

potassium carbonate (310 mg, 2.25 mmol) and water (1 mL) under nitrogen. The reaction mixture was stirred at 100 °C for 2 hours. The resulting mixture was cooled to 25 °C. The precipitated solid was filtered and dried to afford Compound **240A**.

[000915] To a solution of Compound **240A** (68 mg, 0.24 mmol) in DMF (3 mL) was added Intermediate **C** (71 mg, 0.24 mmol) and HATU (137 mg, 0.36 mmol). The reaction mixture was stirred at 10 °C overnight. The mixture was purified with prep-HPLC to yield the product Compound **240**. LC-MS (m/z) 559 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.15-2.22 (m, 4H), 2.94-2.95 (m, 2H), 3.08-3.09 (m, 2H), 3.49-3.50 (m, 1H), 3.56-3.57 (m, 1H), 3.91-3.94 (m, 2H), 4.23-4.27 (m, 5H), 4.49-4.52 (m, 1H), 5.12-5.13 (m, 1H), 6.73-6.78 (m, 2H), 7.58-7.61 (m, 1H), 7.69-7.71 (m, 2H), 7.79-7.81 (m, 1H), 7.85-7.90 (m, 2H), 7.99 (s, 1H), 8.19-8.21 (m, 2H).

Example 241



[000916] To a solution of Compound **241A** (3.1 g, 27.6 mmol) and potassium carbonate (4.15 g, 30.0 mmol) in DMF (50 mL) was added 4-bromobenzaldehyde (5.0 g, 27.6 mmol). The reaction mixture was stirred at 130 °C for 12 h. The reaction was quenched with water (50 mL) and extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The remaining residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to furnish Compound **241B**.

[000917] A mixture of Compound **241B** (1.9 g, 8.8 mmol), and sodium metabisulfite (3.3 g, 17.6 mmol) in water (40 mL) was pre-stirred for 1 h, and then NaCN (431.2 mg, 8.8 mmol) was added into the above-mentioned mixture, and the whole reaction solution was stirred at room temperature for 12 h. The reaction was treated with water (100 mL) and

extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30% v/v) to give Compound **241C**.

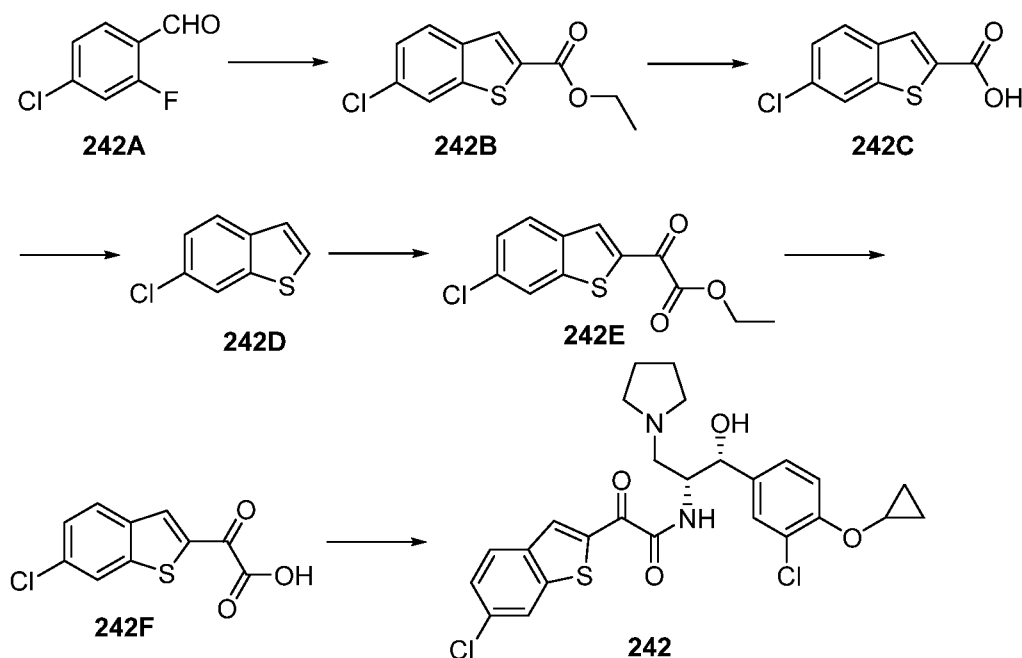
[000918] To a solution of Compound **241C** (1.0 g, 27.6 mmol) in methanol (50 mL) was bubbled with HCl (gas), which was prepared with condensed H₂SO₄ and NaCl. After 4 h later, the reaction was quenched with water (50 mL) and extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The remaining residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30% v/v) to afford Compound **241D**.

[000919] To a solution of Compound **241D** (170 mg, 0.62 mmol) in dichloromethane (15 mL) was added Dess-Martin periodinane (313 mg, 0.74 mmol). The reaction was stirred at 0 °C for 0.5 h. The reaction was treated with water (50 mL) and extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The remaining residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 3% v/v) to furnish Compound **241E**.

[000920] To a solution of Compound **241E** (160 mg, 0.58 mmol) in methanol (15 mL) was added LiOH solution (1 N, 0.6 mL, 0.60 mmol). The reaction was stirred at 0 °C for 0.5 h. The reaction was quenched with water (50 mL) and neutralized to pH 1 with HCl (1 M). The mixture was extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to afford Compound **241F**.

[000921] To a solution of Compound **241F** (100 mg, 0.38 mmol) in a mixture of dichloromethane (14 mL) and DMF (2 mL) was added Intermediate **G** (119 mg, 0.38 mmol) and HATU (175 mg, 0.46 mmol). The mixture was stirred at room temperature for 12 h. The reaction was quenched with water (50 mL) and extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The remaining residue was purification with prep-HPLC to give Compound **241**. LC-MS (ESI) m/z: 553 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.65-0.82 (m, 4H), 2.14 (s, 4H), 2.66-2.96 (m, 4H), 3.51-3.90 (m, 4H), 4.54 (s, 1H), 5.12 (s, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.00-7.12 (m, 4H), 7.16-7.26 (m, 2H), 7.34-7.37 (m, 1H), 7.97-8.03 (m, 3H), 11.60 (s, 1H).

Example 242



[000922] Compound **242A** (2.44 g, 15.4 mmol) and potassium carbonate (2.76 g, 20.0 mmol) were suspended in dry DMF (15 mL) and the resulting mixture was cooled to 0 °C. Ethyl thioglycolate (1.7 mL, 15.5 mmol) was added in portions over 1 h and the reaction mixture was warmed slowly to room temperature and stirred at 25 °C for 16 h. The reaction was heated at 60 °C for 5.5 h before cooling and adding water (30 mL). The resulting mixture was stirred at room temperature for 30 min and filtered. The residue was washed with water (5 mL x 2) and dried to afford the Compound **242B**.

[000923] Compound **242B** (500 mg, 2.08 mmol) was dissolved in hot ethanol (12 mL) and a solution of potassium hydroxide (642 mg, 11.5 mmol) in water (12 mL) was added to the mixture. The suspension was heated at reflux for 1.5 h during which time it mostly dissolved. After cooling slightly aqueous HCl solution (6 N, 5 mL) was added dropwise. Ethanol was evaporated in *vacuo* and the residual solid was filtered. The filtered cake was washed with water (20 mL) and dried to give Compound **242C**.

[000924] Compound **242C** (420 mg, 1.98 mmol) and copper powder (63 mg, 0.99 mmol) were suspended in quinoline (10 mL) and the resulting mixture was heated at 185 °C for 2 h. After cooling down to room temperature, ethyl acetate (25 mL) was added and the suspension was filtered. The filtered cake was washed with ethyl acetate (5 mL x 2) and the combined organic layers were washed with aqueous HCl solution (2 N, 10 mL x 2). After drying over anhydrous sodium sulfate, the solution was filtered and evaporated in *vacuo* to

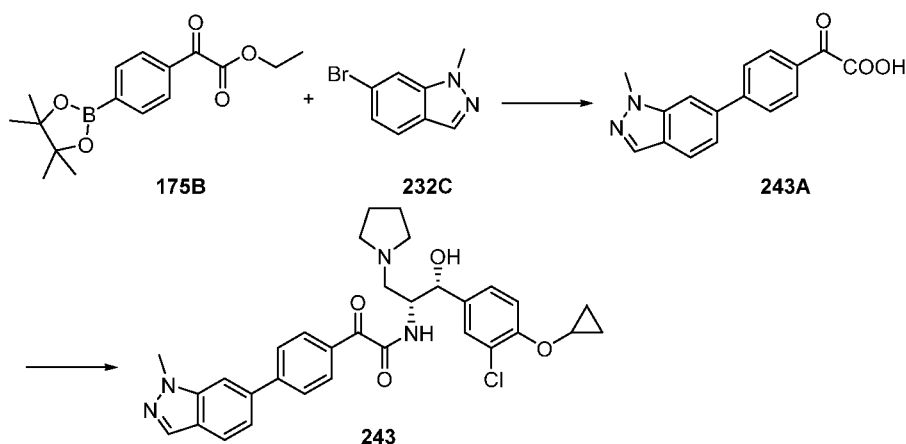
give a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound **242D**.

[000925] To a solution of Compound **242D** (310 mg, 1.85 mmol) in dry THF (20 mL) was added dropwise n-BuLi (2.4 M solution in hexane, 1.2 mL, 2.78 mmol) under nitrogen at -78 °C. After stirring for 30 min, diethyl oxalate (808 mg, 5.54 mmol) was added quickly. The mixture was stirred at -78 °C for about an hour. The resulting mixture was quenched with saturated aqueous NH₄Cl solution (5 mL), extracted with ethyl acetate (50 mL x 3), washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **242E**.

[000926] To a solution of Compound **242E** (150 mg, 0.56 mmol) in THF (10 mL) was added dropwise a solution of LiOH·H₂O (25 mg, 0.62 mmol) in water (2.5 mL) at -30 °C. The mixture was stirred at -30 °C for half an hour. The reaction solution was adjusted to pH 3 with aqueous HCl solution (1 N, 2.5 mL) and separated. The organic layer was dried directly over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **242F**.

[000927] To a solution of Intermediate **G** (129 mg, 0.42 mmol) in DMF (10 mL) was added Compound **242F** (100 mg, 0.42 mmol), HATU (237 mg, 0.62 mmol), and *N,N*-diisopropylethylamine (107 mg, 0.83 mmol) under nitrogen. The mixture was stirred at 25 °C overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **242**. LC-MS (ESI) m/z: 533 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.58-0.70 (m, 2H), 0.73-0.79 (m, 2H), 2.01-2.04 (m, 2H), 2.16-2.21 (m, 2H), 3.20-3.26 (m, 2H), 3.49-3.53 (m, 1H), 3.70-3.76 (m, 4H), 4.58-4.60 (m, 1H), 4.91 (d, *J* = 2.8 Hz, 1H), 7.32-7.34 (m, 2H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.04 (s, 1H), 8.38 (s, 1H).

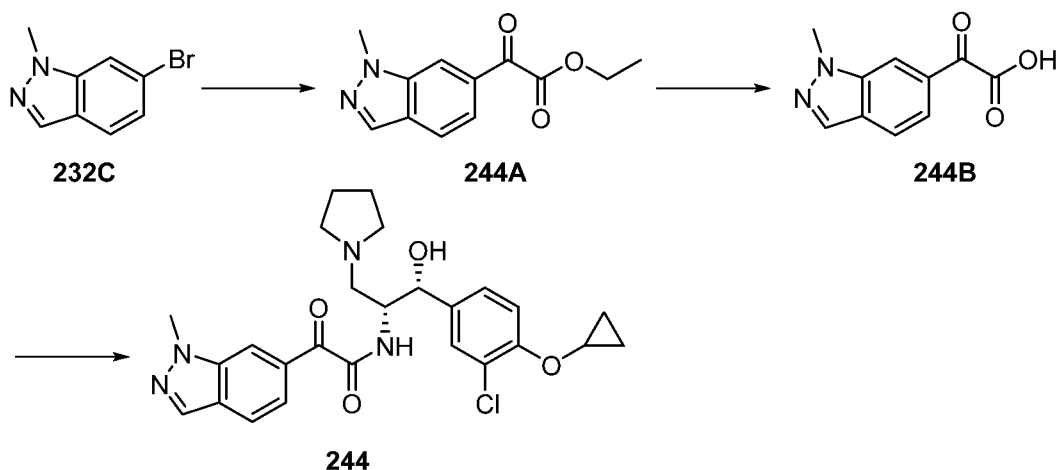
Example 243



[000929] A mixture of Compound **232C** (600 mg, 2.84 mmol), Compound **175B** (863 mg, 2.84 mmol), Pd(dppf)Cl₂ (116 mg, 0.14 mmol), and K₂CO₃ (1.18 g, 8.52 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was treated with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and filtered. The cake was washed with water (20 mL) and dried in *vacuo* to give Compound **243A**.

[000930] A mixture of Compound **243A** (100 mg, 0.36 mmol), HATU (205 mg, 0.54 mmol), and Intermediate **A** (112 mg, 0.36 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to furnish Compound **243**. LC-MS (ESI) m/z: 573 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.72-0.82 (m, 4H), 2.07-2.08 (m, 2H), 2.23-2.24 (m, 2H), 3.31-3.32 (m, 2H), 3.60-3.63 (m, 1H), 3.71-3.77 (m, 2H), 3.83-3.89 (m, 2H), 4.15-4.16 (m, 3H), 4.72-4.76 (m, 1H), 5.02 (s, 1H), 7.41 (s, 2H), 7.50 (s, 1H), 7.53-7.55 (m, 1H), 7.70-7.72 (m, 2H), 7.79-7.81 (m, 2H), 7.88-7.89 (m, 2H), 8.07 (s, 1H).

Example 244

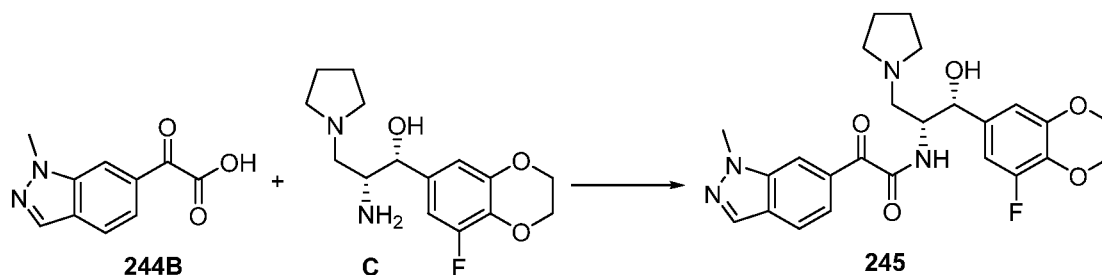


[000931] To a solution of Compound **232C** (800 mg, 3.79 mmol) in dry THF (10 mL) was added n-BuLi (2.5 *N* solution in hexane, 1.53 mL) under nitrogen at -78 °C. The resulting solution was stirred at -78 °C for 30 min and transferred into a stirred solution of diethyl oxalate (1.39 g, 9.5 mmol) in dry THF (5 mL) at -78 °C. The solution was stirred at -78 °C for 1 h, quenched with addition of saturated NH₄Cl solution (10 mL), poured into water (100 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give a solid. This solid was triturated with methanol and filtered. The filtrate was concentrated to give the desired Compound **244A** which was used for the next step without further purification.

[000932] To a solution of Compound **244A** (500 mg, 2.16 mmol) in methanol (10 mL) was added a solution of LiOH·H₂O (200 mg, 4.32 mmol) in water (5 mL). The mixture was stirred at room temperature overnight and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 7% v/v) to furnish Compound **244B**.

[000933] A mixture of Compound **244B** (70 mg, 0.34 mmol), HATU (194 mg, 0.51 mmol), and Intermediate **G** (105 mg, 0.34 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to afford Compound **244**. LC-MS (ESI) *m/z*: 497 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.62-0.82 (m, 4H), 1.88-1.91 (m, 2H), 2.03-2.05 (m, 2H), 3.13-3.20 (m, 2H), 3.47-3.59 (m, 4H), 3.89-3.90 (m, 1H), 4.14 (s, 3H), 4.54-4.56 (m, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 7.33-7.39 (m, 2H), 7.45-7.49 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 8.21 (s, 1H), 8.27 (s, 1H), 8.83 (d, *J* = 9.2 Hz, 1H), 9.32 (brs, 1H).

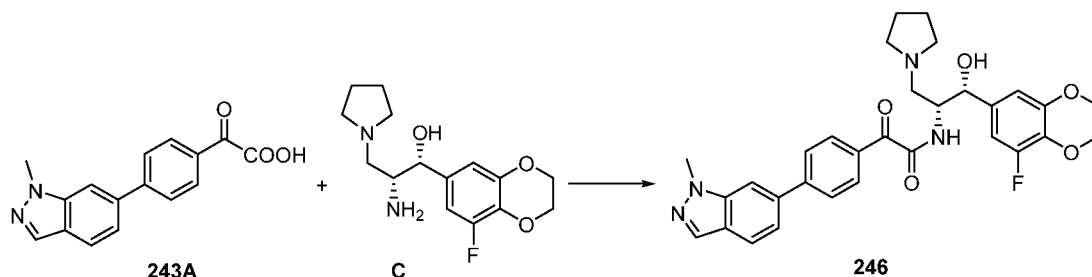
Example 245



[000934] A mixture of Compound **244B** (60 mg, 0.29 mmol), HATU (167 mg, 0.44 mmol), and Intermediate **C** (86 mg, 0.29 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to afford Compound **245**. LC-MS (ESI) *m/z*: 483 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.87-2.04 (m, 4H), 3.08-3.21 (m, 2H), 3.43-3.46 (m, 2H), 3.54-3.57 (m, 2H), 4.12 (s, 3H), 4.22-4.32 (m, 4H), 4.48-4.55 (m, 1H), 4.77 (d, *J* = 2.8 Hz, 1H), 6.77 (s, 1H), 6.84 (dd, *J* = 11.6, 1.6 Hz, 1H), 7.51 (dd, *J* = 8.4, 0.8

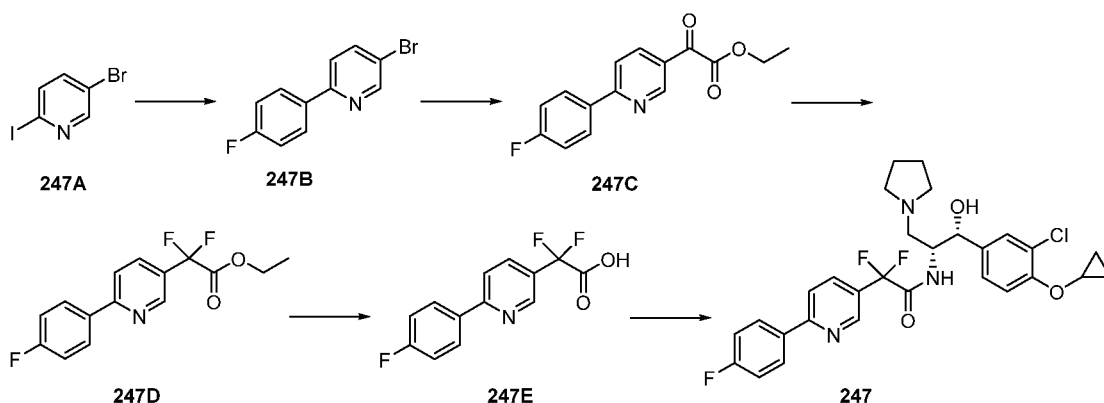
Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 8.21 (s, 1H), 8.31 (s, 1H), 8.81 (d, $J = 9.2$ Hz, 1H), 9.31 (brs, 1H).

Example 246



[000935] A mixture of Compound **243A** (100 mg, 0.36 mmol), HATU (205 mg, 0.54 mmol), and Intermediate **C** (107 mg, 0.36 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was purified with prep-HPLC to furnish Compound **246**. LC-MS (ESI) m/z : 559 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.73-1.74 (m, 4H), 2.54-2.61 (m, 5H), 2.66-2.71 (m, 1H), 4.13 (s, 3H), 4.27-4.31 (m, 5H), 4.78 (d, $J = 2.8$ Hz, 1H), 6.76 (s, 1H), 6.83 (dd, $J = 11.2, 1.2$ Hz, 1H), 7.52 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.79-7.92 (m, 5H), 8.05 (s, 1H), 8.11 (s, 1H), 8.66 (d, $J = 9.6$ Hz, 1H).

Example 247



[000936] A mixture of Compound **247A** (14.2 g, 50 mmol), Compound (4-fluorophenyl)boronic acid (7.7 g, 55 mmol), $Pd(dppf)Cl_2$ (2.05 g, 2.5 mmol) and K_2CO_3 (20.7 g, 150 mmol) in dioxane (600 mL) and water (80 mL) was heated to reflux for 2 h. Ethyl acetate (500 mL) was added. The organic layers were washed with water (50 mL), saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **247B**.

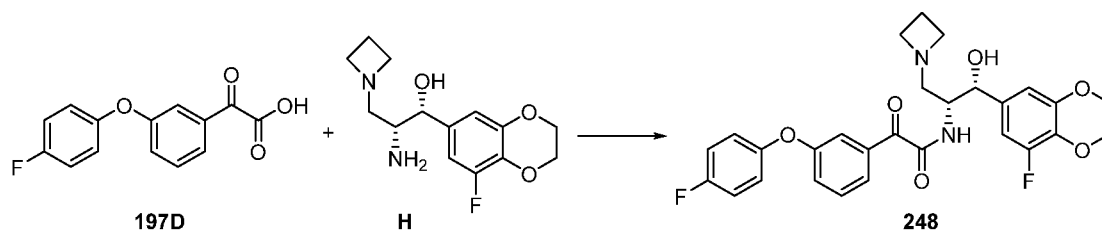
[000937] To a solution of Compound **247B** (2.51 g, 10 mmol) in THF (20 mL) was added n-BuLi (4.4 mL, 2.4 M in hexane, 11 mmol) dropwise under nitrogen at -76 °C. The reaction mixture was stirred at -76 °C for 15 minutes. The reaction was added to a solution of diethyl oxalate (4.7 mL, 35 mmol) in THF (10 mL) under nitrogen at -60 °C for 30 minutes. The reaction mixture was quenched with saturated NH₄Cl solution (10 mL) and water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **247C**.

[000938] To a solution of Compound **247C** (445 mg, 1.64 mmol) in dry dichloromethane (10 mL) was added DAST (0.55 mL, 4.09 mmol). The mixture was stirred at 25 °C for 14 hours. After the reaction was completed, dichloromethane (35 mL) was added. The organic layer was washed with water (20 mL), saturated sodium bicarbonate solution (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 20% v/v) to furnish Compound **247D**.

[000939] To a solution of Compound **247D** (458 mg, 1.57 mmol) in THF/water/MeOH (9 mL, 1:1:1, v/v) was added LiOH·H₂O (98 mg, 2.35 mmol). The mixture was stirred at 28 °C for 1 h. After the reaction was completed, it was adjusted to pH 6 with 2 N HCl. The reaction mixture was concentrated in *vacuo*. The crude product was lyophilized to furnish Compound **247E**.

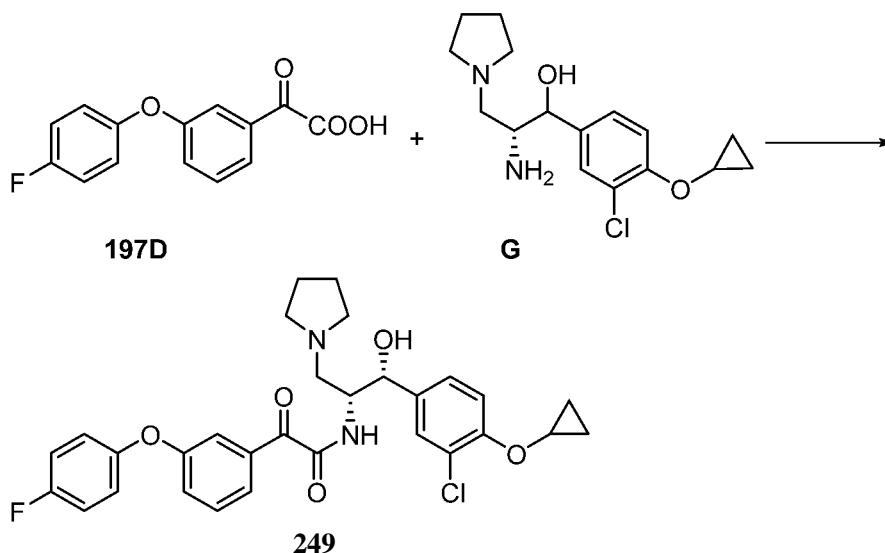
[000940] A mixture of Compound **247E** (88 mg, 0.33 mmol), Intermediate **G** (128 mg, 0.41 mmol), EDCI·HCl (96 mg, 0.49 mmol), and HOBt (67 mg, 0.49 mmol) in dichloromethane (15 mL) and DMF (2 mL) was stirred at 25 °C for 5 h. It was treated with water (20 mL), extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to furnish Compound **247**. LC-MS (ESI) m/z: 560 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.65-0.68 (m, 4H), 2.12-2.15 (m, 4H), 3.00-3.02 (m, 2H), 3.38-3.45 (m, 2H), 3.53-3.62 (m, 2H), 3.75-3.82 (m, 2H), 4.50-4.52 (m, 1H), 4.94-4.96 (d, *J* = 2.8 Hz, 1H), 7.07 (s, 2H), 7.20 (t, *J* = 8.8 Hz, 2H), 7.32-7.34 (m, 1H), 7.65-7.71 (m, 2H), 8.00-8.04 (m, 2H), 8.68 (s, 1H).

Example 248



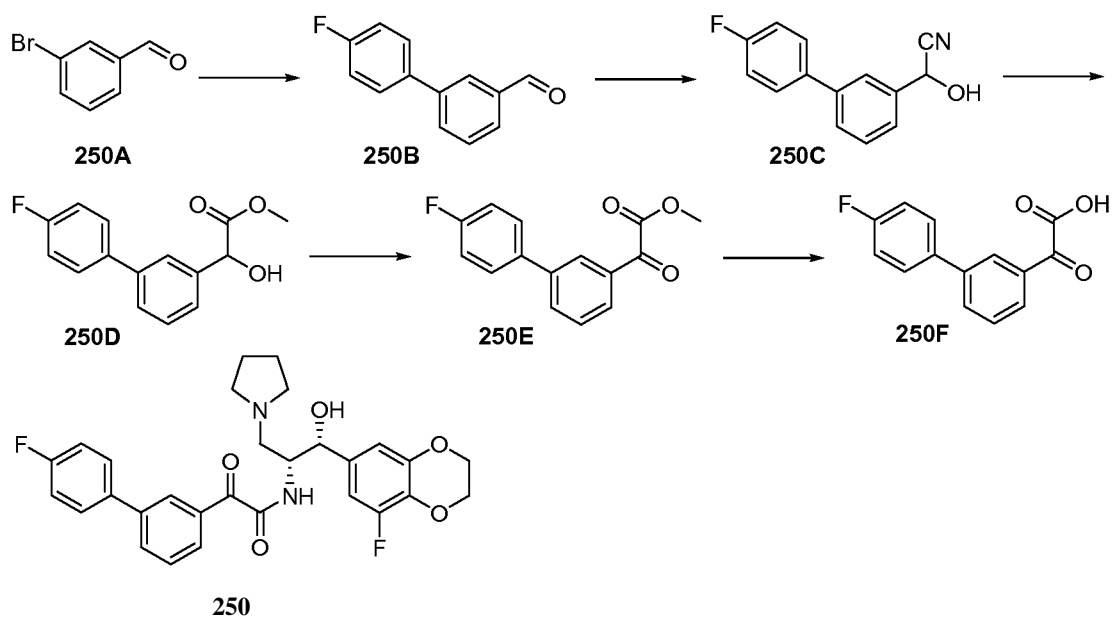
[000941] A mixture of Compound **197D** (52 mg, 0.20 mmol), Intermediate **H** (63 mg, 0.20 mmol), and HATU (119 mg, 0.30 mmol) in DMF (5 mL) was stirred at 10 °C for 3 h. The mixture was purified with prep-HPLC to furnish Compound **248**. LC-MS (ESI) m/z : 525 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.34-2.46 (m, 1H), 2.55-2.66 (m, 1H), 3.34 (s, 1H), 3.41-3.47 (m, 1H), 3.56 (dd, $J = 8, 12$ Hz, 1H), 4.07-4.15 (s, 5H), 4.22-4.29 (m, 3H), 4.85 (s, 1H), 6.62-6.63 (m, 2H), 6.66-7.02 (m, 4H), 7.13 (d, $J = 8$ Hz, 1H), 7.31 (t, $J = 8$ Hz, 1H), 7.52 (t, $J = 8$ Hz, 2H).

Example 249



[000942] To a mixture of Compound **197D** (130 mg, 0.5 mmol) and intermediate **G** (148 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 50% v/v) to furnish Compound **249**. LC-MS (ESI) m/z : 553 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.67-0.68 (m, 2H), 0.81-0.82 (m, 2H), 1.63-1.69 (m, 4H), 2.462-2.468 (m, 2H), 2.56-2.63 (m, 4H), 3.91-3.92 (m, 1H), 4.21-4.25 (m, 1H), 4.80 (s, 1H), 5.69 (s, 1H), 7.11-7.13 (m, 2H), 7.27-7.54 (m, 9H), 8.64-8.66 (d, $J = 8.6$ Hz, 1H).

Example 250



[000943] A mixture of Compound **250A** (5.0 g, 27 mmol), 4-fluorophenylboronic acid (4.92 g, 35.13 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.19 g, 1.62 mmol), potassium carbonate (11.2 g, 81.07 mmol), water (38 mL) and 1,4-dioxane (38 mL) was stirred under nitrogen atmosphere at 120 °C for 6 h. After cooling, water (20 mL) was added, and the mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed until neutral and dried over anhydrous sodium sulfate. After removal of the solvent in *vacuo*, the crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **250B**.

[000944] To a solution of Compound **250B** (3.0 g, 14.98 mmol) in water (40 mL) was added sodium metabisulfite (2.85 g, 14.98 mmol). The reaction mixture was stirred at room temperature for 1 h. After that, NaCN (1.47 g, 29.97 mmol) was added carefully. The mixture was stirred for 12 h and treated with ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the organic phase was washed with water (20 mL) and brine (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* to afford the crude product, which was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 20% to 40% v/v) to furnish Compound **250C**.

[000945] To a solution of Compound **250C** (2.5 g, 11 mmol) in methanol (25 mL) at 0 °C was bubbled a gentle stream of HCl (gas) (dried over con. H₂SO₄) for 6 h. The reaction mixture was diluted with water (20 mL) and stirred at room temperature for 2 h. An aqueous

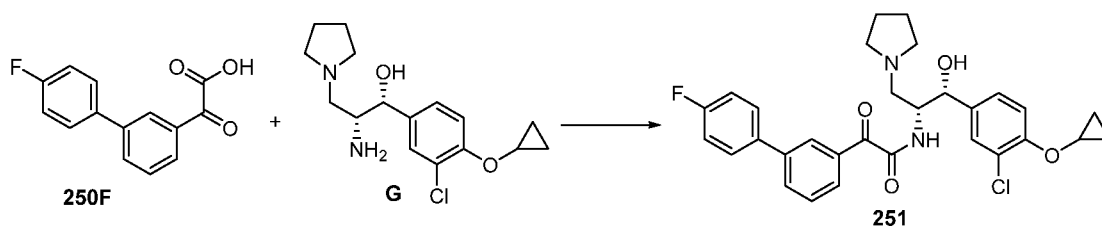
solution of NaOH (2 M) was added dropwise into the reaction mixture until the pH was adjusted to 7. The mixture was extracted with dichloromethane (50 mL x 3) and washed with water (50 mL) and brine (50 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product. The crude compound was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 15% to 20% v/v) to furnish Compound **250D**.

[000946] To a solution of Compound **250D** (2.3 g, 8.84 mmol) in dichloromethane (30 mL) was added 1,2-benziodoxol-3(1H)-one (2.41 g, 9.72 mmol) at 0 °C. The mixture was stirred at this temperature for 4 h. After that, the reaction solution was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (30 mL x 3). The organic phase was washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude product. The crude oil was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **250E**.

[000947] To a solution of Compound **250E** (1.80 g, 6.97 mmol) in THF (20 mL) was added LiOH·H₂O (335 mg, 7.98 mmol) in water (14 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction mixture was treated with ice water (10 mL) and extracted with ethyl acetate (50 mL). The water layer was adjusted to pH 2 with diluted HCl and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resulting solid was washed with petroleum ether and filtered off to afford Compound **250F**.

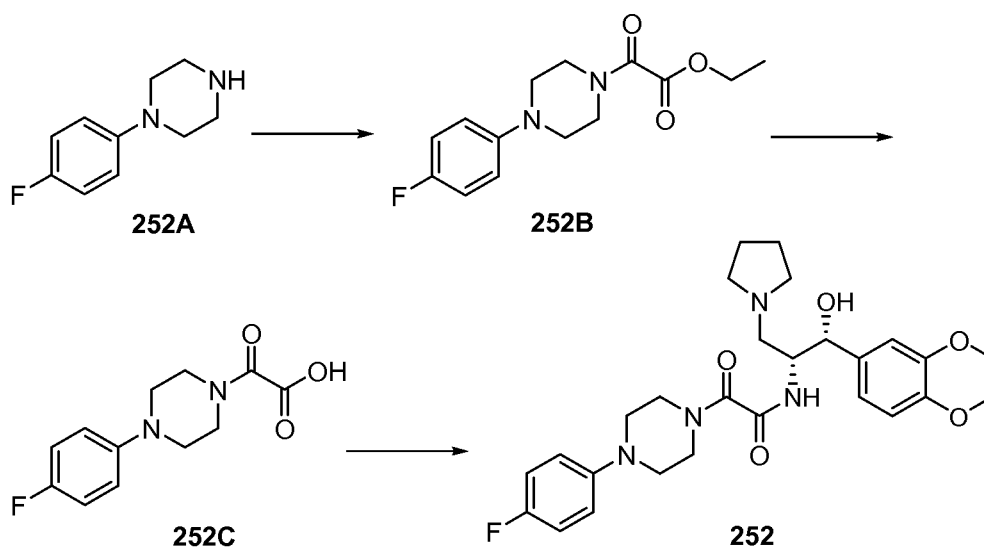
[000948] A mixture of Compound **250F** (110 mg, 0.45 mmol), Intermediate C (146 mg, 0.49 mmol), and HATU (205 mg, 0.54 mmol) in dichloromethane (3 mL) and DMF (3 mL) was stirred at 0 °C for 4 h. The mixture was concentrated in *vacuo* and the resulting residue was purified with prep-HPLC to furnish the crude product as a white solid. The crude solid was further purified with prep-TLC on silica gel (ethyl acetate in petroleum ether, 30% v/v) to furnish Compound **250**. LC-MS (ESI) m/z: 523 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.82-1.85 (m, 4H), 2.72-2.78 (m, 4H), 2.99-3.03 (m, 2H), 4.23-4.31 (m, 5H), 5.05 (d, *J* = 2.1, 1H), 6.70 (s, 1H), 6.74 (dd, *J* = 11.3, 1.9 Hz, 1H), 7.15 (t, *J* = 8.7 Hz, 3H), 7.42-7.59 (m, 3H), 7.79 (d, *J* = 8.3, 1H), 8.20 (d, *J* = 6.7, 1H), 8.44 (s, 1H). Chiral separation condition: n-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30 : 60, column: OD-H (250 * 4.6 mm 5 μm), retention time: 4.09 min.

Example 251



[000949] A mixture of Compound **250F** (130 mg, 0.53 mmol), Intermediate **G** (182 mg, 0.58 mmol), and HATU (304 mg, 0.79 mmol) in dichloromethane (3 mL) and DMF (3 mL) was stirred at 0 °C for 4 h. The mixture was concentrated in *vacuo* and purified with prep-HPLC to furnish the crude product as a yellow solid. The crude solid was further purified with prep-TLC on silica gel (ethyl acetate in petroleum ether, 30% v/v) to furnish Compound **251**. LC-MS (ESI) m/z : 537 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.71 (dd, $J = 10.7, 4.5$ Hz, 4H), 1.89 (s, 1H), 2.08 (s, 4H), 3.12 (s, 2H), 3.48-3.71 (m, 2H), 3.83-3.94 (m, 3H), 4.55 (s, 1H), 5.07 (s, 1H), 7.08-7.12 (m, 2H), 7.15-7.23 (m, 2H), 7.35 (d, $J = 1.8$ Hz, 1H), 7.38-7.49 (m, 3H), 7.71 (d, $J = 7.9$ Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 8.12 (s, 1H).

Example 252

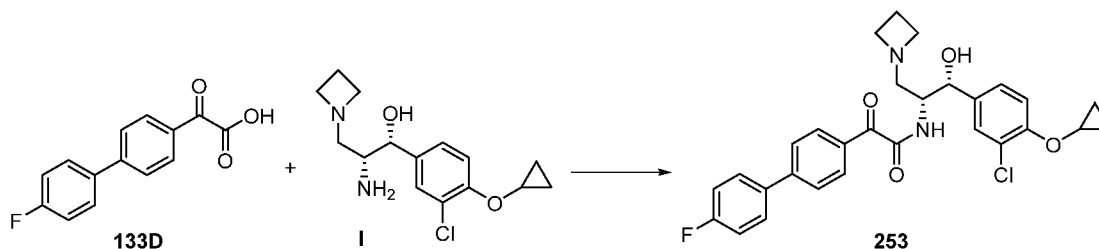


[000950] To a mixture of Compound **252A** (1.8 g, 0.01 mol) and triethylamine (3 g, 0.03 mol) in dichloromethane (100 mL) was added ethyl 2-chloro-2-oxoacetate (2.1 g, 0.015 mol). The mixture was stirred at room temperature for about 2 h until it was complete by thin layer chromatography analysis. The resulting mixture was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50%, v/v) to furnish Compound **252B**.

[000951] To a solution of Compound **252B** (2.8 g, 0.01 mol) in ethanol/water (40 mL/10 mL) was added LiOH·H₂O (840 mg, 0.02 mol). The mixture was stirred at room temperature for about 2 h until it was complete by thin layer chromatography analysis. The reaction mixture was acidified to pH 2 with aqueous HCl solution (1.0 N, 40 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **252C**.

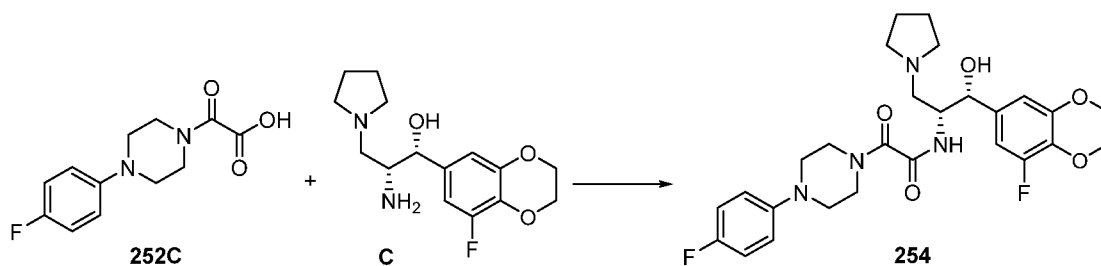
[000952] To a mixture of Compound **252C** (126 mg, 0.5 mmol) and Intermediate A (139 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **252**. LC-MS (ESI) m/z: 513 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 1.83-1.84 (m, 4H), 2.68-2.72 (m, 5H), 2.88-2.94 (m, 2H), 3.03-3.06 (m, 2H), 3.09-3.14 (m, 1H), 3.33-3.37 (m, 2H), 3.58-3.66 (m, 1H), 3.75-3.81 (m, 1H), 4.20-4.21 (m, 4H), 4.37-4.39 (m, 1H), 4.84-4.85 (m, 1H), 6.79-6.81 (m, 1H), 6.86-6.88 (m, 1H), 6.96 (s, 1H), 7.01-7.04 (m, 4H);

Example 253



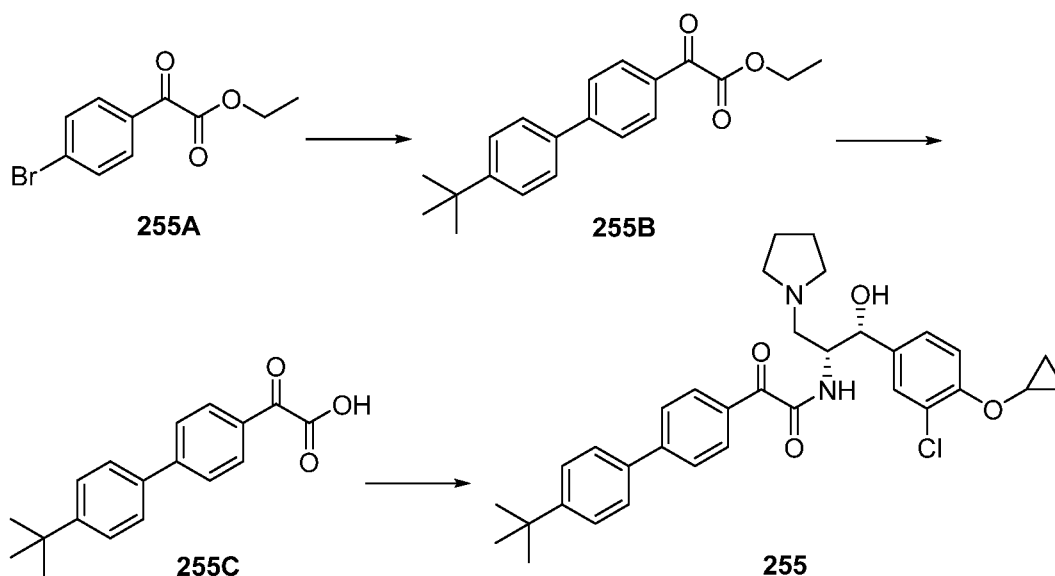
[000953] A mixture of Compound **133D** (146 mg, 0.60 mmol), EDCI (193 mg, 0.90 mmol), HOBt (119 mg, 0.9 mmol) and Intermediate **I** (178 mg, 0.60 mmol) in DCM (20 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (50 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **253**. LC-MS (ESI) m/z: 523.1 [M+H]⁺, ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.71-0.84 (m, 4H), 2.45-2.66 (m, 2H), 3.57-3.67 (m, 2H), 3.84-3.86 (m, 1H), 4.21-4.36 (m, 5H), 4.55-4.57 (m, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 7.21-7.28 (m, 2H), 7.35-7.40 (m, 2H), 7.52 (s, 1H), 7.64-7.67 (m, 4H), 7.73-7.77 (m, 2H).

Example 254



[000954] To a mixture of Compound **252C** (126 mg, 0.5 mmol) and Intermediate **C** (150 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **254**. LC-MS (ESI) m/z : 531 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.86-2.01 (m, 4H), 2.87-3.84 (m, 14H), 4.27 (s, 4H), 4.40-4.43 (m, 1H), 4.47 (s, 1H), 6.73 (s, 1H), 6.80-6.81 (m, 1H), 6.83-6.85 (m, 2H), 7.06-7.18 (m, 2H), 8.68 (d, $J = 9.6$ Hz, 1H), 9.83 (brs, 1H).

Example 255

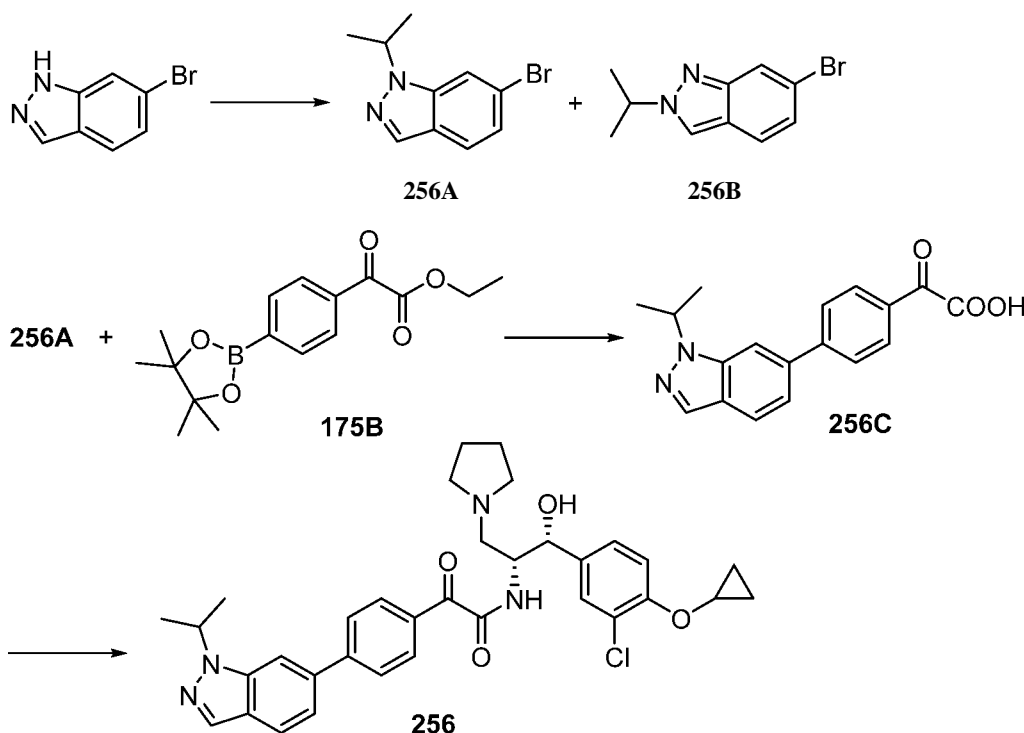


[000955] A mixture of Compound **255A** (0.72 g, 2.8 mmol), K_3PO_4 (1.78 g, 8.4 mmol), (4-(tert-butyl)phenyl)boronic acid (0.5 g, 2.8 mmol), and $Pd(dppf)Cl_2$ (20 mg, 0.28 mmol) in toluene (10 mL) was stirred under nitrogen at 100 °C for 16 h. The mixture was cooled to 25 °C, diluted with ethyl acetate (50 mL), washed with water (20 mL x 2) and brine (20 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound **255B**.

[000956] A mixture of Compound **255B** (0.45 g, 1.5 mmol) and LiOH·H₂O (0.09 g, 2.2 mmol) in THF (5 mL) and water (2 mL) was stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to afford Compound **255C**.

[000957] A mixture of Compound **255C** (0.1 g, 0.35 mmol), HATU (0.2 g, 0.5 mmol), and Intermediate **G** in dichloromethane (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **255**. LC-MS (ESI) m/z: 575 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.67-0.68 (m, 2H), 0.82-0.83 (m, 2H), 1.33 (s, 9H), 1.88-1.90 (m, 2H), 2.04 (s, 2H), 3.13-3.23 (m, 2H), 3.48-3.56 (m, 4H), 3.93 (s, 1H), 4.54-4.59 (m, 1H), 4.88 (s, 1H), 6.05 (s, 1H), 7.36-7.44 (m, 3H), 7.53-7.56 (m, 2H), 7.68-7.77 (m, 6H), 8.78-8.81 (m, 1H), 9.36 (s, 1H).

Example 256



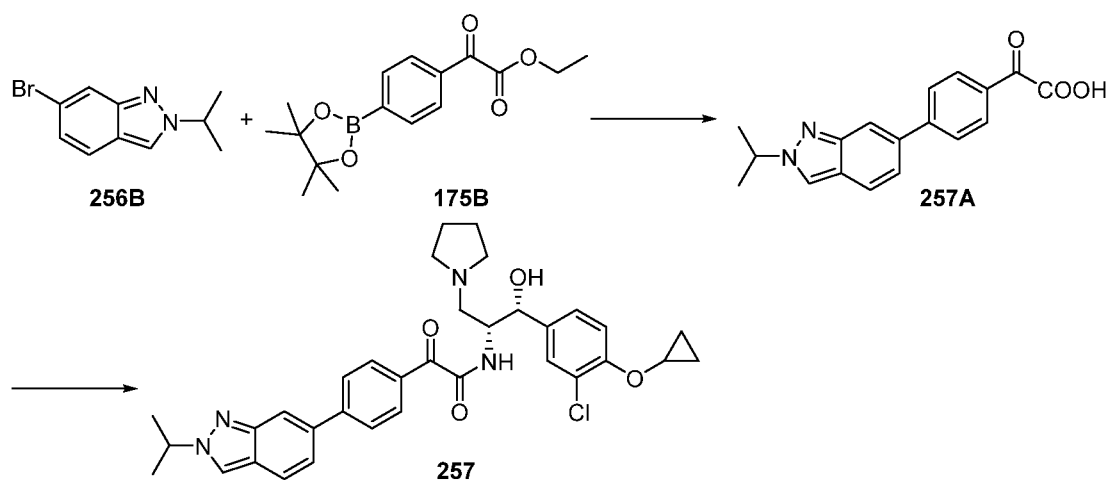
[000958] To 6-bromoindazole (3.2 g, 16.2 mmol) in DMF (30 mL) was added sodium hydride (60% in mineral, 712 mg, 17.8 mmol) with ice bath cooling. The mixture was stirred at room temperature for 30 min. Compound 2-iodopropane (8.3 g 48.6 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried

over anhydrous sodium sulfate, and concentrated. Purification with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 1% v/v) gave Compound **256A** and Compound **256B**.

[000959] A mixture of Compound **256A** (1.0 g, 4.2 mmol), Compound **175B** (1.28 g, 4.2 mmol), Pd(dppf)Cl₂ (171 mg, 0.21 mmol), and K₂CO₃ (1.74 g, 12.6 mmol) in dioxane (20 mL) and water (20 mL) was stirred under nitrogen at 100 °C for 3.5 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **256C**.

[000960] A mixture of Compound **256C** (100 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol), and Intermediate **G** (99 mg, 0.32 mmol) in DMF (5 mL) was stirred for 18 h at 10 °C. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **256**. LC-MS (ESI) m/z: 601 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.63-0.85 (m, 4H), 1.52 (dd, *J* = 6.4, 1.6 Hz, 6H), 1.89-2.05 (m, 4H), 3.13-3.25 (m, 2H), 3.41-3.58 (m, 4H), 3.93-3.98 (m, 1H), 4.57-4.62 (m, 1H), 4.91 (s, 1H), 5.12-5.18 (m, 1H), 6.10 (s, 1H), 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43-7.48 (m, 2H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 3H), 8.09 (s, 1H), 8.14 (s, 1H), 8.84 (d, *J* = 9.6 Hz, 1H), 9.59 (brs, 1H).

Example 257

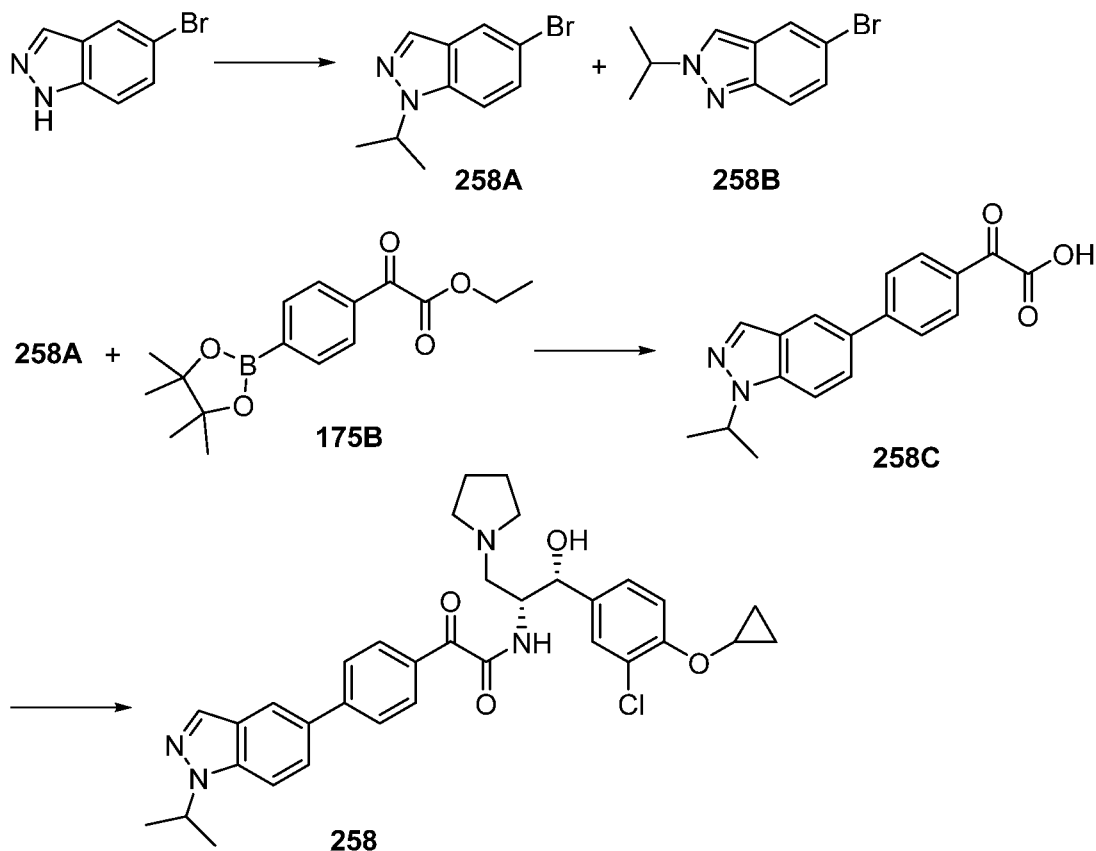


[000961] A mixture of Compound **175B** (500 mg, 2.1 mmol), Compound **256B** (638 mg, 2.1 mmol), Pd(dppf)Cl₂ (92 mg, 0.11 mmol), and K₂CO₃ (869 mg, 6.3 mmol) in dioxane

(10 mL) and water (10 mL) was stirred under nitrogen at 100 °C for 3.5 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **257A**.

[000962] A mixture of Compound **257A** (100 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol), and Intermediate **G** (99 mg, 0.32 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL x 2) and brine (50 mL), and dried over anhydrous sodium sulfate. After evaporation, the crude product was purified with prep-HPLC to furnish Compound **257**. LC-MS (ESI) *m/z*: 601 [M+H]⁺; ¹H-NMR (*O**M**S**O*-*d*₆, 400 MHz): δ (ppm) 0.68-0.84 (m, 4H), 1.58 (d, *J* = 6.4 Hz, 6H), 1.89-2.04 (m, 4H), 3.09-3.22 (m, 2H), 3.43-3.58 (m, 4H), 3.93-3.97 (m, 1H), 4.56-4.61 (m, 1H), 4.84-4.92 (m, 2H), 6.08-6.09 (m, 1H), 7.35-7.38 (m, 1H), 7.41-7.46 (m, 3H), 7.75-7.77 (m, 2H), 7.82-7.85 (m, 3H), 8.01 (s, 1H), 8.48 (s, 1H), 8.83 (d, *J* = 10.0 Hz, 1H), 9.65 (brs, 1H).

Example 258



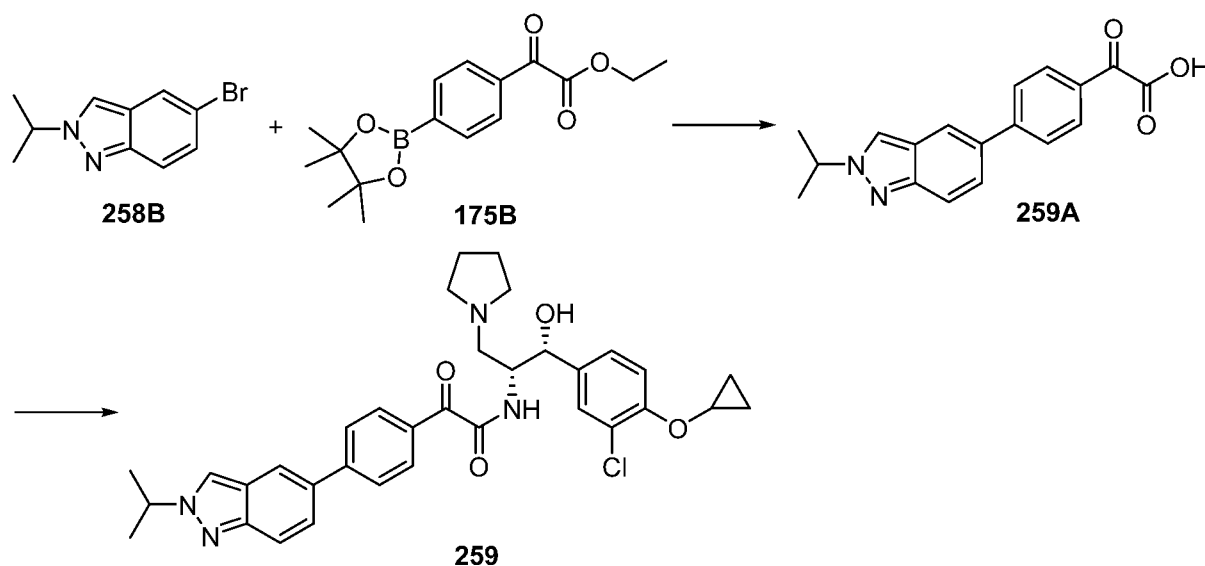
[000963] To a solution of 5-bromo-1H-indazole (5.91 g, 30 mmol) in anhydrous DMF (100 mL) was added 2-bromopropane (8.67 g, 70.5 mmol) and cesium carbonate (29.2 g, 90

mmol) at room temperature. After stirring the reaction mixture at room temperature for 3 h, 2 *N* hydrochloric acid was added until a neutral pH was reached. The aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic extracts were washed with brine (100 mL x 2) and dried over anhydrous sodium sulfate. After filtration, the solvent was removed in *vacuo* and the residue was purified with flash column chromatography on silica gel to give Compound **258A** and Compound **258B**.

[000964] To a solution of Compound **258A** (180 mg, 0.75 mmol) in 1,4-dioxane (15 mL) was added Compound **175B** (250 mg, 0.825 mmol), Pd(dppf)Cl₂ (30 mg, 0.0375 mmol), potassium carbonate (310 mg, 2.25 mmol) and water (1 mL) under nitrogen. The reaction mixture was stirred at 100 °C for 2 hours. The resulting mixture was cooled to 25 °C. The precipitated solid was filtered and dried to afford Compound **258C**.

[000965] To a solution of Compound **258C** (45 mg, 0.146 mmol) in DMF (3 mL) was added Intermediate **G** (45 mg, 0.146 mmol) and HATU (83 mg, 0.219 mmol). The reaction mixture was stirred at 20 °C for 10 h. The mixture was purified with prep-HPLC to yield the product Compound **258**. LC-MS (*m/z*) 601 [M+H]⁺; ¹H-NMR (Acetone-*d*₆, 400 MHz): δ (ppm) 0.71-0.72 (m, 2H), 0.82-0.84 (m, 2H), 1.57 (s, 3H), 1.58 (s, 3H), 2.05-2.25 (m, 4H), 3.45-3.60 (m, 2H), 3.82-4.15 (m, 5H), 4.92-4.97 (m, 1H), 5.02-5.09 (m, 1H), 5.20-5.21 (m, 1H), 5.47-5.50 (m, 1H), 7.42-7.44 (m, 2H), 7.51-7.52 (m, 1H), 7.79-7.83 (m, 4H), 7.97-7.99 (m, 2H), 8.12-8.16 (m, 2H), 8.19-8.21 (m, 1H), 8.94 (brs, 1H).

Example 259

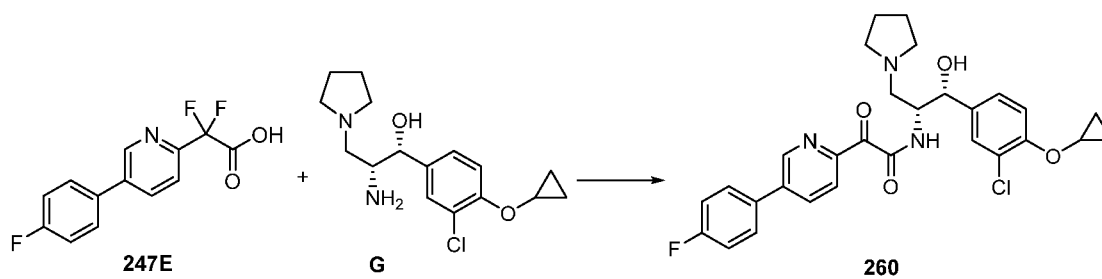


[000966] To a solution of Compound **258B** (180 mg, 0.75 mmol) in 1,4-dioxane (15 mL) was added Compound **175B** (250 mg, 0.825 mmol), Pd(dppf)Cl₂ (30 mg, 0.0375 mmol),

potassium carbonate (310 mg, 2.25 mmol) and water (1 mL) under nitrogen. The reaction mixture was stirred at 100 °C for 2 hours. The resulting mixture was cooled to 25 °C. The precipitated solid was filtered and dried to afford Compound **259A**.

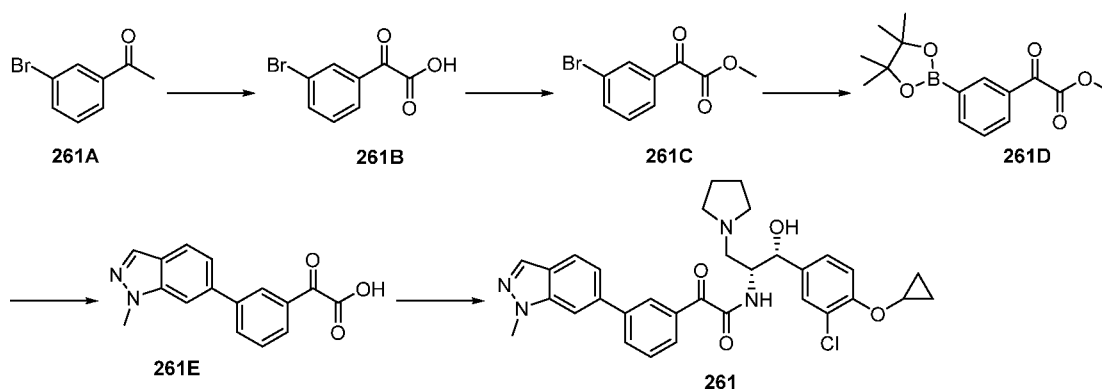
[000967] To a solution of Compound **259A** (74 mg, 0.24 mmol) in DMF (3 mL) was added Intermediate **G** (74 mg, 0.24 mmol) and HATU (136 mg, 0.36 mmol). The reaction mixture was stirred at 20 °C for 10 h. The mixture was purified with prep-HPLC to yield the product Compound **259**. LC-MS (*m/z*) 601 [M+H]⁺; ¹H-NMR (acetone-*d*₆, 400 MHz): δ (ppm) 0.70-0.72 (m, 2H), 0.79-0.84 (m, 2H), 1.68 (s, 3H), 1.70 (s, 3H), 2.05-2.13 (m, 2H), 2.26-2.28 (m, 2H), 3.43-3.56 (m, 2H), 3.85-3.91 (m, 3H), 4.06-4.09 (m, 2H), 4.93-5.01 (m, 2H), 5.20-5.21 (m, 1H), 7.39-7.46 (m, 2H), 7.51-7.52 (m, 1H), 7.75-7.82 (m, 4H), 7.97-7.99 (m, 2H), 8.16-8.21 (m, 2H), 8.58-8.59 (m, 1H), 8.82 (brs, 1H).

Example 260



[000968] To a mixture of Compound **247E** (100 mg, 0.3 mmol) in THF (10 mL) and DMF (2 mL) was added EDCI (106 mg, 0.55 mmol), HOBt (74 mg, 0.55 mmol) and Intermediate **G** (115 mg, 0.37 mmol). The mixture was stirred at 25 °C for 15 hours. It was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with prep-HPLC to afford Compound **260**. LC-MS (ESI) *m/z*: 538 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.61-0.75 (m, 4H), 2.06-2.20 (m, 4H), 3.22-3.28 (m, 2H), 3.56-3.80 (m, 5H), 4.61-4.64 (m, 1H), 4.94 (s, 1H), 7.21-7.31 (m, 4H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.77-7.80 (m, 2H), 8.19 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.82 (s, 1H).

Example 261



[000969] A suspension of Compound **261A** (6.00 g, 30.15 mmol) and SeO_2 (5.02 g, 45.22 mmol) in pyridine (50 mL) was stirred at 100 °C for 16 h. It was filtered to remove the resultant solid and the filtrate was evaporated to remove pyridine. The residue was dissolved in aqueous NaOH solution (5% w/w, 200 mL) and extracted with diethyl ether (100 mL x 2). The aqueous was adjusted to pH 1 with con. HCl to form a solid, which was filtered and dried to afford Compound **261B**.

[000970] A mixture of Compound **261B** (3.00 g, 13.22 mmol) and concentrated H_2SO_4 (1 mL) in methanol (50 mL) was stirred at 80 °C for 16. After evaporation, the residue was diluted with ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to furnish Compound **261C**.

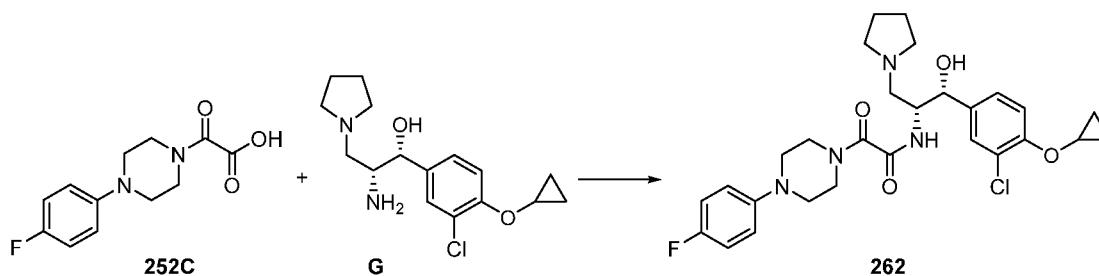
[000971] A mixture of Compound **261C** (1.58 g, 6.53 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.82 g, 7.18 mmol), KOAc (1.92 g, 19.59 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (229 mg, 0.33 mmol) in dioxane (50 mL) was stirred under nitrogen at 90 °C for 16 h. It was diluted with ethyl acetate (150 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and evaporated to afford Compound **261D**.

[000972] A mixture of Compound **261D** (500 mg, 1.72 mmol), 6-bromo-1-methyl-1H-indazole (364 mg, 1.72 mmol), K_2CO_3 (475 mg, 3.44 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (70 mg, 0.09 mmol) in dioxane (10 mL) and water (2 mL) was stirred under nitrogen at 85 °C for 16 h. The mixture was cooled down to room temperature and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to give Compound **261E**.

[000973] A mixture of Compound **261E** (100 mg, 0.36 mmol), Intermediate **G** (111 mg, 0.36 mmol), and HATU (207 mg, 0.54 mmol) in DMF (5 mL) was stirred at room

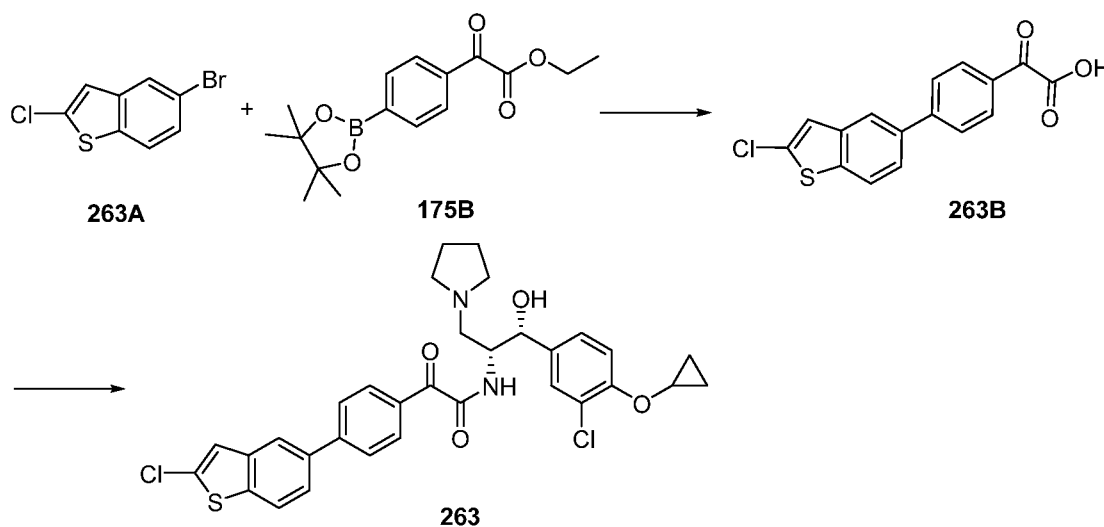
temperature for 16 h. It was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to yield Compound **261**. LC-MS (ESI) m/z : 573 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.63-0.78 (m, 4H), 1.87-2.03 (m, 4H), 3.15 (brs, 2H), 3.49-3.84 (m, 4H), 4.12 (s, 4H), 4.54 (s, 1H), 4.86 (s, 1H), 6.09 (s, 1H), 7.34-7.68 (m, 6H), 7.86-8.31 (m, 5H), 8.81 (s, 1H), 9.42 (s, 1H).

Example 262



[000974] To a mixture of Compound **252C** (126 mg, 0.5 mmol) and Intermediate **G** (160 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with dichloromethane (50 mL), washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **262**. LC-MS (ESI) m/z : 545 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.64-0.65 (m, 2H), 0.81-0.82 (m, 2H), 1.86-2.01 (m, 4H), 2.80-3.65 (m, 14H), 3.91-3.93 (m, 1H), 4.47-4.48 (m, 1H), 4.87-4.88 (m, 1H), 6.04 (br s, 1H), 6.94-6.96 (m, 2H), 7.13-7.18 (m, 2H), 7.68-7.84 (m, 3H), 8.69 (d, $J = 9.6$ Hz, 1H), 10.10 (brs, 1H).

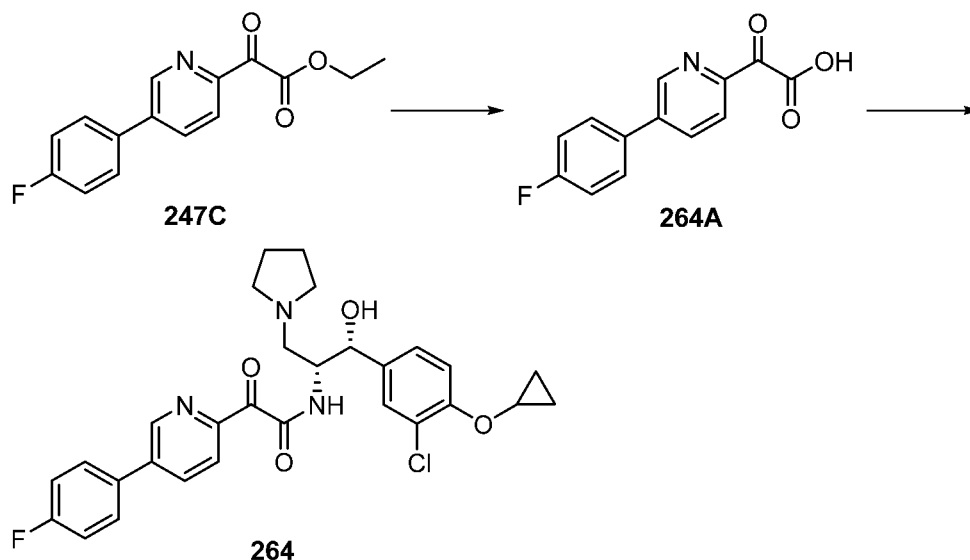
Example 263



[000975] A mixture of Compound **263A** (492 mg, 2 mmol), Compound **175B** (669 mg, 2.2 mmol), K_2CO_3 (828 mg, 6 mmol), and $Pd(dppf)Cl_2$ (50 mg, 0.07 mmol) in dioxane (20 mL) and water (4 mL) was stirred under nitrogen at 100 °C overnight. The solution was cooled to room temperature and adjusted to pH 6 with aqueous hydrochloric acid solution (6 N, 1 mL). The solution was extracted with ethyl acetate (100 mL x 3). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to afford Compound **263B**.

[000976] A mixture of Compound **263B** (156 mg, 0.5 mmol), HATU (342 mg, 0.9 mmol), and Intermediate **G** (155 mg, 0.5 mmol) in dichloromethane (10 mL) and DMF (4 mL) was stirred at 25 °C overnight. The solution was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The crude product was purified with prep-HPLC to afford Compound **263**. LC-MS (ESI) m/z : 609 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.66-0.85 (m, 4H), 2.05-2.25 (m, 4H), 3.42-3.90 (m, 7H), 4.71-4.74 (m, 1H), 5.00 (s, 1H), 7.38-7.39 (m, 2H), 7.42 (s, 1H), 7.47-7.52 (m, 1H), 7.73-7.76 (m, 5H), 7.93-7.95 (m, 1H), 8.08-8.09 (m, 1H).

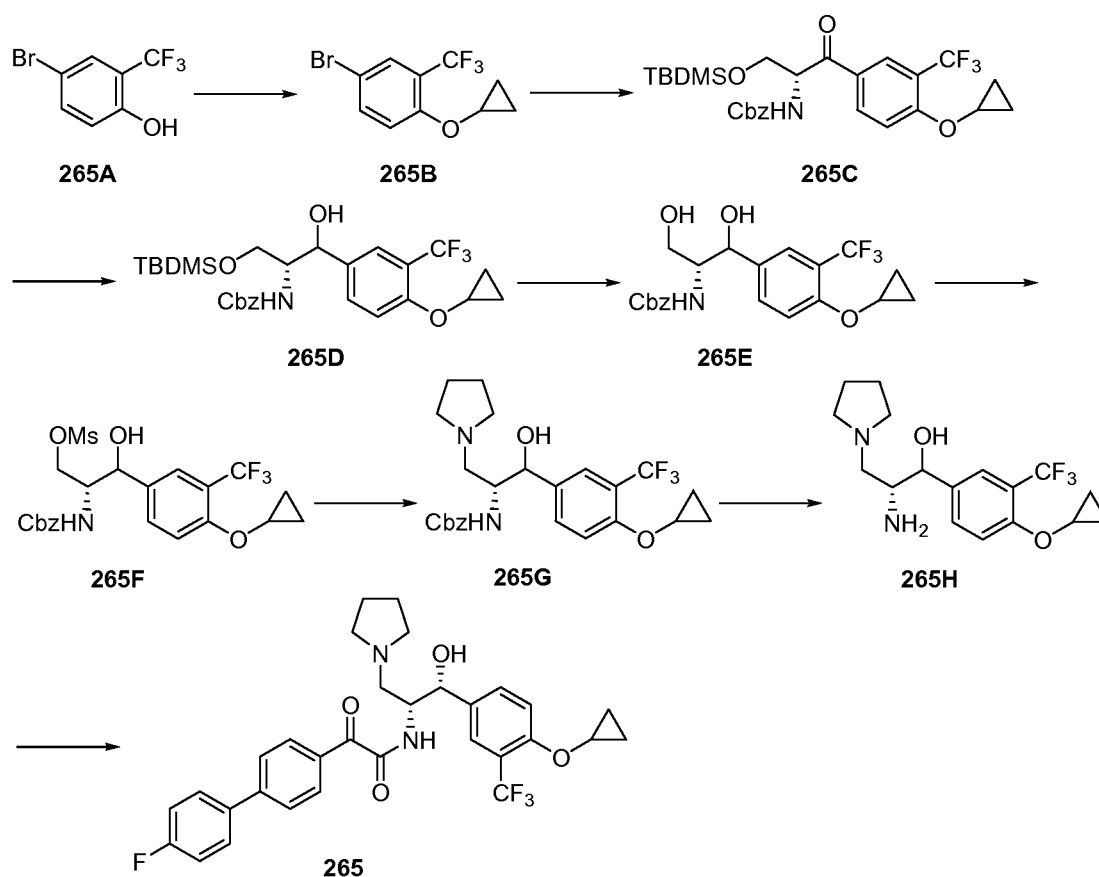
Example 264



[000977] To a solution of Compound **247C** (500 mg, 1.82 mmol) in methanol/water (10 mL, 1:1, v/v) was added $LiOH \cdot H_2O$ (153 mg, 3.64 mmol). The reaction mixture was stirred at 15 °C for 18 h. After the reaction was completed, it was adjusted to pH 6 with aqueous HCl solution (3 N) and concentrated *in vacuo* to give a crude compound. The crude product was lyophilized to furnish Compound **264A**.

[000978] To a mixture of Compound **264A** (90 mg, 0.37 mmol) in dichloromethane (5 mL) was added HATU (213 mg, 0.55 mmol) and Intermediate **G** (115 mg, 0.37 mmol). The mixture was stirred at 15 °C for 18 h. It was treated with water (20 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with prep-HPLC to afford Compound **264**. LC-MS (ESI) m/z : 538 $[M+H]^+$; ¹H-NMR (**DMSO-*d*₆**, 400 MHz): δ (ppm) 0.65-0.84 (m, 4H), 1.87-2.08 (m, 4H), 3.10-3.26 (m, 3H), 3.62-3.72 (m, 3H), 3.91-3.95 (m, 1H), 4.50-4.55 (m, 1H), 4.88 (d, $J = 2.8$ Hz, 1H), 6.09 (brs, 1H), 7.36-7.49 (m, 5H), 7.91-7.94 (m, 2H), 8.06 (d, $J = 8.4$ Hz, 1H), 8.33 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.99 (d, $J = 2.0$ Hz, 1H), 9.13 (d, $J = 9.2$ Hz, 1H), 9.53 (brs, 1H).

Example 265



[000979] To a solution of Compound **265A** (11.6 g, 48 mmol) in 1-methyl-2-pyrrolidinone (150 mL) was added cesium carbonate (33 g, 87 mmol) and bromocyclopropane (16.5 mL, 1999 mmol). The mixture was stirred for 24 h while keeping inner temperature between 145 °C and 155 °C. After the reaction was cooled to ambient temperature, the dark solution was diluted with water (400 mL) and extracted with a mixture of ethyl acetate in petroleum ether (15% v/v) (300 mL x 3). The combined organic phases

were washed with brine (150 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **265B**.

[000980] To a solution of Compound **265B** (6.79 g, 8.1 mmol) in dry THF (200 mL) maintained at -70 °C was added n-BuLi (2.5 M in hexane, 9.76 mL) dropwise under nitrogen atmosphere over a period of 20 minutes. After the reaction was stirred at -70 °C for 40 minutes, Intermediate **A4** (3.2 g, 8.1 mmol) dissolved in dry THF (20 mL) was added slowly to the cold solution at a rate that maintained the internal temperature between -70 °C and -50 °C. After the addition was complete, the solution was left to stir for 1 h. The reaction was quenched with saturated ammonium chloride solution (400 mL) and extracted with ethyl acetate (300 mL x 3). The organic phase was washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude Compound **265C**. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **265C**.

[000981] To a solution of Compound **265C** (5.95 g, 110 mmol) in dry THF (70 mL) was added L-Selectride (1.0 M in THF, 23.7 mL) dropwise under nitrogen atmosphere while keeping the temperature at -90 °C. After the addition was complete, the solution was allowed to stir at this temperature for 1 h. The reaction was quenched with saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (100 mL x 2), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **265D**.

[000982] To a solution of Compound **265D** (5.4 g, 10 mmol) in THF (100 mL) was added tetrabutylammonium fluoride (1.31 g, 5.0 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h. After that, the reaction mixture was evaporated to remove tetrahydrofuran. The mixture was treated with water (50 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic phases were washed with water (150 mL) and brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to furnish Compound **265E**.

[000983] To a solution of Compound **265E** (1.18 g, 2.78 mmol) dissolved in THF (50 mL) was added triethylamine (866 mg, 8.5 mmol). The mixture was cooled to -30 °C, and then methanesulfonyl chloride (389 mg, 3.41 mmol) was added dropwise over a period of 15 minutes. After the addition was complete, the reaction was stirred at -30 °C for 1.5 h, diluted

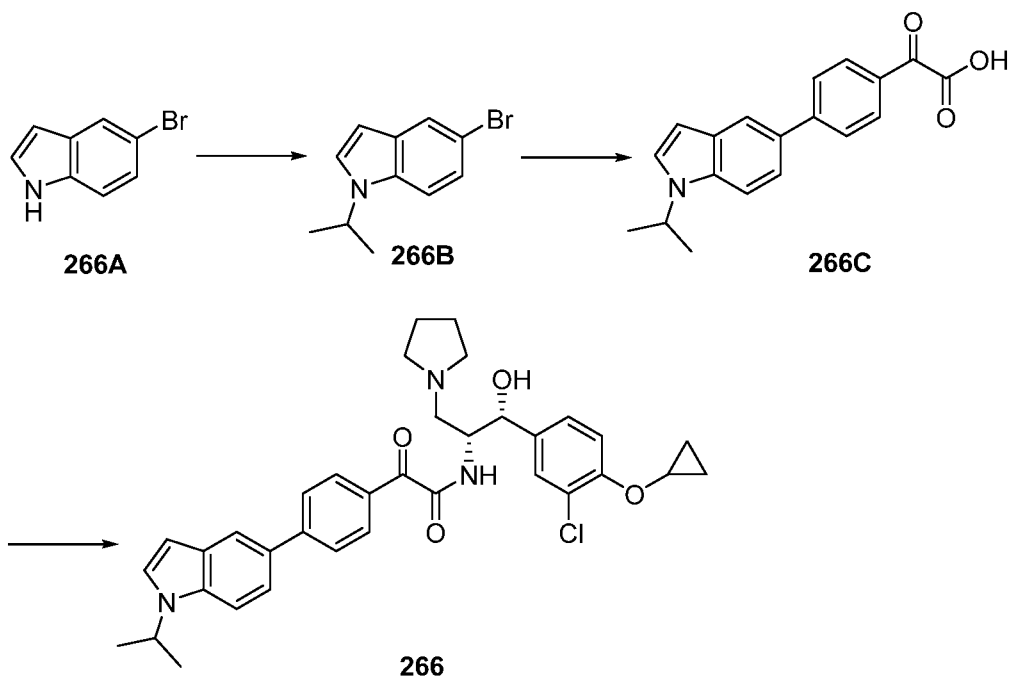
with water (50 mL), and extracted with ethyl acetate (150 mL x 2). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **265F**.

[000984] To a solution of Compound **265F** (1.0 g, 1.98 mmol) in THF (30 mL) was added pyrrolidine (2.3 g, 32 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (100 mL), extracted with ethyl acetate (150 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **265G**.

[000985] To a solution of Compound **265G** (100 mg, 0.21 mmol) in ethanol (8 mL) and water (2 mL) was added LiOH \cdot H₂O (56 mg, 1.33 mmol). The mixture was heated to 80 °C and stirred for 16 h. And then it was diluted with water (15 mL) and extracted with dichloromethane (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **265H**.

[000986] A mixture of Compound **265H** (100 mg, (0.21 mmol), HATU (95 mg, 0.25 mmol), and Intermediate **C** (40.8 mg, 0.17 mmol) in DCM (15 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **265**. LC-MS (ESI) m/z: 571.2 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.66-0.82 (m, 4H), 2.04-2.23 (m, 4H), 3.23-3.26 (m, 1H), 3.60-3.89 (m, 6H), 4.72-4.76 (m, 1H), 5.06 (d, *J* = 2.4 Hz, 1H), 7.22-7.26 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.67-7.77 (m, 8 H).

Example 266



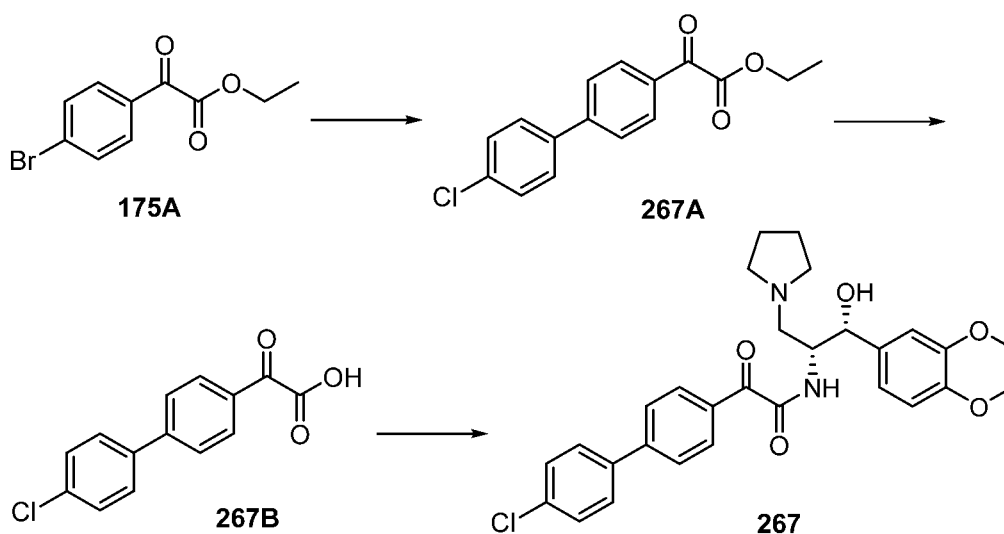
[000987] To a solution of Compound **266A** (1.96 g, 10 mmol) in DMF (50 mL) was added sodium hydride (60% suspend in oil, 800 mg, 20 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and 2-iodopropane (2.55 g, 15 mmol) was added at 0 °C. The resultant mixture was stirred at room temperature overnight, diluted with ethyl acetate (100 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **266B**.

[000988] A mixture of Compound **266B** (500 mg, 2.1 mmol), Pd(dppf)Cl₂ (86 mg, 0.1 mmol), **175B** (638 mg, 2.1 mmol), and K₂CO₃ (668 mg, 6.3 mmol) in dioxane (15 mL) and water (2 mL) was stirred under nitrogen at 100 °C overnight. The mixture was cooled down to room temperature, concentrated, diluted with water (50 mL), and extracted with ethyl acetate (30 mL x 3). The aqueous layer was acidified to pH 2 with aqueous HCl solution (1 N) and extracted with dichloromethane (10 mL x 3). The dichloromethane layer was dried over anhydrous sodium sulfate and filtered to afford Compound **266C**/dichloromethane solution. A solution of Compound **266C** in dichloromethane was directly used for the next step without further purification.

[000989] To a solution of Compound **266C** in dichloromethane (15 mL, from previous step) was added Intermediate **G** (155 mg, 0.5 mmol) and HATU (380 mg, 1 mmol). The mixture was stirred at room temperature overnight. The mixture was purified with prep-

HPLC to furnish Compound **266**. LC-MS (ESI) m/z : 600 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.67-0.71 (m, 2H), 0.81-0.86 (m, 2H), 1.48 (d, $J = 6.4$ Hz, 6H), 1.88-1.92 (m, 2H), 2.03-2.08 (m, 2H), 3.13-3.24 (m, 2H), 3.43-3.52 (m, 4H), 3.93-3.97 (m, 1H), 4.56-4.61 (m, 1H), 4.79-4.86 (m, 1H), 4.89-4.89 (m, 1H), 6.04 (brs, 1H), 6.56 (d, $J = 3.6$ Hz, 1H), 7.35-7.37 (m, 1H), 7.42-7.46 (m, 2H), 7.52-7.55 (m, 1H), 7.59-7.59 (m, 1H), 7.66-7.68 (m, 1H), 7.72-7.74 (m, 2H), 7.78-7.80 (m, 2H), 7.69 (d, $J = 1.6$ Hz, 1H), 8.79 (d, $J = 9.2$ Hz, 1H), 9.34 (brs, 1H).

Example 267

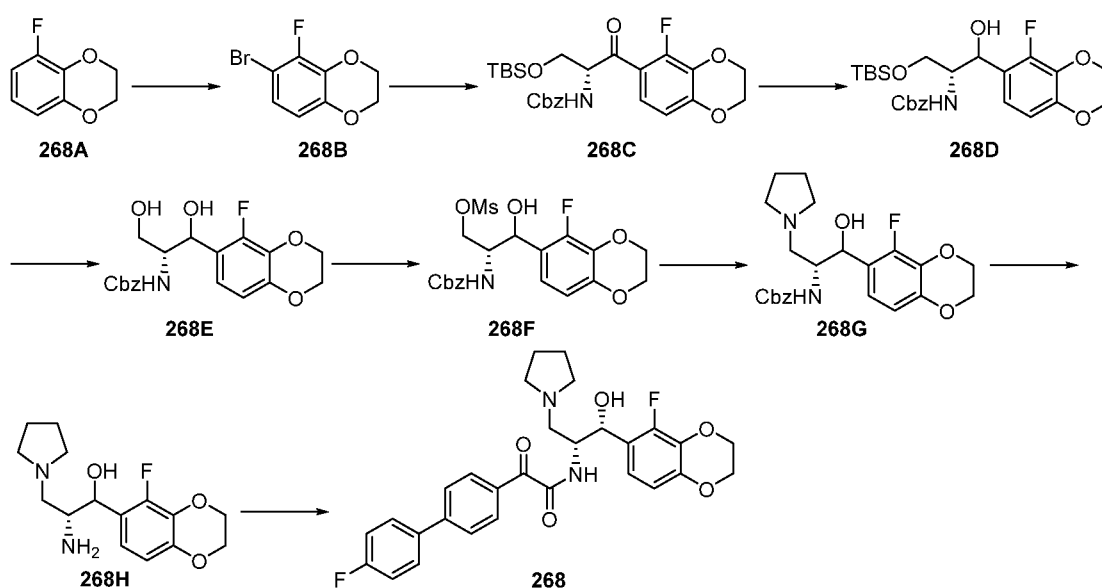


[000990] To a mixture of Compound **175A** (2.56 g, 0.01 mol), 4-chlorophenylboronic acid (2 g, 1.32 mol), and K_3PO_4 (6.4 g, 0.03 mol) in toluene (80 mL) was added $Pd(PPh_3)_4$ (1.156 g, 0.001 mol). The reaction mixture was stirred under nitrogen at 100 °C overnight. The resulting mixture was cooled down to room temperature, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **267A**.

[000991] To a solution of Compound **267A** (2.9 g, 0.01 mol) in ethanol/water (40 mL/10 mL) was added $LiOH \cdot H_2O$ (840 mg, 0.02 mol). The mixture was stirred at room temperature for about 2 h until completion by thin layer chromatography analysis. The reaction mixture was acidified to pH 2 with aqueous HCl solution (1.0 N, 40 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **267B**.

[000992] To a mixture of Compound **267B** (130 mg, 0.5 mmol) and Intermediate **A** (139 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **267**. LC-MS (ESI) m/z : 521 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.66-1.74 (m, 4H), 2.50-2.70 (m, 6H), 4.21-4.22 (m, 5H), 4.75 (s, 1H), 5.57 (s, 1H), 6.82 (s, 2H), 6.87 (s, 1H), 7.58-7.60 (m, 2H), 7.78-7.83 (m, 6H), 8.61 (d, $J = 9.6$ Hz, 1H).

Example 268



[000993] To a solution of Compound **268A** (3.35 g, 21.73 mmol) in methanol (10 mL) was added dropwise bromine (1.34 mL, 26.10 mmol) at -10 °C. The mixture was stirred room temperature for 5 h. It was quenched with saturated aqueous $Na_2S_2O_3$ solution (100 mL) and filtered to remove the resultant solid. The filtrate was evaporated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 3% v/v) to afford Compound **268B**.

[000994] To a solution of Compound **268B** (12.00 g, 51.72 mmol) in THF (30 mL) was added dropwise n -BuLi (2.4 M in hexane, 22 mL, 51.72 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 30 min. A solution of Intermediate **A4** (6.77 g, 17.11 mmol) in THF (20 mL) was added dropwise under nitrogen at -78 °C. The mixture was stirred at -78 °C for 20 min and quenched with saturated aqueous ammonium chloride solution (100 mL). The mixture was diluted with ethyl acetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column

chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to furnish Compound **268C**.

[000995] To a solution of Compound **268C** (7.20 g, 14.72 mmol) in THF (200 mL) was added dropwise L-Selectride (1 M in THF, 29 mL, 29.00 mmol) under nitrogen at -90 °C. The mixture was stirred at -90 °C for 1 h and quenched with saturated aqueous ammonium chloride solution (100 mL). It was diluted with ethyl acetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to afford Compound **268D**.

[000996] A mixture of Compound **268D** (2.00 g, 4.07 mmol) and Bu₄NF (641 mg, 2.04 mmol) in THF (20 mL) was stirred at 20 °C for 16 h. It was diluted with ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 0% to 5% v/v) to give Compound **268E**.

[000997] To a solution of Compound **268E** (1.70 g, 4.50 mmol) and triethylamine (909 mg, 9.00 mmol) in THF (20 mL) was added dropwise methanesulfonyl chloride (565 mg, 4.96 mmol) at -15 °C. The mixture was stirred at -15 °C for 1 h. It was quenched with saturated ice water (50 mL), diluted with ethyl acetate (200 mL), washed with water (150 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 80% v/v) to afford Compound **268F**.

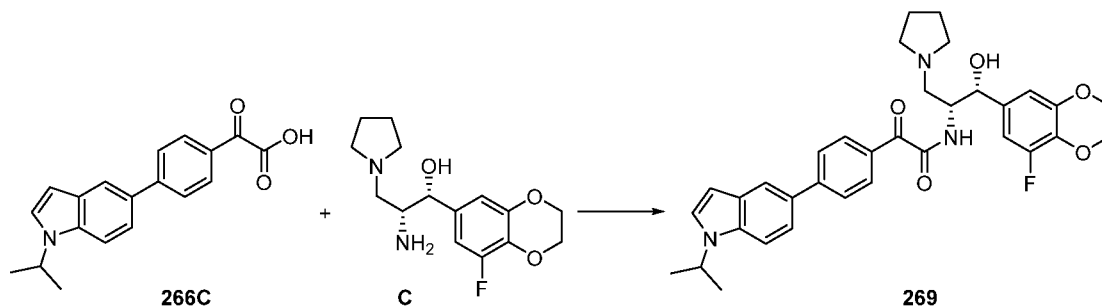
[000998] A solution of Compound **268F** (1.50 g, 3.30 mmol) and pyrrolidine (2.34 g, 32.92 mmol) in THF (10 mL) was stirred at 50 °C for 16 h. It was diluted with ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to furnish Compound **268G**.

[000999] A mixture of Compound **268G** (900 mg, 2.09 mmol) and Pd(OH)₂/C (20%, 500 mg) in methanol (10 mL) was stirred under hydrogen at 20 °C for 16 h. It was filtered to remove Pd(OH)₂/C and the filtrate was evaporated to give Compound **268H**.

[0001000] A mixture of Compound **268H** (100 mg, 0.34 mmol), Compound **133D** (82 mg, 0.34 mmol), and HATU (194 mg, 0.51 mmol) in DMF (5 mL) was stirred at room temperature for 16 h. It was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to yield Compound **268**. LC-MS (ESI) m/z: 523 [M+H]⁺; ¹H-NMR (DMSO-*d*₆,

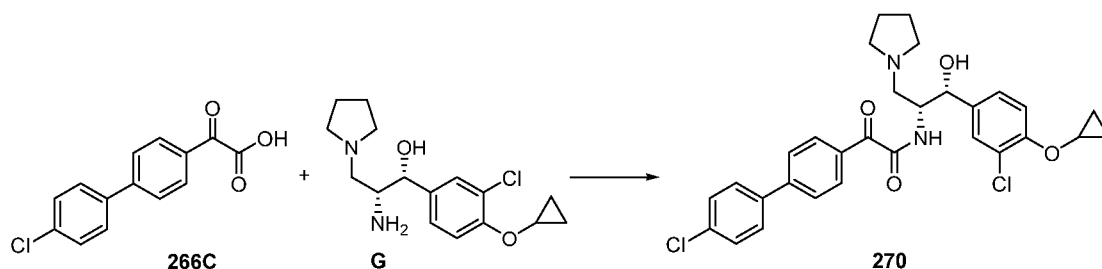
400 MHz): δ (ppm) 1.82-2.03 (m, 4H), 3.08-3.19 (m, 2H), 3.47-3.60 (m, 4H), 4.17-4.30 (m, 4H), 4.4-4.54 (m, 1H), 4.80 (d, $J = 8.0$ Hz, 1H), 6.10 (s, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.92 (t, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.8$ Hz, 2H), 7.79-7.90 (m, 6H), 9.01 (d, $J = 8.8$ Hz, 1H), 9.41 (s, 1H).

Example 269



[0001001] To a solution of Compound **266C** in dichloromethane (15 mL, from previous step) was added Intermediate **C** (150 mg, 0.5 mmol) and HATU (380 mg, 1 mmol). The mixture was stirred at room temperature overnight. The mixture was directly purified with prep-HPLC to afford Compound **269**. LC-MS (ESI) m/z : 586 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.48 (d, $J = 6.8$ Hz, 6H), 1.88-1.89(m, 2H), 2.03-2.03 (m, 2H), 3.12-3.20 (m, 2H), 3.45-3.55 (m, 4H), 4.28-4.30 (m, 4H), 4.51-4.54 (m, 1H), 4.79-4.83 (m, 2H), 6.04-6.05 (m, 1H), 6.57-6.58 (m, 1H), 6.78 (s, 1H), 6.83-6.85 (m, 1H), 7.53-7.55 (m, 1H), 7.58-7.59 (m, 1H), 7.65-7.67 (m, 1H), 7.83-7.89 (m, 4H), 7.96-7.97 (m, 1H), 8.73-8.76 (m, 1H), 9.36 (brs, 1H).

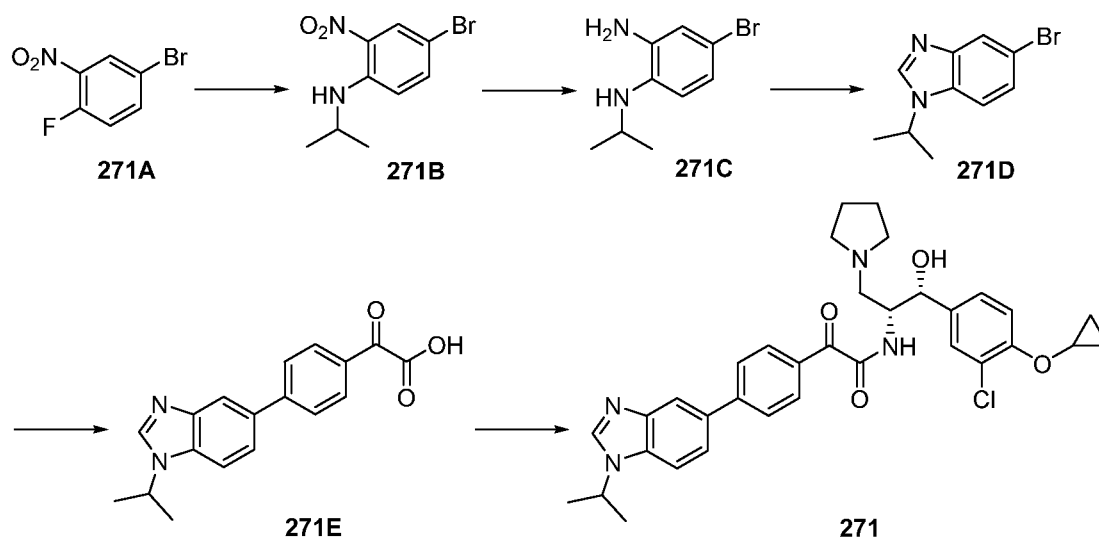
Example 270



[0001002] To a mixture of Compound **266C** (130 mg, 0.5 mmol) and Intermediate **G** (151 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **270**. LC-MS (ESI) m/z : 553 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.66-0.83 (m, 4H), 1.88-2.04 (m, 4H), 3.15-3.20 (m, 2H), 3.49-3.56 (m,

4H), 3.93 (s, 1H), 4.56 (s, 1H), 4.88 (s, 1H), 6.07 (s, 1H), 7.36-7.44 (m, 3H), 7.59-7.62 (m, 2H), 7.77-7.80 (m, 6H), 8.80-8.83 (d, $J = 10.0$ Hz, 1H), 9.48 (s, 1H).

Example 271



[0001003] To a solution of Compound **271A** (6.6 g, 30 mmol) in dichloromethane (30 mL) was added propan-2-amine (3.54 g, 60 mmol) at 0 °C. The mixture was stirred at 40 °C overnight and the mixture was dispersed between water (100 mL) and ethyl acetate (200 mL). After separation, the organic phase was washed with water (10 mL x 3) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the Compound **271B**.

[0001004] To a solution of Compound **271B** (2.0 g, 7.75 mmol) in ethanol (60 mL) was added stannic chloride (5.25 g, 23.3 mmol). The mixture was stirred at reflux for 4 h. After cooling down to room temperature, aqueous sodium hydroxide solution (4 N, 5 mL) was added dropwise to the mixture and the resulting mixture was filtered. After removal of solvent, the residue was extracted with ethyl acetate (50 mL x 3), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to furnish Compound **271C**.

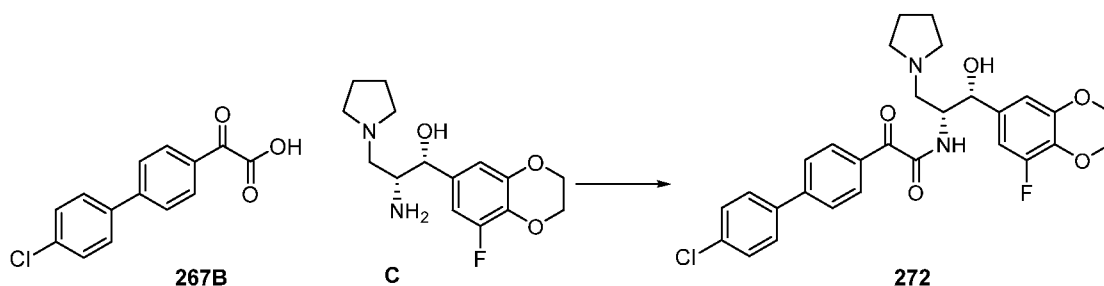
[0001005] To a solution of Compound **271C** (1.3 g, 5.70 mmol) in DMF (30 mL) was added triethoxymethane (4.74 mL, 28.5 mmol) and con. HCl (1.5 mL). The mixture was stirred at 100 °C for 8 h. After cooling down to room temperature, the mixture was poured into water (150 mL) and adjusted to pH 8 with saturated aqueous sodium bicarbonate solution (3.5 mL). The mixture was extracted with ethyl acetate (50 mL x 3) and separated. The combined organic phases were washed with water (10 mL x 2) and brine (10 mL), dried over

anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 50% v/v) to yield Compound **271D**.

[0001006] To a solution of Compound **271D** (476 mg, 2.0 mmol) in dioxane (30 mL) and water (5 mL) was added K_2CO_3 (828 mg, 6.0 mmol), Compound **175B** (608 mg, 2.0 mmol), and $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol). The mixture was stirred under nitrogen at 100 °C for 2 h. After removal of solvent, the residue was dissolved in ethyl acetate (150 mL), washed with water (5 mL x 2) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a crude compound. The crude product was purified with reverse phase chromatography using eluent (methanol in pure water, 50% v/v) to give Compound **271E**.

[0001007] To a solution of Intermediate **G** (121 mg, 0.39 mmol) in DMF (10 mL) was added Compound **271E** (100 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol), and *N,N*-diisopropylethylamine (124 mg, 0.96 mmol). The mixture was stirred under nitrogen at 25 °C overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **271**. LC-MS (ESI) *m/z*: 601 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.82-0.83 (m, 2H), 1.65 (d, *J* = 6.4 Hz, 6H), 1.90-1.93 (m, 2H), 2.02-2.05 (m, 2H), 3.14-3.24 (m, 2H), 3.50-3.59 (m, 4H), 3.93-3.97 (m, 1H), 4.57-4.60 (m, 1H), 4.92 (d, *J* = 2.4 Hz, 1H), 5.02-5.09 (m, 1H), 7.36-7.46 (m, 3H), 7.81-7.88 (m, 4H), 7.92-7.95 (m, 1H), 8.16-8.19 (m, 2H), 9.54 (s, 1H), 9.84 (brs, 1H).

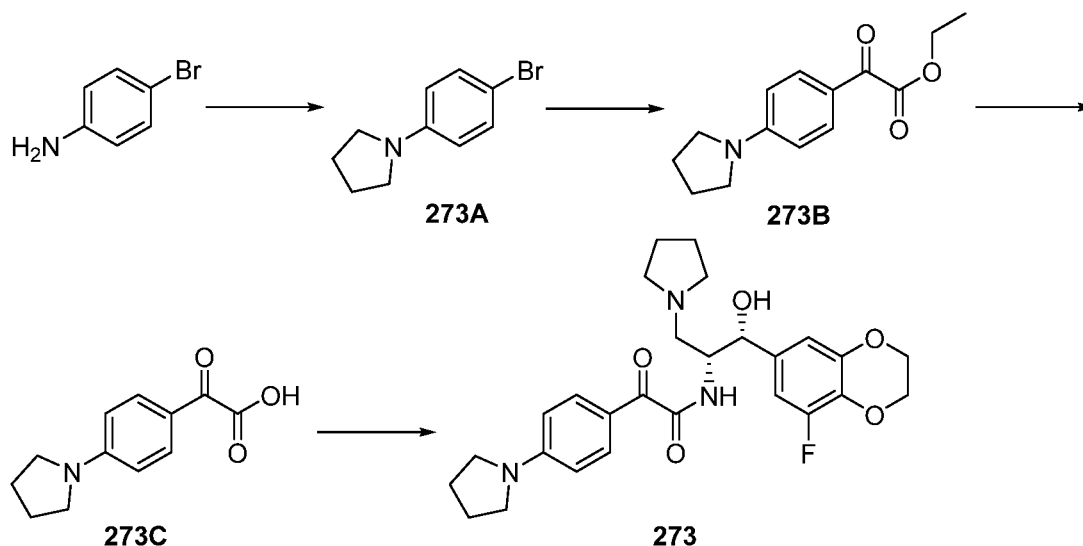
Example 272



[0001008] To a mixture of Compound **267B** (130 mg, 0.5 mmol) and Intermediate **C** (143 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10%

to 55% v/v) to furnish Compound **272**. LC-MS (ESI) m/z : 539 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.87-2.03 (m, 4H), 3.10-3.18 (m, 2H), 3.42-3.54 (m, 4H), 4.23-4.28 (m, 4H), 4.51 (s, 1H), 4.78 (s, 1H), 6.05 (s, 1H), 6.76 (s, 1H), 6.81 (d, $J = 11.6$ Hz, 1H), 7.59 (m, 2H), 7.79-7.84 (m, 4H), 7.91-7.93 (m, 2H), 8.75 (d, $J = 10.0$ Hz, 1H), 9.37 (s, 1H).

Example 273



[0001009] A mixture of 4-bromoaniline (2 g, 11.7 mmol), Cs_2CO_3 (11.4 g, 35.1 mmol), and 1, 4-dibromobutane (3.7 g, 17.5 mmol) in DMF (40 mL) was stirred under nitrogen at 60 °C for 16 h. The mixture was cooled to room temperature, diluted with ethyl acetate (200 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound **273A**.

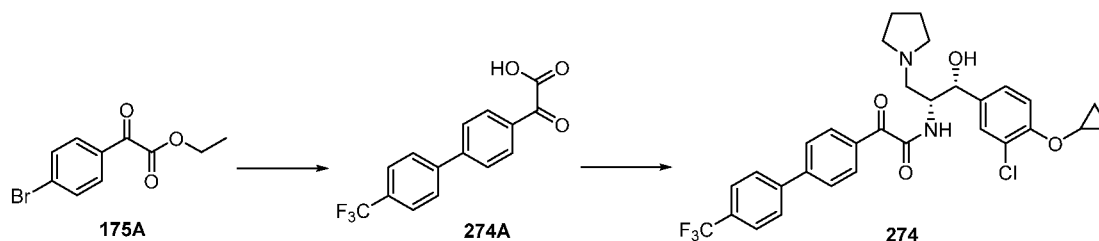
[0001010] To a solution of Compound **273A** (300 mg, 1.3 mmol) in dry THF (10 mL) was added n-BuLi (2.5 N in hexane, 0.6 mL, 1.5 mmol) under nitrogen at -78 °C. The resulting solution was stirred at -78 °C for 30 min and transferred into a stirred solution of diethyl oxalate (0.97 g, 6.6 mmol) in dry THF (5 mL) at this temperature. The solution was stirred at -78 °C for 1 h, quenched with addition of saturated aqueous ammonium chloride solution (10 mL), poured into water (50 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give Compound **273B**.

[0001011] A mixture of Compound **273B** (0.2 g, 0.8 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.6 mmol) in THF (5 mL) and water (2 mL) was stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over

anhydrous sodium sulfate, concentrated, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to afford Compound **273C**.

[0001012] A mixture of Compound **273C** (74 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate **C** (100 mg, 0.3 mmol) in dichloromethane (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **273**. LC-MS (ESI) m/z: 498 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.85 (s, 2H), 1.98 (s, 6H), 3.09-3.17 (m, 2H), 3.41-3.53 (m, 4H), 3.98-4.11 (m, 4H), 4.27 (m, 4H), 4.47 (s, 1H), 4.74 (s, 1H), 6.55 (d, *J* = 9.2 Hz, 2H), 6.72-6.81 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 8.42 (d, *J* = 9.6 Hz, 1H), 9.28 (s, 1H).

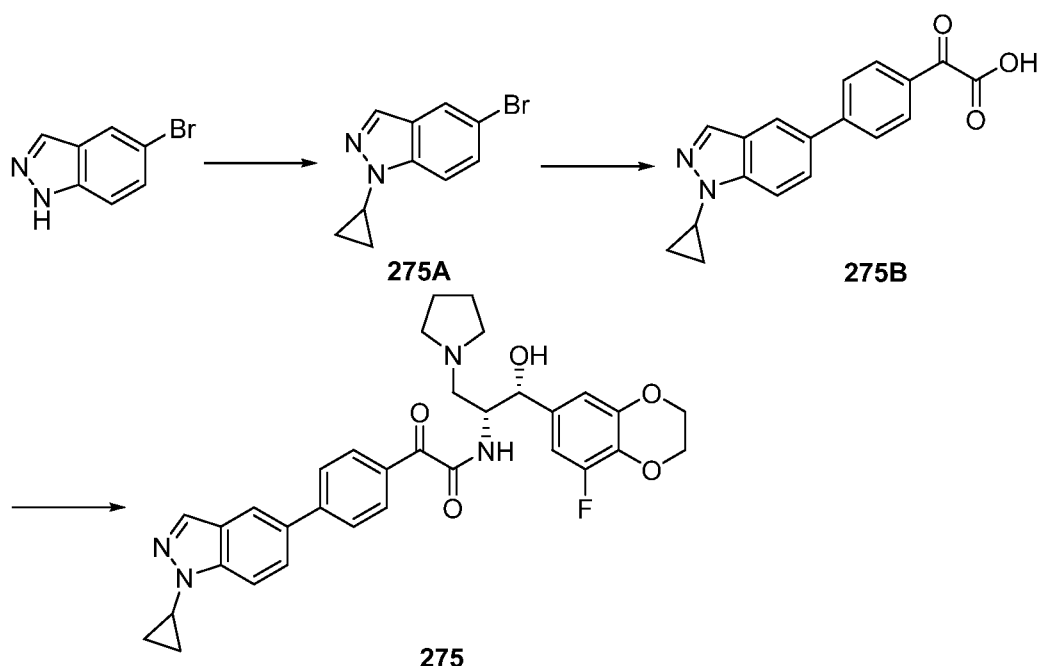
Example 274



[0001013] A mixture of (4-(trifluoromethyl)phenyl)boronic acid (500 mg, 2.63 mmol), Compound **175A** (615 mg, 2.39 mmol), Pd(dppf)Cl₂ (87.5 mg, 0.12 mmol), potassium carbonate (992 mg, 7.18 mmol), water (3 mL), and 1,4-dioxane (10 mL) was heated under nitrogen atmosphere at 90 °C for 2 h. After cooling, water (5 mL) was added, and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed until neutralization and dried over anhydrous sodium sulfate. After removal of the solvent in *vacuo*, the crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 20% v/v) to furnish Compound **274A**.

[0001014] A mixture of Compound **274A** (130 mg, 0.44 mmol), Intermediate **G** (164 mg, 0.53 mmol), and HATU (252 mg, 0.66 mmol) in dichloromethane (10 mL) was stirred under nitrogen atmosphere at 25 °C for 5 h. The mixture was quenched with water (5 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **274**. LC-MS (ESI) m/z: 587 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.64-0.68 (m, 2H), 0.79-0.84 (m, 2H), 1.88-1.91 (m, 2H), 1.99-2.04 (m, 2H), 3.14-3.19 (m, 2H), 3.47-3.49 (m, 3H), 3.87-3.95 (m, 1H), 4.55 (t, *J* = 4.0 Hz, 1H), 4.87 (s, 1H), 6.05 (d, *J* = 4.0 Hz, 1H), 7.33-7.44 (m, 3H), 7.85-7.89 (m, 4H), 7.91-7.99 (m, 4H), 8.82 (d, *J* = 9.7 Hz, 1H), 9.34 (brs, 1H).

Example 275



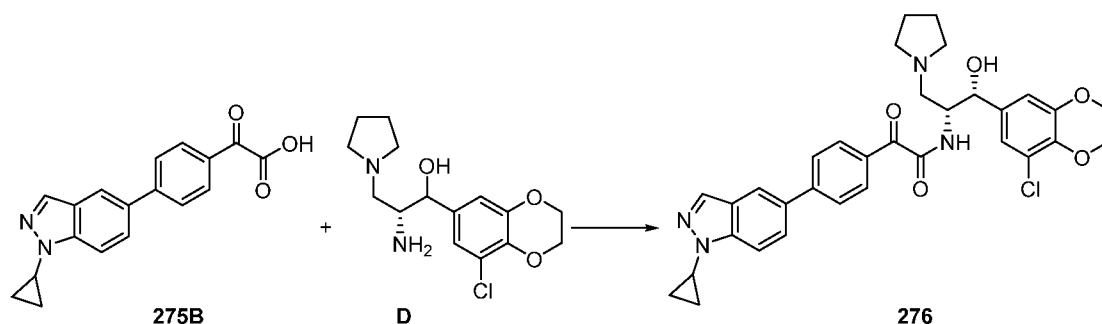
[0001015] To a suspension of 5-bromo-1H-indazole (600 mg, 3.1 mmol) in 1,2-dichloroethane (30 mL) was added cyclopropylboronic acid (532 mg, 6.2 mmol), copper acetate (562 mg, 6.2 mmol), sodium carbonate (658 mg, 6.2 mmol), 2,2'-bipyridine (967 mg, 6.2 mmol) and molecular sieve (2.0 g) at room temperature. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane (50 mL x 2). The combined organic extracts were washed with brine (100 mL x 2) and dried over anhydrous sodium sulfate. After filtration, the solvent was removed in *vacuo* and the residue was purified with prep-TLC (ethyl acetate in petroleum ether, 10% v/v) to give Compound **275A**.

[0001016] To a solution of Compound **275A** (575 mg, 2.43 mmol) in 1,4-dioxane (15 mL) was added **175B** (738 mg, 2.43 mmol), Pd(dppf)Cl₂ (98 mg, 0.12 mmol), potassium carbonate (1.06 g, 7.29 mmol) and water (1 mL) under nitrogen. The reaction mixture was stirred at 110 °C for 3 hours. The resulting mixture was cooled to 25 °C. The precipitated solid was filtered and dried to afford Compound **275B**.

[0001017] To a solution of Compound **275B** (60 mg, 0.196 mmol) in DMF (5 mL) was added Intermediate **C** (58 mg, 0.196 mmol) and HATU (111 mg, 0.294 mmol). The reaction mixture was stirred at 20 °C for 2 h. The mixture was purified with prep-HPLC to yield the product Compound **275**. LC-MS (m/z) 585 [M+H]⁺; ¹H-NMR (acetone-*d*₆, 400 MHz): δ (ppm) 1.27-1.29 (m, 4H), 2.06-2.13 (m, 2H), 2.28-2.30 (m, 2H), 3.50-3.63 (m, 2H), 4.04-4.11

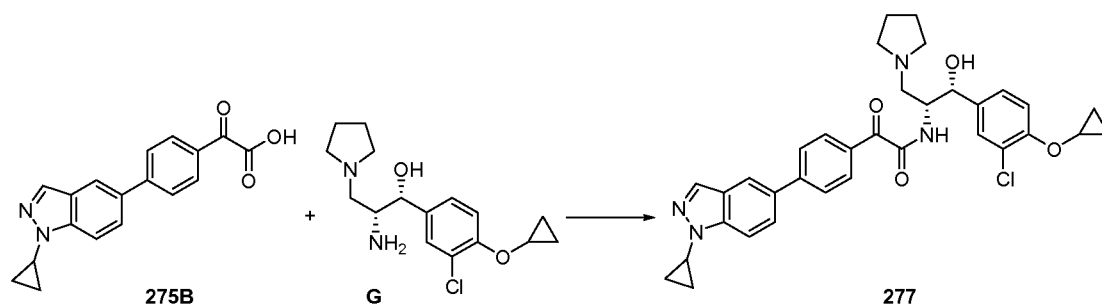
(m, 5H), 4.23-4.31 (m, 5H), 4.90-4.91 (m, 1H), 5.10-5.11 (m, 1H), 6.82-6.88 (m, 2H), 7.87-7.95 (m, 4H), 8.11-8.14 (m, 3H), 8.24-8.25 (m, 1H), 8.35 (s, 1H).

Example 276



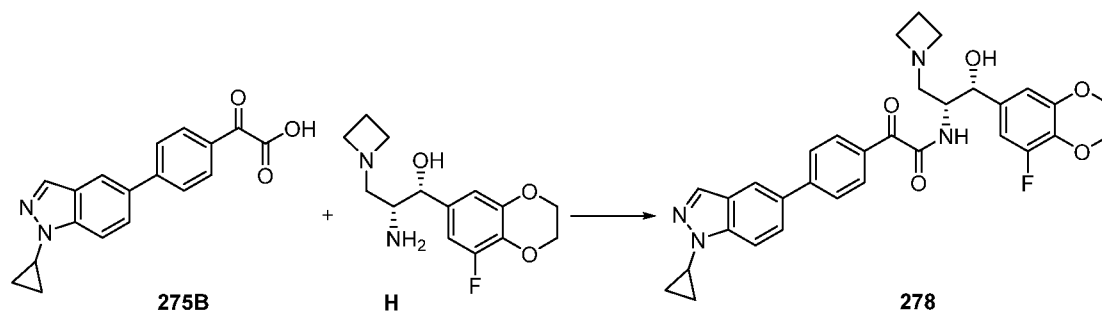
[0001018] A mixture of Intermediate **D** (97 mg, 0.31 mmol), Compound **275B** (80 mg, 0.26 mmol), and HATU (150 mg, 0.40 mmol) in DMF (5 mL) was stirred at 10 °C for 1.5 h. And then it was purified with prep-HPLC to yield Compound **276**. LC-MS (ESI) m/z : 601 $[M+H]^+$; 1H -NMR ($(CD_3)_2CO$, 400 MHz): δ (ppm) 1.18-1.19 (m, 4H), 2.03-2.17 (m, 2H), 2.24 (s, 2H), 3.47 (m, 3H), 3.73-3.83 (m, 2H), 3.88-3.99 (m, 3H), 4.20-4.38 (m, 4H), 4.87 (s, 1H), 5.14 (d, $J = 2.0$ Hz, 1H), 6.96 (d, $J = 2.0$ Hz, 1H), 7.09 (d, $J = 2.0$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 4H), 8.03 (d, $J = 9.6$ Hz, 3H), 8.15 (d, $J = 10.4$ Hz, 2H), 9.93 (brs, 1H).

Example 277



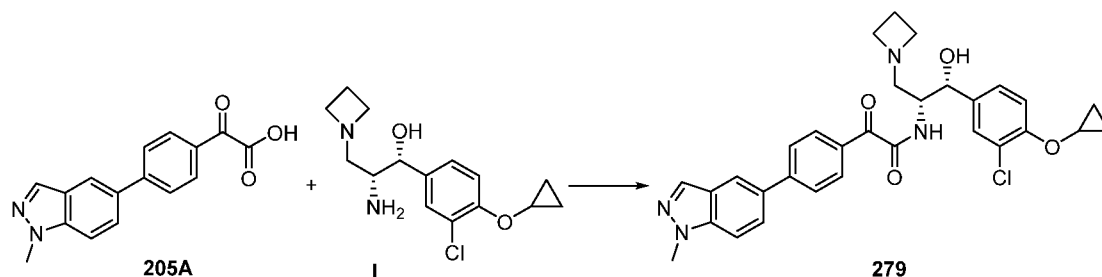
[0001019] To a solution of Compound **275B** (60 mg, 0.196 mmol) in DMF (5 mL) was added Intermediate **G** (60 mg, 0.196 mmol) and HATU (111 mg, 0.294 mmol). The reaction mixture was stirred at 20 °C for 2 h. The mixture was purified with prep-HPLC to yield Compound **277**. LC-MS (m/z) 599 $[M+H]^+$; 1H -NMR (acetone- d_6 , 400 MHz): δ (ppm) 0.69-0.71 (m, 2H), 0.79-0.84 (m, 2H), 1.18-1.20 (m, 4H), 2.06-2.09 (m, 1H), 2.25-2.27 (m, 2H), 3.46-3.55 (m, 2H), 3.77-3.78 (m, 1H), 3.88-3.92 (m, 2H), 3.96-4.08 (m, 4H), 4.90-4.94 (m, 1H), 5.20 (s, 1H), 7.36-7.46 (m, 2H), 7.51-7.52 (m, 1H), 7.80-7.82 (m, 4H), 7.98-8.00 (m, 2H), 8.05 (s, 1H), 8.14 (s, 1H), 8.17-8.20 (m, 1H), 9.14 (brs, 1H).

Example 278

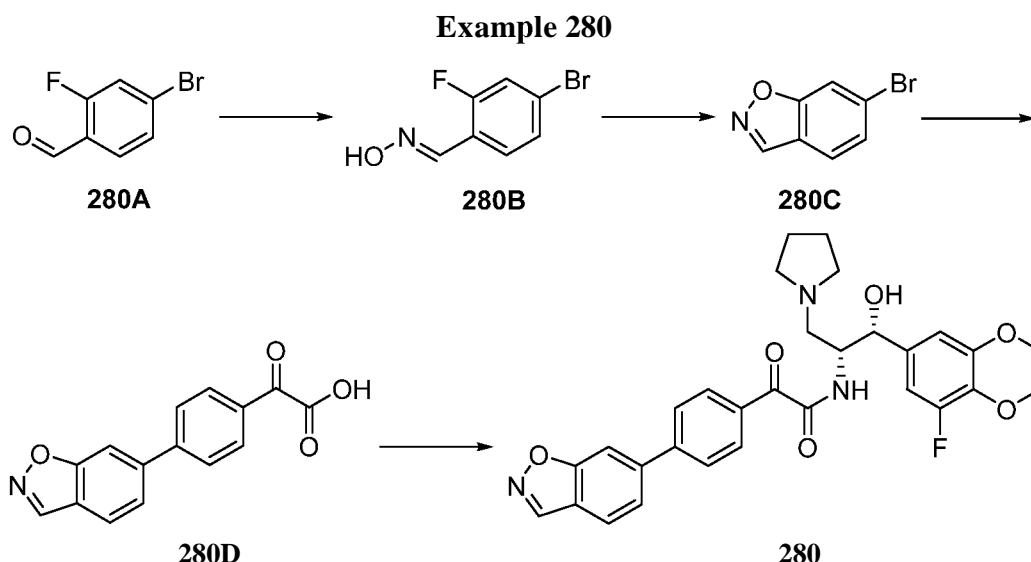


[0001021] To a solution of Compound **275B** (60 mg, 0.196 mmol) in DMF (5 mL) was added Intermediate **H** (55 mg, 0.196 mmol) and HATU (111 mg, 0.294 mmol). The reaction mixture was stirred at 20 °C for 2 h. The mixture was purified with prep-HPLC to yield Compound **278**. LC-MS (ESI) m/z : 571 $[M+H]^+$; 1H -NMR (acetone- d_6 , 400 MHz): δ (ppm) 1.33-1.37 (m, 4H), 2.60-2.62 (m, 1H), 2.71-2.74 (m, 1H), 3.92-3.95 (m, 3H), 4.27-4.31 (m, 4H), 4.61-4.64 (m, 4H), 4.73-4.74 (m, 1H), 5.10-5.11 (m, 1H), 6.82-6.88 (m, 2H), 7.88-7.90 (m, 2H), 7.98-8.10 (m, 4H), 8.31 (s, 1H), 8.56 (s, 1H).

Example 279



[0001022] To a solution of Compound **205A** (70 mg, 0.25 mmol) in DMF (3 mL) was added Intermediate **I** (74 mg, 0.25 mmol) and HATU (142 mg, 0.375 mmol). The reaction mixture was stirred at 15 °C overnight. The mixture was purified with prep-HPLC to yield Compound **279**. LC-MS (m/z) 559 $[M+H]^+$; 1H -NMR (acetone- d_6 , 400 MHz): δ (ppm) 0.70-0.73 (m, 2H), 0.80-0.84 (m, 2H), 2.56-2.57 (m, 1H), 2.71-2.74 (m, 1H), 3.86-3.96 (m, 4H), 4.13 (s, 3H), 4.47-4.60 (m, 4H), 4.77-4.78 (m, 1H), 5.20-5.21 (m, 1H), 7.39-7.45 (m, 2H), 7.50-7.51 (m, 1H), 7.71-7.74 (m, 1H), 7.79-7.82 (m, 3H), 7.93-7.95 (m, 2H), 8.09 (s, 1H), 8.13-8.15 (m, 2H), 9.51 (brs, 1H).



[0001023] A mixture of Compound **280A** (2 g, 10 mmol), hydroxylamine hydrochloride (830 mg, 12 mmol), and sodium acetate (656 mg, 8 mmol) in water (5 mL) and ethanol (20 mL) was stirred under nitrogen at 25 °C for 5 h. The solution was concentrated to dryness. The crude product was washed with water (5 mL) and dried to afford Compound **280B**.

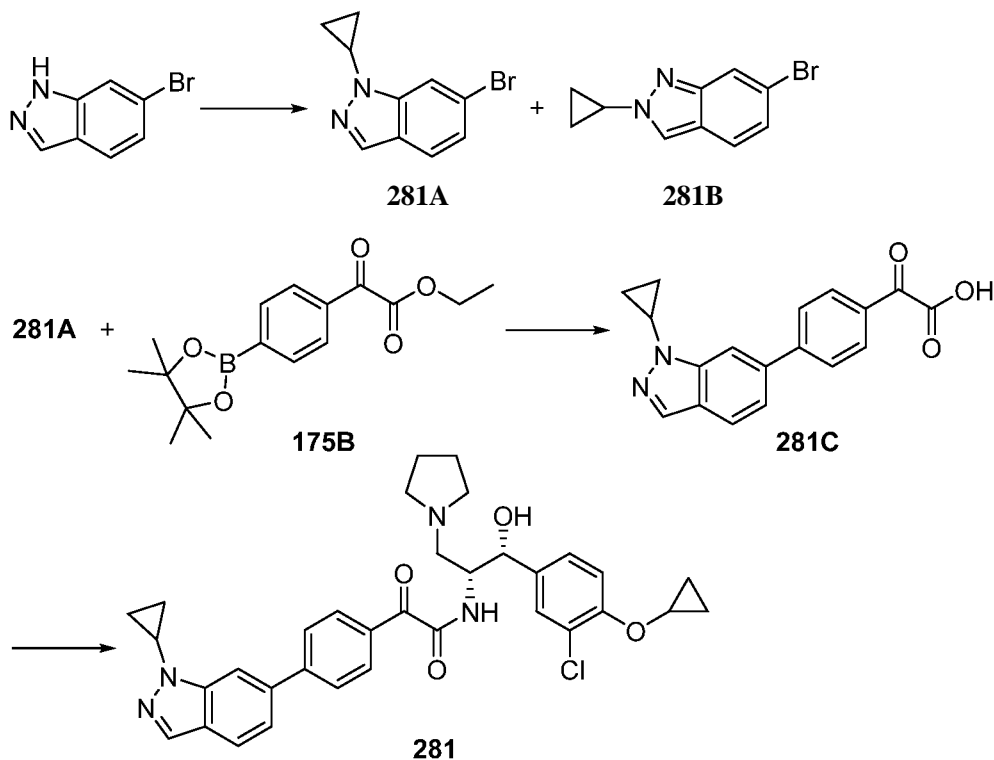
[0001024] To a solution of Compound **280B** (717 mg, 3.3 mmol) in DMSO (10 mL) was added potassium carbonate (638 mg, 4.6 mmol) at 25 °C. The mixture was stirred at 120 °C overnight. The solution was cooled to room temperature and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give Compound **280C**.

[0001025] A mixture of Compound **280C** (197 mg, 1 mmol), Compound **175B** (334 mg, 1.1 mmol), potassium carbonate (414 mg, 3 mmol), and Pd(dppf)Cl₂ (20 mg, 0.04 mmol) in dioxane (10 mL) and water (2 mL) was stirred under nitrogen at 100 °C overnight. The solution was cooled to room temperature, adjusted to pH 4 with aqueous hydrochloric acid solution (6 N, 2 mL), and extracted with ethyl acetate (100 mL x 3). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to afford Compound **280D**.

[0001026] A mixture of Compound **280D** (133.5 mg, 0.5 mmol), HATU (342 mg, 0.9 mmol), and Intermediate **C** (148 mg, 0.5 mmol) in dichloromethane (10 mL) and DMF (4 mL) was stirred at 25 °C overnight. The solution was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The residue was purified with prep-HPLC to furnish Compound **280**. LC-MS (ESI) m/z: 546 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.84-2.03 (m, 4H), 3.09-3.20 (m, 2H), 3.45-3.53 (m,

4H), 4.22-4.32 (m, 4H), 4.47-4.50 (m, 1H), 4.77 (s, 1H), 6.04 (s, 1H), 6.76-6.84 (m, 2H), 7.29-7.32 (m, 2H), 7.76-7.79 (m, 3H), 7.92-7.94 (m, 2H), 8.76-8.79 (m, 1H), 9.24-9.26 (m, 1H), 11.41 (s, 1H).

Example 281



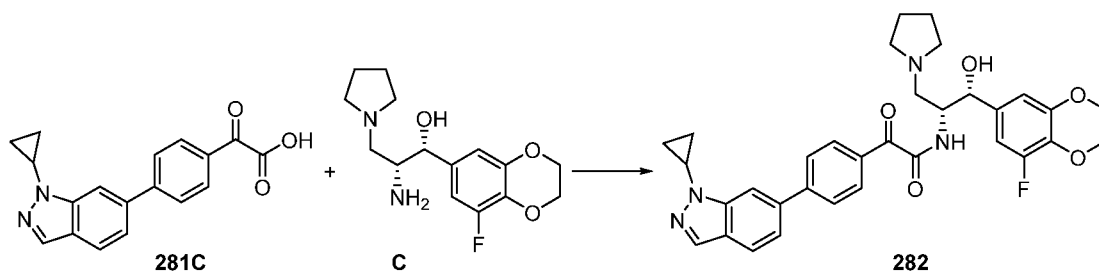
[0001027] Solvent 1,2-dichloroethane (30 mL) was added to a 500 mL of round-bottomed flask containing 6-bromoindazole (3 g, 15.2 mmol), cyclopropylboronic acid (2.6 g, 30.4 mmol), $\text{Cu}(\text{OAc})_2$ (5.5 g, 30.4 mmol), Na_2CO_3 (3.2 g, 30.4 mmol), bipyridine (1.7 g, 30.4 mmol), and 4 Å molecular sieve (8 g). The flask was equipped with a drying tube. The mixture was stirred at room temperature for 4 days and filtered through celite. The filtrate was diluted with water (200 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to give Compound **281A** and Compound **281B**.

[0001028] A mixture of Compound **281A** (600 mg, 2.53 mmol), Compound **175B** (769 mg, 2.53 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (106 mg, 0.13 mmol), and K_2CO_3 (1.05 g, 7.59 mmol) in dioxane (10 mL) and water (10 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The organic layers were

discarded off. The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **281C**.

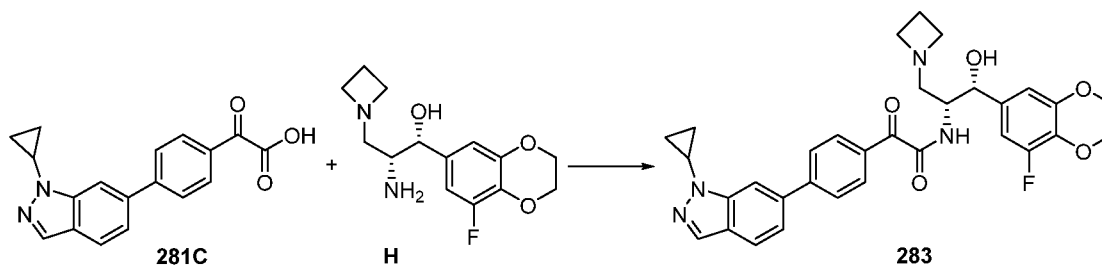
[0001029] A mixture of Compound **281C** (100 mg, 0.33 mmol), HATU (190 mg, 0.50 mmol), and Intermediate **G** (102 mg, 0.33 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **281**. LC-MS (ESI) *m/z*: 599 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.66-0.85 (m, 4H), 1.17-1.19 (m, 4H), 1.88-2.08 (m, 4H), 3.12-3.25 (m, 2H), 3.48-3.59 (m, 4H), 3.83-3.88 (m, 1H), 3.93-3.98 (m, 1H), 4.56-4.63 (m, 1H), 4.90 (s, 1H), 6.17 (brs, 1H), 7.37 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.43-7.47 (m, 2H), 7.55 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.88-7.92 (m, 3H), 8.03 (s, 1H), 8.09 (s, 1H), 8.86 (d, *J* = 10.0 Hz, 1H), 9.41 (brs, 1H).

Example 282



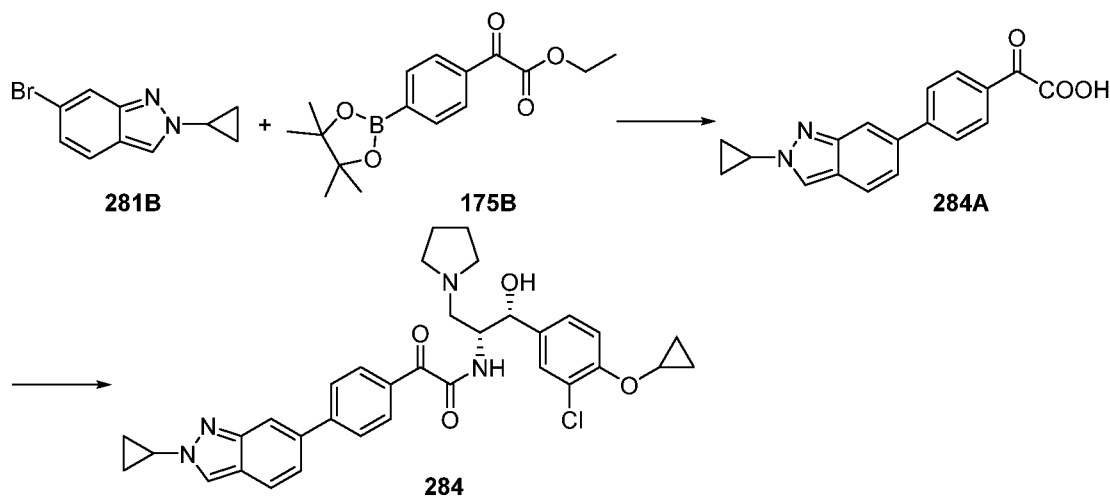
[0001030] A mixture of Compound **281C** (100 mg, 0.33 mmol), HATU (190 mg, 0.50 mmol), and Intermediate **C** (98 mg, 0.33 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **282**. LC-MS (ESI) *m/z*: 585 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.17-1.19 (m, 4H), 1.88-2.08 (m, 4H), 3.11-3.22 (m, 2H), 3.46-3.56 (m, 4H), 3.84-3.89 (m, 1H), 4.29-4.31 (m, 4H), 4.52-4.54 (m, 1H), 4.80 (d, *J* = 2.4 Hz, 1H), 6.05 (brs, 1H), 6.79 (s, 1H), 6.84 (d, *J* = 12.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.89-7.94 (m, 5H), 8.04 (s, 1H), 8.09 (s, 1H), 8.79 (d, *J* = 9.2 Hz, 1H), 9.33 (brs, 1H).

Example 283



[0001031] A mixture of Compound **281C** (100 mg, 0.33 mmol), HATU (190 mg, 0.50 mmol), and Intermediate **H** (93 mg, 0.33 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **283**. LC-MS (ESI) m/z : 571 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 1.16-1.18 (m, 4H), 2.26-2.30 (m, 1H), 2.40-2.48 (m, 1H), 3.32-3.39 (m, 1H), 3.49-3.54 (m, 1H), 3.84-3.89 (m, 1H), 4.05-4.40 (m, 9H), 4.76 (d, $J = 3.2$ Hz, 1H), 6.03 (brs, 1H), 6.78 (s, 1H), 6.83 (dd, $J = 11.2, 1.6$ Hz, 1H), 7.55 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.85-7.94 (m, 5H), 8.03 (s, 1H), 8.09 (s, 1H), 8.79 (d, $J = 9.6$ Hz, 1H), 9.65 (brs, 1H).

Example 284

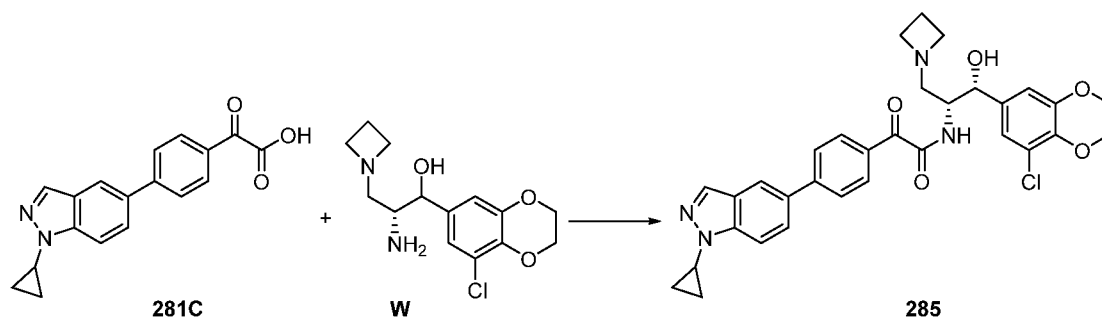


[0001032] A mixture of Compound **281B** (100 mg, 0.42 mmol), Compound **175B** (128 mg, 0.42 mmol), $Pd(dppf)Cl_2$ (17 mg, 0.02 mmol), and K_2CO_3 (174 mg, 1.26 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (100 mL), extracted with ethyl acetate (100 mL x 2), and the organic layer was discarded off. The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **284A**.

[0001033] A mixture of Compound **284A** (80 mg, 0.26 mmol), HATU (148 mg, 0.39 mmol), and Intermediate **G** (81 mg, 0.26 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **284**. LC-MS (ESI) m/z : 599 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.67-0.85 (m, 4H), 1.12-1.34 (m, 4H), 1.87-1.92 (m, 4H), 3.11-3.24 (m, 2H), 3.46-3.58 (m, 4H), 3.92-3.96 (m, 1H), 4.18-4.23 (m, 1H), 4.43-4.56 (m, 1H), 4.89 (d, $J = 2.8$ Hz, 1H), 6.05 (brs, 1H), 7.35-7.46 (m, 4H), 7.77

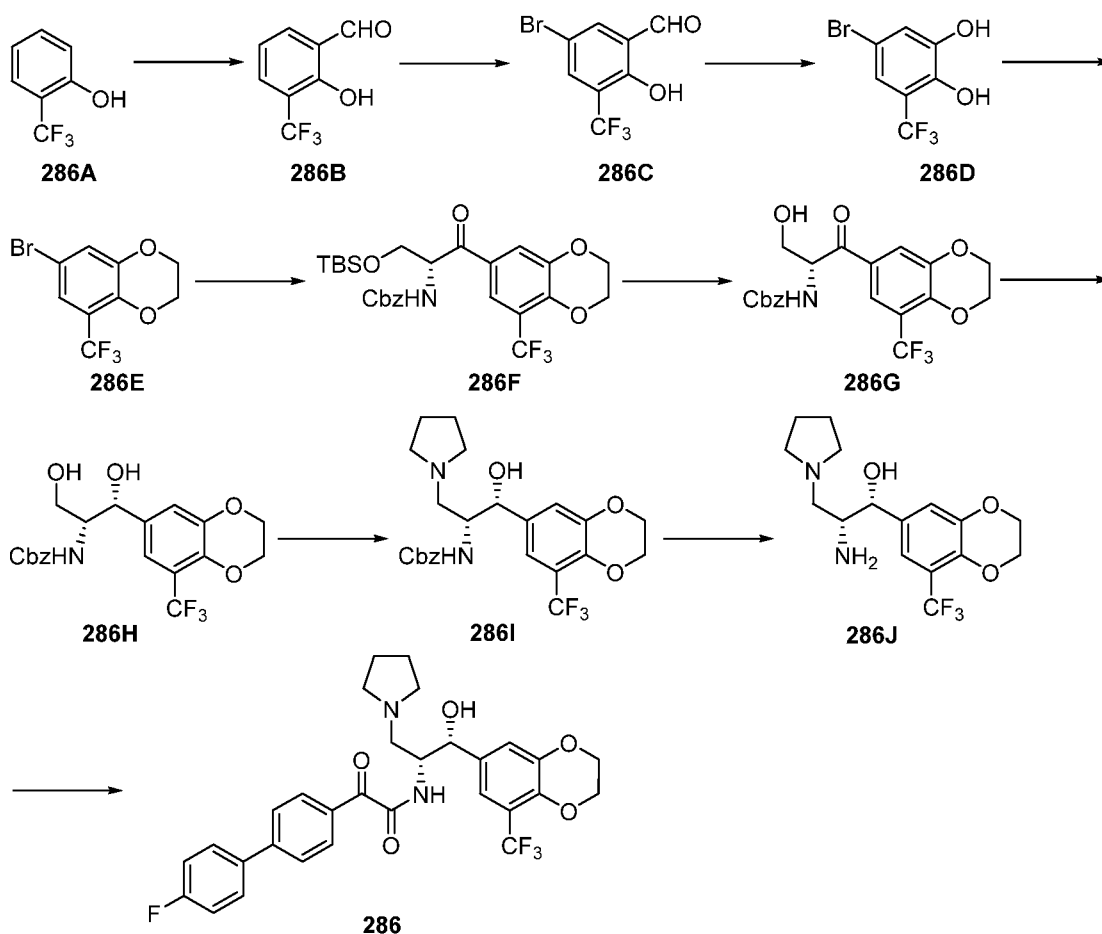
(d, $J = 8.4$ Hz, 2H), 7.81-7.85 (m, 3H), 7.97 (s, 1H), 8.55 (s, 1H), 8.83 (d, $J = 10.0$ Hz, 1H), 9.38 (brs, 1H).

Example 285



[0001034] A mixture of Intermediate **W** (89 mg, 0.30 mmol), Compound **281C** (90 mg, 0.30 mmol), and HATU (148 mg, 0.39 mmol) in DMF (4 mL) was stirred at 10 °C for 1.5 h. And then it was purified with prep-HPLC to yield Compound **285**. LC-MS (ESI) m/z : 587 $[M+H]^+$; 1H -NMR ($(CD_3)_2CO$, 400 MHz): δ (ppm) 1.21-1.23 (m, 4H), 2.56-2.65 (m, 1H), 2.69-2.81 (m, 1H), 3.77-3.82 (m, 1H), 3.91-4.05 (m, 2H), 4.21-4.39 (m, 4H), 4.50-4.68 (m, 4H), 4.72-4.78 (m, 1H), 5.11 (d, $J = 2.8$ Hz, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 7.08 (d, $J = 2.0$ Hz, 1H), 7.85 (d, $J = 8.8$ Hz, 4H), 8.02 (t, $J = 8.4$ Hz, 2H), 8.10 (d, $J = 9.6$ Hz, 1H), 8.14 (s, 1H), 8.18 (s, 1H), 8.86 (brs, 1H).

Example 286



[0001035] To a solution of Compound **286A** (5 g, 31 mmol) in 2,2,2-trifluoroacetic acid (50 mL) was added hexamethylenetetramine (4.7 g, 33.6 mmol). The reaction solution was heated at reflux overnight. After cooling, the mixture was treated with 50% H₂SO₄ (20 mL) at room temperature for 4 h and extracted with ether (50 mL x 3). The combined ether phases were washed with aqueous HCl solution (5 M, 50 mL), water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **286B**.

[0001036] To a solution of Compound **286B** (1 g, 5.3 mmol) in acetonitrile (15 mL) was added NBS (0.88 g, 5.3 mmol) and ammonium formate (32 mg, 0.5 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The solvent was removed to give yellow solid. The yellow solid was diluted with ethyl acetate (100 mL), washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to yield Compound **286C**.

[0001037] To a solution of Compound **286C** (1.3 g, 4.8 mmol) in THF (10 mL) was added dropwise aqueous NaOH solution (0.05 N, 18 mL) at 0 °C, and 30% H₂O₂ (2.3 mL)

was added dropwise. The mixture was stirred at room temperature for 2 h. Other portion of 30% H₂O₂ (2.3 mL) was added dropwise. The mixture was stirred for 4 h. It was cooled to 0 °C and aq. NaOH solution (2 N, 2 mL) was added dropwise until pH 10-11. The mixture was stirred at 25 °C for 0.5 h, adjusted to pH 2~3 with concentrated HCl at 0 °C, and extracted with dichloromethane (20 mL x 3). The organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated to give Compound **286D**.

[0001038] To a mixture of Compound **286D** (1.2 g, 4.7 mol) and K₂CO₃ (1.9 g, 14.1 mol) in DMF (12 mL) was added 1, 2-dibromoethane (4.4 g, 23.5 mol). The mixture was stirred at 80 °C for 4 h. It was cooled down to room temperature and filtered. The cake was washed with ethyl acetate (50 mL). The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with water (50 mL x 5) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 5% v/v) to furnish Compound **286E**.

[0001039] To a solution of Compound **286E** (0.9 g, 3.2 mmol) in dry THF (10 mL) was added n-BuLi solution (2.5 N in hexane, 1.3 mL) under nitrogen at -60 °C. The above mixture was stirred at -60 °C for 0.5 h. A solution of Compound **A4** (0.4 g, 1.1 mmol) in THF (4 mL) was added. The resulting mixture was stirred at -60 °C for 0.5 h, quenched with saturated aqueous ammonium chloride solution (20 mL), extracted with ethyl acetate (30 mL x 2), washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **286F**.

[0001040] To a solution of Compound **286F** (4.8 g, 8.9 mmol) in THF (25 mL) and water (25 mL) was added acetic acid (75 mL). The resulting mixture was stirred at 35 °C for 16 h, diluted with brine (150 mL), and adjusted to pH 8 with saturated aqueous sodium bicarbonate solution (75 mL). The mixture was extracted with ethyl acetate (100 mL x 2), washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to afford Compound **286G**.

[0001041] To a solution of Compound **286G** (2 g, 4.7 mmol) in dry THF (60 mL) was added dropwise DIBAL-H (1 N in toluene, 9.4 mL, 9.4 mmol) under nitrogen at -80 °C. The resultant mixture was stirred at -80 °C for 30 min and additional DIBAL-H (1 N in toluene, 9.4 mL, 9.4 mmol) was added dropwise again. The mixture was stirred at -80 °C for 1 h and quenched with aqueous HCl solution (2 N, 28 mL) at -20 °C. The mixture was extracted with

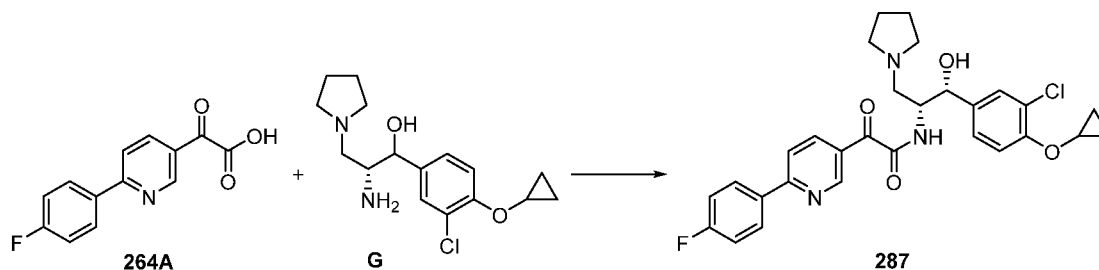
ethyl acetate (200 mL x 2), washed with water (200 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 50% v/v) to furnish Compound **286H**.

[0001042] To a solution of Compound **286H** (1.5 g, 3.5 mmol) in THF (50 mL) was added triethylamine (1.1 g, 10.5 mmol). The mixture was cooled to -20 °C and MsCl (0.44 g, 3.9 mmol) was added slowly. The mixture was stirred at -20 °C for about half an hour and pyrrolidine (2.1 g, 30 mmol) was added to the mixture. The resulting mixture was stirred at -60 °C for 16 h and cooled to 25 °C. The mixture was diluted with ethyl acetate (200 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 5% to 10% v/v) to give Compound **286I**.

[0001043] To a solution of Compound **286I** (0.5 g, 1.2 mmol) in methanol (10 mL) was added Pd(OH)₂ (100 mg). The mixture was stirred under hydrogen at room temperature overnight. After removal of Pd(OH)₂ by filtration, the filtrate was evaporated to furnish Compound **286J**.

[0001044] A mixture of Compound **286I** (0.1 g, 0.28 mmol), HATU (0.16 g, 0.43 mmol), and Intermediate **C** (70 mg, 0.28 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to yield Compound **286**. LC-MS (ESI) m/z: 573 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.88-1.89 (m, 2H), 2.03-2.04 (m, 2H), 3.14-3.20 (m, 2H), 3.52-3.55 (m, 4H), 4.29-4.35 (m, 4H), 4.53-4.56 (m, 1H), 4.87 (s, 1H), 6.10 (d, *J* = 4 Hz, 1H), 7.20-7.23 (m, 2H), 7.35-7.40 (m, 2H), 7.79-7.88 (m, 6H), 8.77-8.79 (m, 1H), 9.30 (s, 1H).

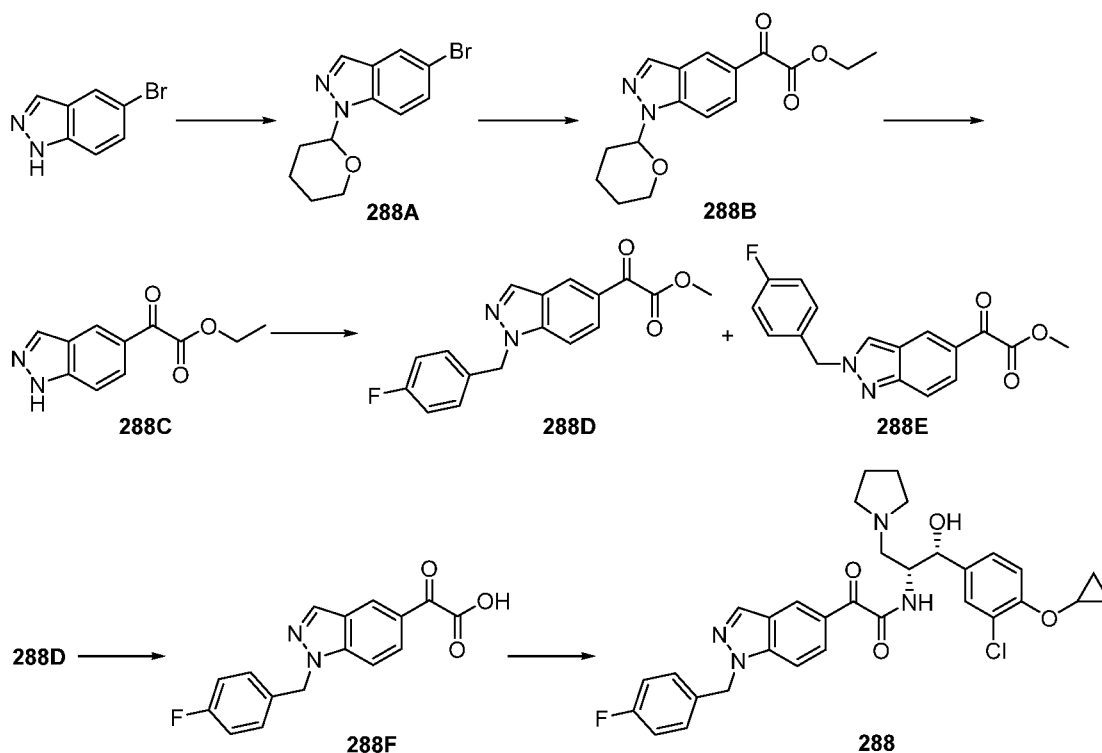
Example 287



[0001045] A mixture of Compound **264A** (100 mg, 0.40 mmol), Intermediate **G** (150 mg, 0.48 mmol), and HATU (233 mg, 0.60 mmol) in dichloromethane (2 mL) and DMF (2 mL) was stirred at 25 °C for 15 h. After the reaction was completed, it was poured into water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layers were

dried over anhydrous sodium sulfate, concentrated *in vacuo*, and purified with prep-HPLC to afford Compound **287**. LC-MS (ESI) m/z : 538 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.68-0.81 (m, 4H), 1.88-2.04 (m, 5H), 3.01-3.20 (m, 3H), 3.41-3.55 (m, 4H), 4.51-4.53 (m, 1H), 4.86 (s, 1H), 7.32-7.44 (m, 5H), 8.12-8.31 (m, 4H), 8.76-8.81 (m, 1H), 9.01 (s, 1H).

Example 288



[0001046] A mixture of 5-bromoindazole (4 g, 20.3 mmol), 4-methylbenzenesulfonic acid (1.9 g, 10.1 mmol), and DHP (3.4 g, 40.6 mmol) in dichloromethane (50 mL) was stirred at room temperature for 18 hours. The reaction mixture was treated with ethyl acetate (500 mL), washed with sodium bicarbonate solution (500 mL x 3) and water (500 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 33% v/v) to furnish Compound **288A**.

[0001047] To a solution of Compound **288A** (4.2 g, 14.8 mmol) in dry THF (50 mL) was added dropwise *n*-BuLi (2.0 M, 7.5 mL, 17.8 mmol) under nitrogen at -70 °C. After stirring for 30 min., diethyl oxalate (6.5 g, 44.4 mmol) was added quickly. The mixture was stirred at -70 °C for one hour. It was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The residue was purified with flash column chromatography

on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to afford Compound **288B**.

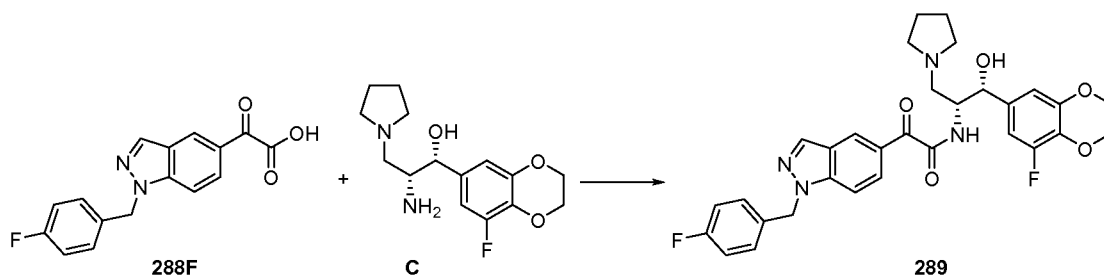
[0001048] To a solution of Compound **288B** (1.4 g, 4.6 mmol) in ethanol (10 mL) was added dropwise 2 *N* hydrogen chloride (10 mL, 18.5 mmol). The reaction mixture was stirred at room temperature for 8 h. Sodium bicarbonate solution was added to adjust pH 7, followed by extraction with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **288C**.

[0001049] A mixture of Compound **288C** (500 mg, 2.29 mmol), 1-(bromomethyl)-4-fluorobenzene (647 mg, 3.44 mmol), and CS_2CO_3 (897 mg, 2.75 mmol) in 1-methylpyrrolidin-2-one (20 mL) was stirred at room temperature for 18 hours. The reaction mixture was treated with H_2O (50 mL) and ethyl acetate (50 mL), washed with water (500 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 33% v/v) to furnish Compound **288D** and Compound **288E**.

[0001050] To a solution of Compound **288D** (300 mg, 0.91 mmol) in THF (2 mL) was added dropwise 1 *N* lithium hydroxide (2 mL, 2 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction mixture was concentrated, 2 *N* HCl (1 mL) was added to adjust pH 7, and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **288F**.

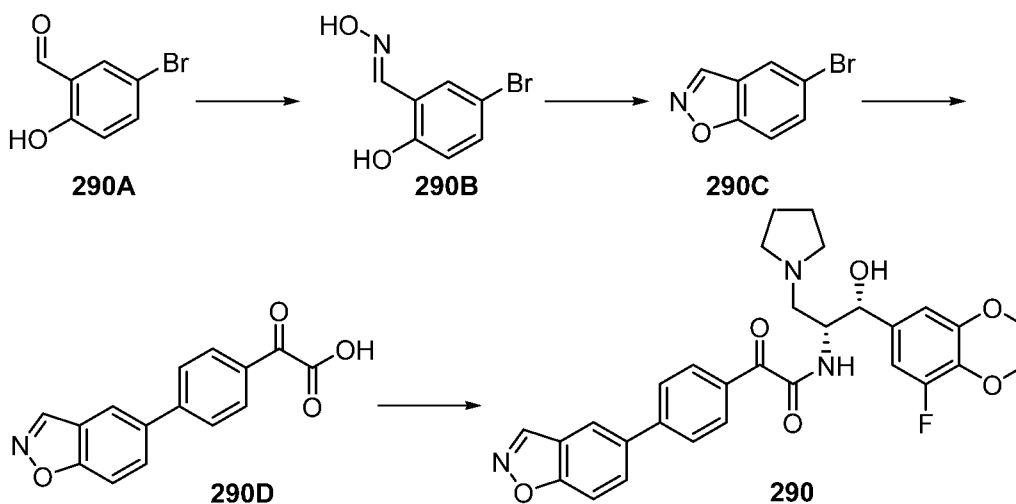
[0001051] To a solution of Compound **288F** (50 mg, 0.167 mmol) in dichloromethane (3 mL) was added Intermediate **G** (62 mg, 0.201 mmol) and HATU (95 mg, 0.25 mmol). The mixture was stirred at room temperature for 2 h. It was concentrated and the resulting residue was purified with prep-HPLC to afford Compound **288**. LC-MS (ESI) *m/z*: 591 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.68-0.91 (m, 4H), 2.1 1-2.15 (m, 4H), 2.97-3.05 (m, 2H), 3.48-3.50 (m, 1H), 3.65-3.68 (m, 1H), 3.70-3.85 (m, 1H), 3.87-3.91 (m, 2H), 4.53-4.57 (m, 1H), 5.01-5.06 (m, 1H), 5.56 (s, 2H), 6.96-7.00 (m, 2H), 7.13-7.19 (m, 3H), 7.20-7.23 (m, 1H), 7.28-7.31 (m, 1H), 7.38 (s, 1H), 7.93-7.95 (m, 1H), 8.1 1-8.13 (m, 2H), 8.58 (s, 1H), 11.48 (brs, 1H).

Example 289



[0001052] To a solution of Compound **288F** (50 mg, 0.167 mmol) in dichloromethane (3 mL) was added Intermediate **C** (59 mg, 0.201 mmol) and HATU (95 mg, 0.25 mmol). The mixture was stirred at room temperature for 2 hours. It was concentrated and the resulting residue was purified with prep-HPLC to afford Compound **289**. LC-MS (ESI) m/z : 577 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.18-2.19 (m, 4H), 3.01-3.05 (m, 2H), 3.49-3.51 (m, 1H), 3.71-3.79 (m, 2H), 3.96-4.02 (m, 2H), 4.18-4.22 (m, 4H), 4.45-4.47 (m, 1H), 5.10 (d, $J = 3.2$ Hz, 1H), 5.56 (s, 2H), 6.72-6.73 (m, 2H), 6.97-7.03 (m, 2H), 7.16-7.19 (m, 2H), 7.35-7.37 (m, 1H), 7.68-7.70 (m, 1H), 8.02-8.04 (m, 1H), 8.18 (s, 1H), 8.73 (s, 1H).

Example 290



[0001053] A mixture of Compound **290A** (2 g, 9.85 mmol) and aminooxysulfonic acid (1.67 g, 14.78 mmol) in ethanol (50 mL) was stirred at room temperature for 2 h. The mixture was diluted with DCM (200 mL), washed with water (200 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to afford Compound **290B**.

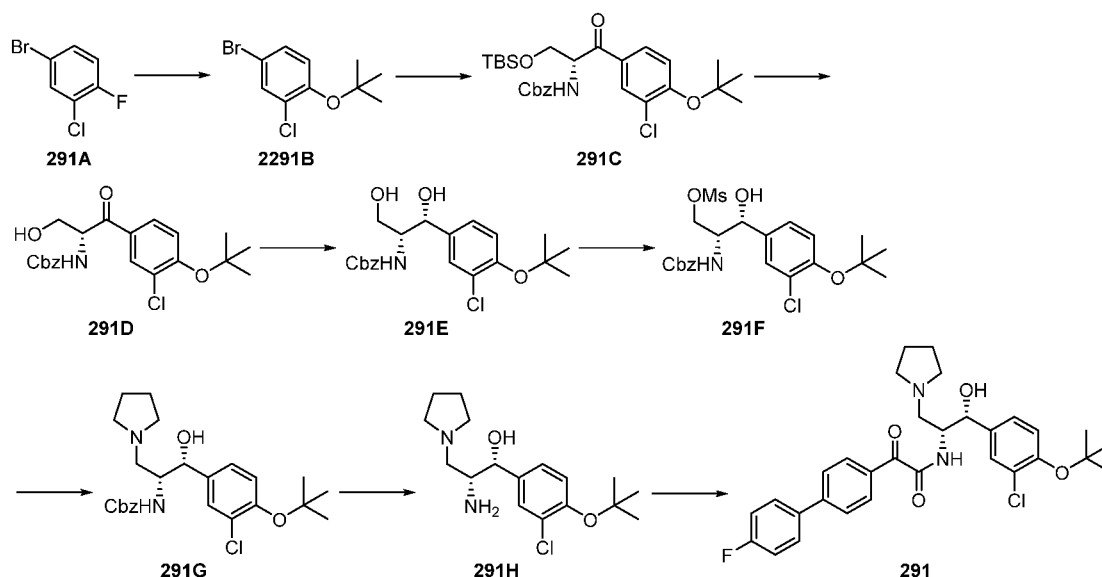
[0001054] To a solution of PPh_3 (3.44 g, 13.12 mmol) in DCM (40 mL) was added DDQ (2.98 g, 13.12 mmol) in portions at room temperature and the resultant mixture was stirred for 5 min. Compound **290B** (1.89 g, 8.75 mmol) was added. The reaction mixture was stirred for 5 min, diluted with DCM (100 mL), and filtered. The filtrate was washed with water (100 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified

with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **290C**.

[0001055] A mixture of Compound **290C** (198 mg, 1 mmol), Compound **175B** (456 mg, 1.5 mmol), Pd(PPh₃)₂Cl₂ (70 mg, 0.1 mmol), and K₂CO₃ (256 mg, 2 mmol) in dioxane (5 mL) and water (0.5 mL) was stirred at 80 °C for 2 h. The mixture was cooled down and filtered. The precipitate was dissolved in water and filtered. The filtrate was purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to yield Compound **290D**.

[0001056] A mixture of Compound **290D** (100 mg, 0.374 mmol), Intermediate **C** (111 mg, 0.374 mmol), and HATU (171 mg, 0.449 mmol) in DCM (3 mL) was stirred at room temperature overnight. The mixture was diluted with DCM (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **290**. LC-MS (ESI) m/z: 546 [M+H]⁺; 1H-NMR (acetone-d₆, 400 MHz): δ (ppm) 2.09-2.22 (m, 4H), 3.27-3.40 (m, 3H), 3.72-3.77 (m, 2H), 3.87-3.96 (m, 2H), 4.26-4.33 (m, 4H), 4.77-4.82 (m, 1H), 5.12-5.13 (m, 1H), 6.84-6.90 (m, 2H), 7.36 (dd, *J*₁ = 1.2 Hz, *J*₂ = 8.0 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.72-7.78 (m, 3H), 8.05 (d, *J* = 8.8 Hz, 2H), 8.18-8.20 (m, 1H).

Example 291



[0001057] To a solution of Compound **291A** (10.00 g, 47.85 mmol) in DMF (100 mL) was added *t*-BuOK (8.04 mL, 71.77 mmol) at room temperature. The mixture was stirred room temperature for 2 h and quenched with water (100 mL). The mixture was diluted with ethylacetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over

anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 5% v/v) to afford Compound **291B**.

[0001058] To a solution of Compound **291B** (11.00 g, 0.042 mol) in THF (30 mL) was added dropwise n-BuLi solution (2.5 M in hexane, 16.8 mL, 0.042 mol) under nitrogen at -68 °C. The mixture was stirred at -78 °C for 30 min and a solution of Compound **A4** (5.50 g, 13.89 mmol) in THF (20 mL) was added dropwise under nitrogen at -78 °C. The mixture was stirred at -78 °C for 20 min and quenched with saturated aqueous ammonium chloride solution (100 mL). The mixture was diluted with ethyl acetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to furnish Compound **291C**.

[0001059] A solution of Compound **291C** (6.00 g, 11.56 mmol) in THF (40 mL), AcOH (120 mL), and water (40 mL) was stirred at 25 °C for 48 h. The mixture was evaporated to remove solvent, diluted with ethyl acetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 50% v/v) to afford Compound **291D**.

[0001060] To a solution of Compound **291D** (3.20 g, 7.90 mmol) in THF (20 mL) was added dropwise DIBAL-H solution (1 M in toluene, 15.8 mL, 15.80 mmol) under nitrogen at -80 °C. After 30 min, additional DIBAL-H solution (1 M in toluene, 15.8 mL, 15.80 mmol) was added dropwise under nitrogen at -80 °C. The mixture was stirred under nitrogen at -80 °C for 2 h and quenched with saturated aqueous ammonium chloride solution (200 mL) at -20 °C. The mixture was diluted with ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 0% to 5% v/v) to give Compound **291E**.

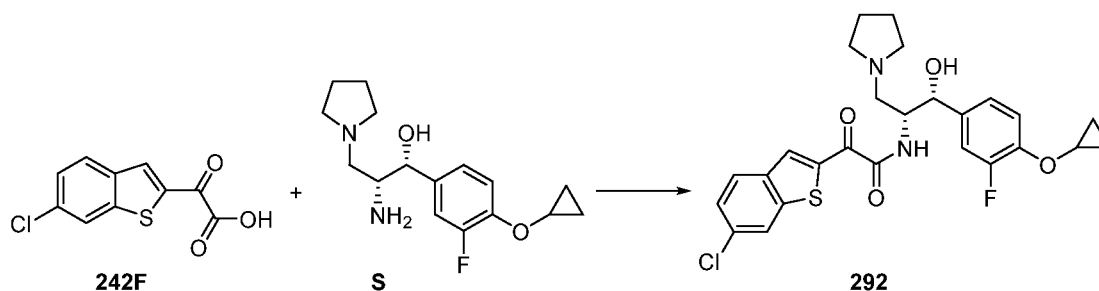
[0001061] To a solution of Compound **291E** (1.10 g, 2.70 mmol) and triethylamine (818 mg, 8.10 mmol) in THF (10 mL) was added dropwise methanesulfonyl chloride (370 mg, 3.24 mmol) at -15 °C. The mixture was stirred at -15 °C for 1 h. It was quenched with saturated ice water (50 mL), diluted with ethyl acetate (200 mL), washed with water (150 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and evaporated to afford Compound **291F**. The target compound was directly used for the next step without further purification.

[0001062] A solution of Compound **291F** (1.10 g, 2.27 mmol) and pyrrolidine (1.68 g, 22.68 mmol) in THF (10 mL) was stirred at 50 °C for 16 h. The mixture was cooled down to room temperature and diluted with ethyl acetate (200 mL). The organic layer was washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 0% to 8% v/v) to furnish Compound **291G**.

[0001063] A mixture of Compound **291G** (300 mg, 0.65 mmol) and LiOH·H₂O (356 mg, 6.52 mmol) in methanol (10 mL) and water (2 mL) was stirred at 80 °C for 16 h. It was diluted with ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to furnish Compound **291H**.

[0001064] A mixture of Compound **291H** (110 mg, 0.34 mmol), Intermediate **C** (82 mg, 0.34 mmol), and HATU (190 mg, 0.51 mmol) in DMF (5 mL) was stirred at room temperature for 16 h. It was diluted with ethyl acetate (120 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and purified with prep-HPLC to afford Compound **291**. LC-MS (ESI) m/z: 553 [M+H]⁺; ¹H-NMR (OMSO-*d*₆, 400 MHz): δ (ppm) 1.33 (s, 9H), 1.84-1.93 (m, 2H), 2.00-2.06 (m, 2H), 3.11-3.24 (m, 2H), 3.49-3.53 (m, 4H), 4.52-4.57 (m, 1H), 4.91 (s, 1H), 6.08 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.27-7.30 (m, 1H), 7.37 (t, *J* = 8.8 Hz, 2H), 7.47 (s, 1H), 7.78-7.85 (m, 6H), 8.79 (d, *J* = 9.2 Hz, 1H), 7.43 (s, 1H).

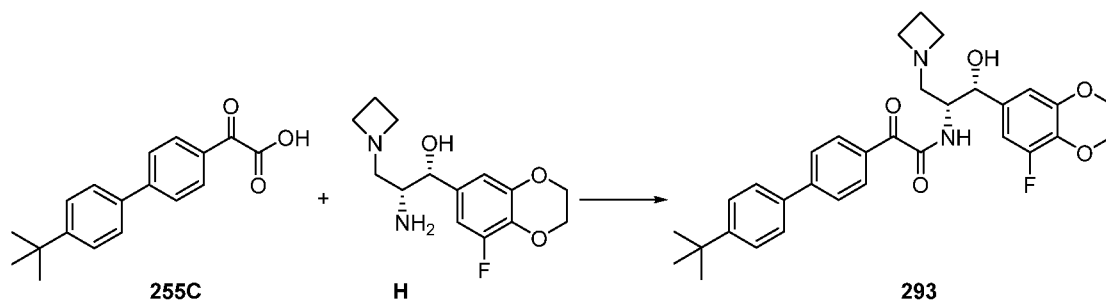
Example 292



[0001065] To a solution of Compound **S** (118 mg, 0.40 mmol) in DMF (10 mL) was added Compound **242F** (80 mg, 0.33 mmol), HATU (190 mg, 0.50 mmol), and *N,N*-diisopropylethylamine (129 mg, 1.0 mmol). The mixture was stirred under nitrogen at 25 °C overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with

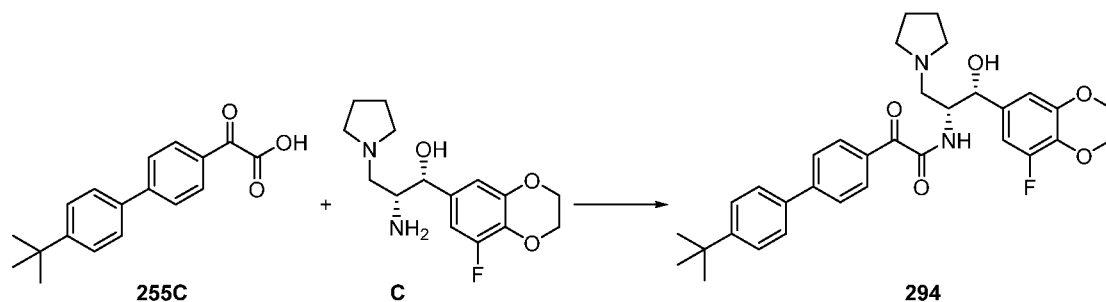
prep-HPLC to furnish Compound **292**. LC-MS (ESI) m/z : 517 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.64-0.76 (m, 4H), 1.84-2.00 (m, 4H), 3.09-3.17 (m, 2H), 3.33-3.38 (m, 1H), 3.50-3.56 (m, 3H), 3.86-3.90 (m, 1H), 4.43-4.48 (m, 1H), 4.79 (s, 1H), 6.06 (s, 1H), 7.14-7.20 (m, 2H), 7.35 (t, $J = 8.8$ Hz, 1H), 7.55 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.30 (d, $J = 2.0$ Hz, 1H), 8.58 (s, 1H), 8.63 (d, $J = 10.0$ Hz, 1H), 9.06 (s, 1H).

Example 293



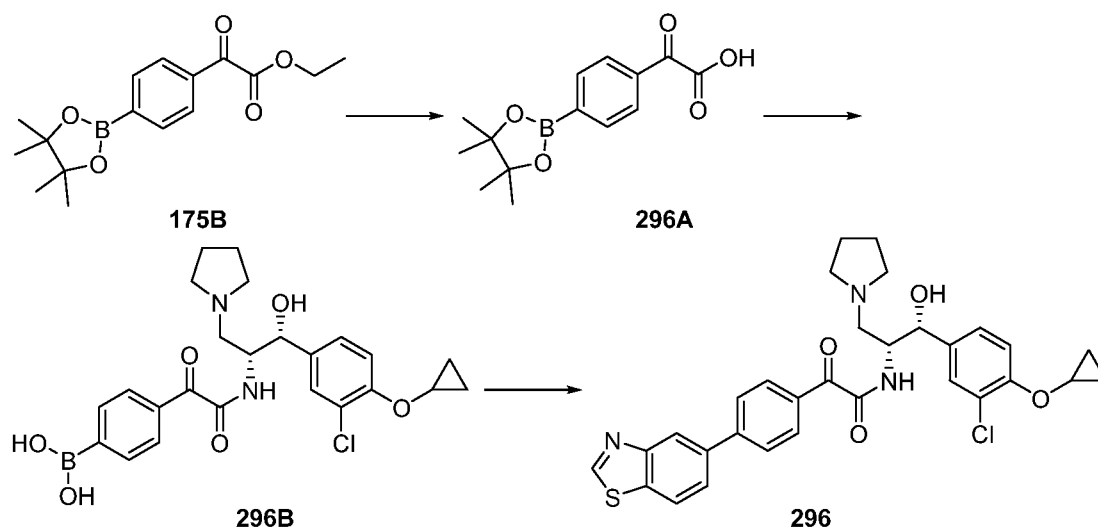
[0001066] A mixture of Compound **255C** (50 mg, 0.18 mmol), HATU (100 mg, 0.27 mmol), and Intermediate **H** (50 mg, 0.18 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **293**. LC-MS (ESI) m/z : 547 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.33 (s, 9H), 2.26-2.45 (m, 2H), 3.36-3.48 (m, 2H), 4.07-4.30 (m, 9H), 4.74 (s, 1H), 6.02 (s, 1H), 6.76-6.84 (m, 2H), 7.54-7.56 (m, 2H), 7.69-7.71 (m, 2H), 7.78-7.84 (m, 4H), 8.75 (d, $J = 9.6$ Hz, 1H), 9.67 (s, 1H).

Example 294



[0001067] A mixture of Compound **255C** (50 mg, 0.18 mmol), HATU (100 mg, 0.27 mmol), and Intermediate **C** (53 mg, 0.18 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **294**. LC-MS (ESI) m/z : 561 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.33 (s, 9H), 1.87-2.03 (m, 4H), 3.12-3.19 (m, 2H), 3.46-3.55 (m, 4H), 4.26-

Example 296



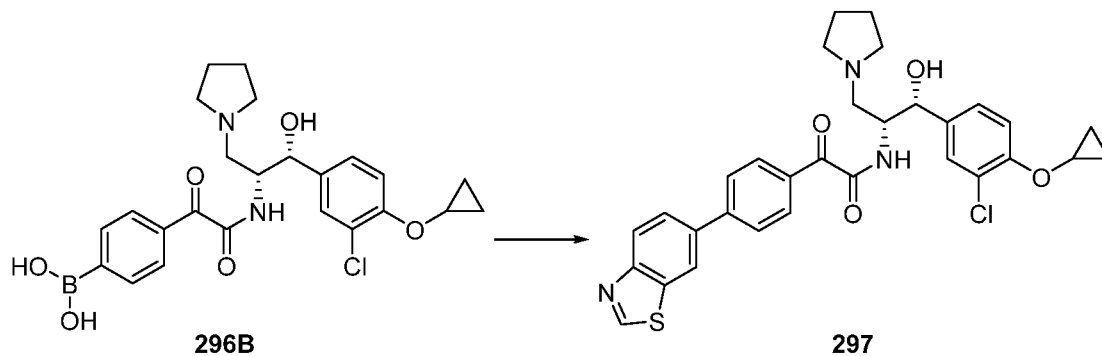
[0001070] To a solution of Compound **175B** (600 mg, 1.97 mmol) in THF (20 mL) was added LiOH·H₂O (124 mg, 2.96 mmol) dissolved in water (3 mL) at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction mixture was treated with water (10 mL) and extracted with ethyl acetate (10 mL). The water layer was adjusted to pH 6 with diluted HCl and extracted with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, and concentrated to afford Compound **296A**, which was used for the next step without further purification.

[0001071] A mixture of Compound **296A** (480 mg, 1.74 mmol), Intermediate **G** (594 mg, 1.91 mmol), and HATU (991 mg, 2.61 mmol) in dichloromethane (20 mL) was stirred at 25 °C for 10 h. The mixture was quenched with water (10 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **296B**.

[0001072] A mixture of 5-bromobenzo[d]thiazole (35 mg, 0.16 mmol), Compound **296B** (104 mg, 0.22 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6 mg, 8.2 μmol), potassium carbonate (68 mg, 0.49 mmol), water (0.5 mL), and 1,4-dioxane (2 mL) was heated under nitrogen atmosphere at 100 °C for 1 h. After cooling, water (5 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a black oil. The oil was purified with prep-HPLC to furnish Compound **296**. LC-MS (ESI) m/z: 576 [M+H]⁺; ¹H-NMR ((CD₃)₂CO, 400 MHz): δ (ppm) 0.71-0.73 (m, 2H), 0.81-0.84 (m, 2H), 2.09-2.13 (m, 2H), 2.28 (s, 2H), 3.55 (s, 1H), 3.89-3.90 (m, 2H), 4.05-4.08 (m, 4H), 4.94 (s,

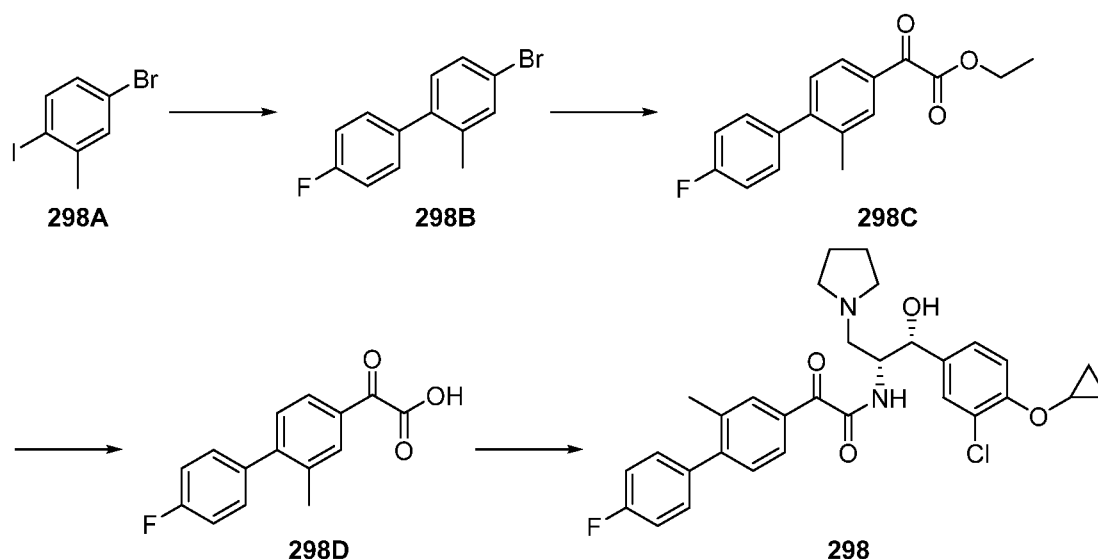
1H), 5.21 (d, $J = 2$ Hz, 1H), 7.42-7.43 (m, 2H), 7.51 (d, $J = 1.6$ Hz, 1H), 7.91 (dd, $J = 8.5, 3.0$ Hz, 4H), 8.03 (d, $J = 8.5$ Hz, 2H), 8.21 (d, $J = 9.7$ Hz, 1H), 8.31 (d, $J = 8.5$ Hz, 1H), 8.45 (d, $J = 1.5$ Hz, 1H), 9.37 (s, 1H).

Example 297



[0001073] A mixture of 6-bromobenzo[d]thiazole (30 mg, 0.14 mmol), Compound **296B** (90 mg, 0.18 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6 mg, 8.2 μmol), potassium carbonate (58 mg, 0.42 mmol), water (0.5 mL), and 1,4-dioxane (2 mL) was heated under nitrogen atmosphere at 100 °C for 1 h. After cooling, water (5 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a black oil. The oil was purified with prep-HPLC to furnish Compound **297**. LC-MS (ESI) m/z : 576 $[M+H]^+$; $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$, 400 MHz): δ (ppm) 0.60-0.86 (m, 4H), 2.06-2.38 (m, 4H), 3.27 (s, 1H), 3.52-3.64 (m, 2H), 3.89-3.91 (m, 2H), 4.01 (d, $J = 5.7$ Hz, 1H), 4.06-4.16 (m, 2H), 4.92-4.97 (m, 1H), 5.20 (d, $J = 2.1$ Hz, 1H), 7.35-7.45 (m, 2H), 7.49 (d, $J = 1.7$ Hz, 1H), 7.83-7.90 (m, 2H), 7.95 (dd, $J = 8.6, 1.8$ Hz, 1H), 8.03 (d, $J = 8.6$ Hz, 2H), 8.19-8.23 (m, 2H), 8.55 (d, $J = 1.6$ Hz, 1H), 9.36 (s, 1H).

Example 298



[0001074] To a mixture of Compound **298A** (2.96 g, 0.01 mol), 4-fluorophenylboronic acid (2 g, 1.32 mol), and K_3PO_4 (6.4 g, 0.03 mol) in 1,2-dimethoxyethane (80 mL) was added $Pd(dppf)Cl_2$ (733 mg, 1.0 mmol). The reaction mixture was stirred under nitrogen at room temperature overnight. The resulting mixture washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **298B**.

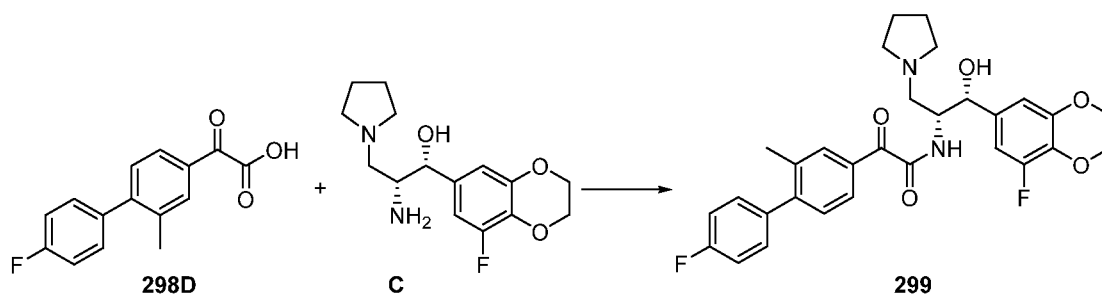
[0001075] To a solution of Compound **298B** (2.64 g, 10 mmol) in THF (30 mL) was added dropwise n-BuLi solution (2.5 M in hexane, 4 mL, 10 mmol) under nitrogen at $-78\text{ }^\circ\text{C}$. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 0.5 h and the solution was added to a solution of diethyl oxalate (3 g, 20 mmol) in THF (20 mL) under nitrogen at $-78\text{ }^\circ\text{C}$. The mixture was stirred at room temperature overnight and quenched with saturated aqueous ammonium chloride solution (40 mL). The reaction mixture was extracted with ethyl acetate (50 mL x 3), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to give Compound **298C**.

[0001076] To a solution of Compound **298C** (2.8 g, 0.01 mol) in ethanol/water (40 mL/10 mL) was added $LiOH \cdot H_2O$ (840 mg, 0.02 mol). The mixture was stirred at room temperature for about 2 h until completion by thin layer chromatography analysis. The reaction mixture was acidified to pH 2 with aqueous HCl solution (1.0 N, 40 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with

brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **298D**.

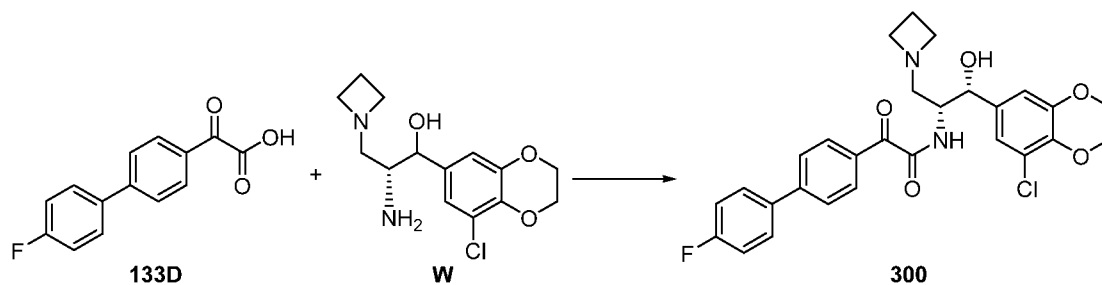
[0001077] To a mixture of Compound **298D** (126 mg, 0.5 mmol) and Intermediate **G** (155 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC to furnish Compound **298**. LC-MS (ESI) m/z : 551 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.62-0.87 (m, 4H), 1.88-2.04 (m, 4H), 2.26 (s, 3H), 3.13-3.21 (m, 2H), 3.50-3.56 (m, 4H), 3.88-3.89 (m, 1H), 4.54-4.56 (m, 1H), 4.87 (s, 1H), 6.05 (s, 1H), 7.27-7.45 (m, 8H), 7.53 (d, $J = 6.8$ Hz, 1H), 7.76 (s, 1H), 8.80 (d, $J = 9.2$ Hz, 1H), 9.40 (s, 1H).

Example 299



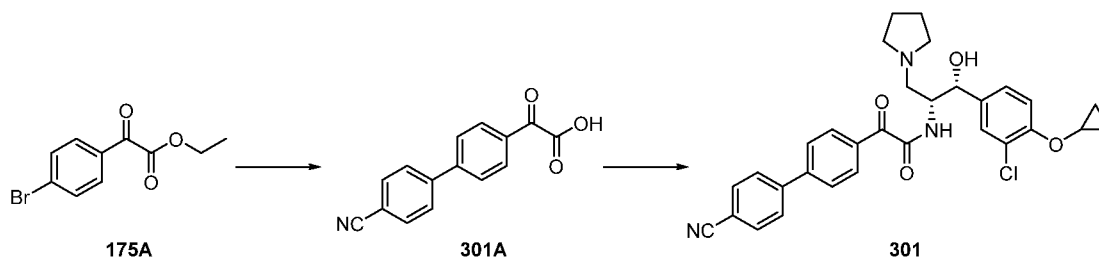
[0001078] To a mixture of Compound **298D** (130 mg, 0.5 mmol) and Intermediate **C** (143 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC to furnish Compound **299**. LC-MS (ESI) m/z : 537 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.86-2.04 (m, 4H), 2.27 (s, 3H), 3.11-3.18 (m, 2H), 3.42-3.54 (m, 4H), 4.23-4.28 (m, 4H), 4.49 (s, 1H), 4.77 (s, 1H), 6.04 (s, 1H), 6.75 (s, 1H), 6.81-6.84 (m, 1H), 7.31-7.35 (m, 3H), 7.42-7.46 (m, 2H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.80 (s, 1H), 8.75 (d, $J = 9.6$ Hz, 1H), 9.30 (s, 1H).

Example 300



[0001079] A mixture of Compound **133D** (110 mg, 0.37 mmol), Intermediate **W** (90 mg, 0.37 mmol), and HATU (182 mg, 0.48 mmol) in dichloromethane (10 mL) was stirred at 10 °C for 15 h. And then it was treated with water (10 mL) and extracted with dichloromethane (10 mL x 3 mL). The organic layers were washed with water (20 mL x 3), dried over anhydrous sodium sulfate, concentrated in *vacuo*, and purified with prep-HPLC to yield Compound **300**. LC-MS (ESI) *m/z*: 525 [M+H]⁺; ¹H-NMR ((CD₃)₂CO, 400 MHz): δ (ppm) 2.58 (s, 1H), 2.70-2.77 (m, 1H), 3.88-4.01 (m, 2H), 4.22-4.38 (m, 4H), 4.49-4.64 (m, 4H), 4.71-4.77 (m, 1H), 5.12 (s, 1H), 5.47 (s, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.30 (t, *J* = 8.8 Hz, 2H), 7.77-7.84 (m, 4H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 9.6 Hz, 1H), 9.19 (s, 1H).

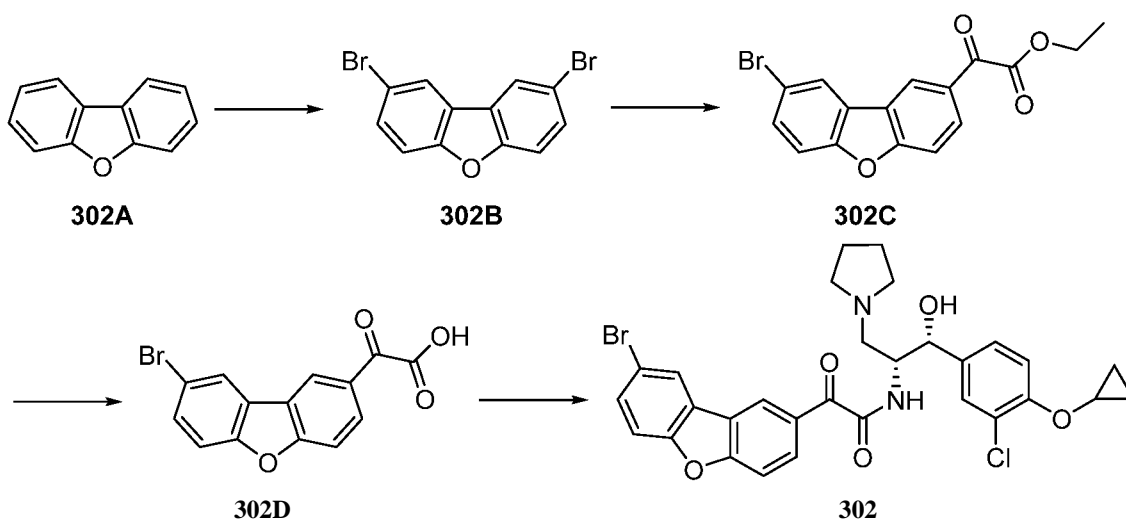
Example 301



[0001080] A mixture of Compound **175A** (512 mg, 2 mmol), 4-cyanophenylboronic acid (294 mg, 2 mmol), potassium carbonate (828 mg, 6 mmol), and Pd(dppf)Cl₂ (40 mg, 0.08 mmol) in dioxane (20 mL) and water (4 mL) was stirred under nitrogen at 100 °C overnight. The solution was cooled down to room temperature, adjusted to pH 4 with aqueous hydrochloric acid solution (6 N, 2 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to afford Compound **301A**.

[0001081] A mixture of Compound **301A** (100 mg, 0.4 mmol), HATU (273 mg, 0.72 mmol), and Intermediate **G** (124 mg, 0.4 mmol) in dichloromethane (10 mL) and DMF (2 mL) was stirred at 25 °C overnight. The solution was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The residue was purified with prep-HPLC to furnish Compound **301**. LC-MS (ESI) *m/z*: 544 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.66-0.82 (m, 4H), 1.88-2.02 (m, 4H), 3.12-3.21 (m, 2H), 3.47-3.64 (m, 4H), 3.88-3.93 (m, 1H), 4.53-4.61 (m, 1H), 4.87 (s, 1H), 6.05 (s, 1H), 7.33-7.43 (m, 3H), 7.85-7.86 (m, 3H), 7.95-8.03 (m, 5H), 8.81-8.83 (m, 1H), 9.39 (s, 1H).

Example 302



[0001082] To a solution of Compound **302A** (1 g, 0.59 mmol) in CHCl_3 (6 mL) was added bromine (0.68 mL, 13.26 mmol) at 0 °C. The mixture was stirred at 25 °C for 48 h. It was poured into aq. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to furnish the crude product. It was recrystallized from methanol to give Compound **302B**.

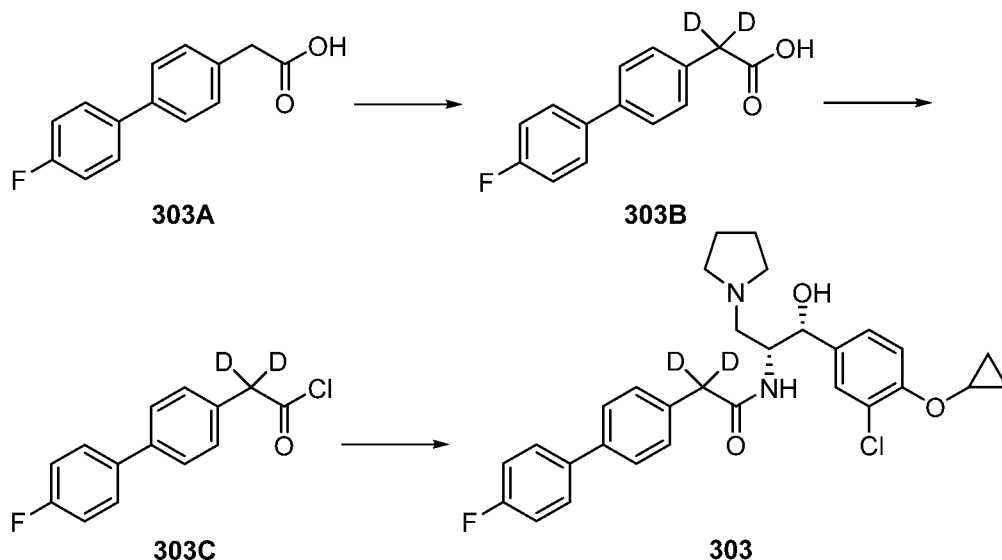
[0001083] To a solution of Compound **302B** (324 mg, 1 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M, 0.4 mL, 1.06 mmol) under nitrogen at -60 °C. It was stirred at -60 °C for 0.5 h. And then a solution of diethyl oxalate (0.4 mL, 3 mmol) in THF (5 mL) was added. The mixture was stirred at -60 °C for 0.5 h, quenched with saturated ammonium chloride solution (200 mL), extracted with ethyl acetate (20 mL x 3), washed with brine (20 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to furnish Compound **302C**.

[0001084] To a solution of Compound **302C** (39 mg, 0.11 mmol) in THF/water (6 mL, 5:1, v/v) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (52 mg, 0.12 mmol). The mixture was stirred at 0 °C for 1 h. After the reaction was completed, water (20 mL) was added. It was extracted with ethyl acetate (20 mL). The water was adjusted to pH 2. It was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in *vacuo* to give the crude Compound **302D**.

[0001085] A mixture of Compound **302D** (35 mg, 0.11 mmol), Intermediate **G** (43 mg, 0.14 mmol), and HATU (54 mg, 0.14 mmol) in DMF (4 mL) was stirred at 10 °C for 3 h. And then it was purified with prep-HPLC to give Compound **302**. LC-MS (ESI) *m/z*: 611 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$, 400 MHz): δ (ppm) 0.58-0.83 (m, 4H), 2.07-2.16 (m, 2H),

2.24 (s, 2H), 3.45 (s, 2H), 3.80-3.85 (m, 2H), 3.96 (s, 3H), 4.90 (s, 1H), 5.20 (s, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.44 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 7.53 (d, $J = 2.0$ Hz, 1H), 7.69-7.77 (m, 3H), 8.17 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 8.23 (d, $J = 9.6$ Hz, 1H), 8.43 (d, $J = 2$ Hz, 1H), 8.84 (d, $J = 1.2$ Hz, 1H), 10.19 (brs, 1H).

Example 303

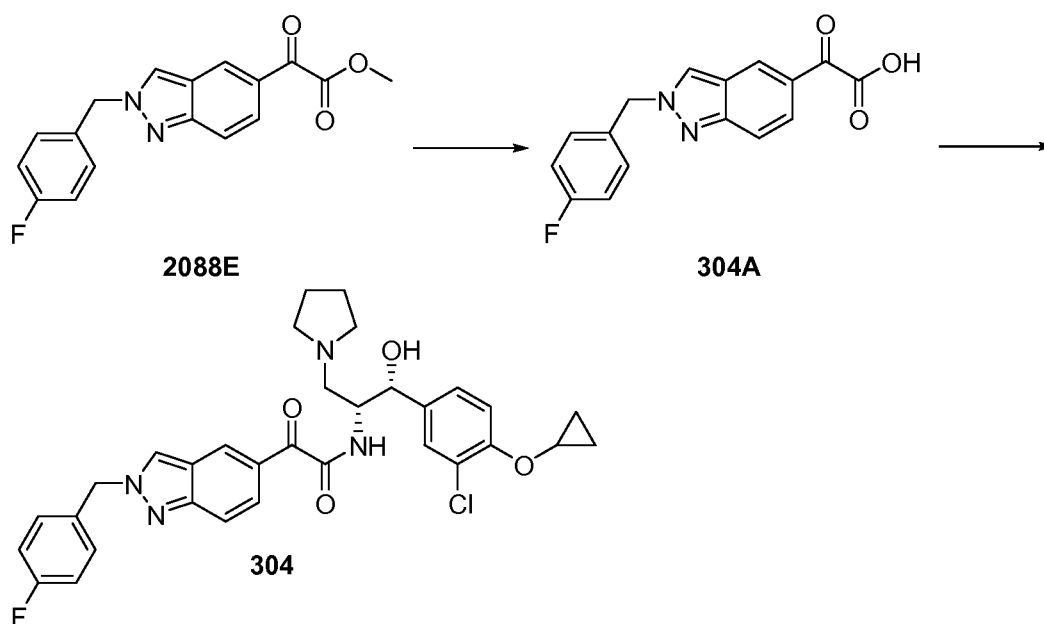


[0001086] A mixture of Compound **303A** (191 mg, 0.83 mmol), K_2CO_3 (456 mg, 3.3 mmol), and D_2O (12 mL) was stirred at 110 °C overnight. The mixture was acidified with the addition of 1 M HCl, extracted with DCM (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **303B**.

[0001087] A mixture of Compound **303B** (145 mg, 0.63 mmol) in $SOCl_2$ (4.5 mL) was stirred at 25 °C for 2 h. The mixture was concentrated to give Compound **303C** (160 mg, yield 100%) as a yellow oil, which was directly used for the next step without further purification.

[0001088] A solution of Intermediate **G** (200 mg, 0.63 mmol) in CD_3OD was evaporated to dryness and the residue was dissolved $CDCl_3$ (8 mL). The solution was added to Compound **303C** (200 mg, 0.63 mmol). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was treated with water (20 mL), extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **303**. LC-MS (ESI) m/z : 525.2 $[M+H]^+$; 1H-NMR (CD_3OD , 400 MHz): δ (ppm) 0.57-0.66 (m, 4H), 2.02-2.23 (m, 4H), 3.13-3.30 (m, 2H), 3.48-3.68 (m, 4H), 3.80-3.88 (m, 1H), 4.51-4.54 (m, 1H), 4.87 (d, $J = 2.4$ Hz, 1H), 7.06-7.20 (m, 6H), 7.42-7.49 (m, 3H), 7.62-7.66 (m, 2H).

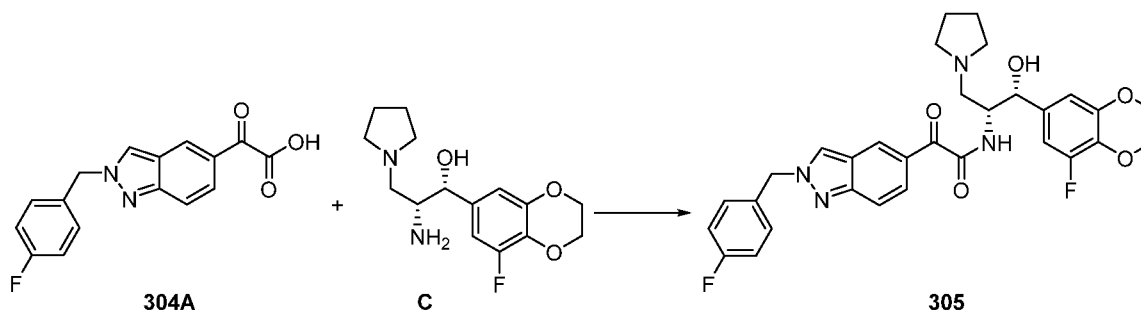
Example 304



[0001089] To a solution of Compound **288E** (150 mg, 0.45 mmol) in THF (1 mL) was added dropwise 1 *N* lithium hydroxide (1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction mixture was concentrated, 2 *N* HCl (1 mL) added to adjust pH 7, and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **304A**.

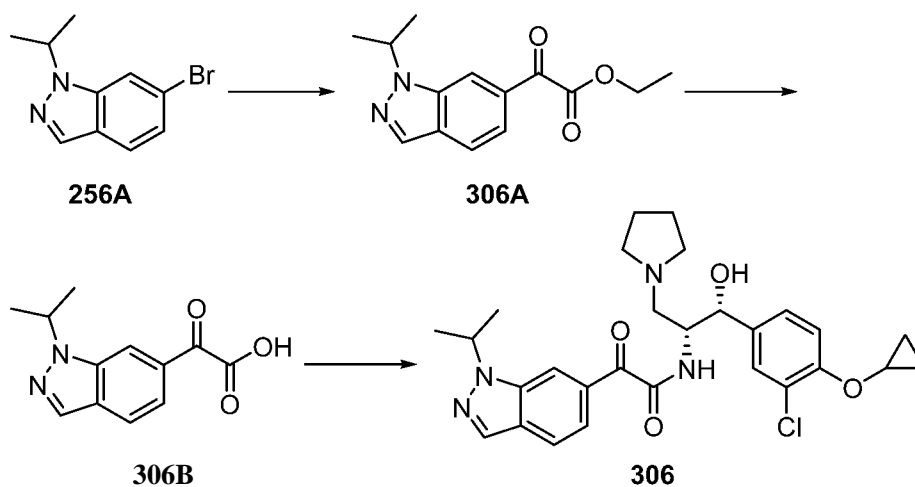
[0001090] To a solution of Compound **304A** (50 mg, 0.167 mmol) in dichloromethane (3 mL) was added Intermediate **G** (62 mg, 0.201 mmol) and HATU (95 mg, 0.25 mmol). The mixture was stirred at room temperature for 2 h. It was concentrated and the resulting residue was purified with prep-HPLC to afford Compound **304**. LC-MS (ESI) *m/z*: 591 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.74-0.76 (m, 4H), 2.13-2.15 (m, 4H), 3.01-3.05 (m, 1H), 3.50-3.58 (m, 1H), 3.59-3.81 (m, 3H), 3.87-4.01 (m, 2H), 4.53-4.57 (m, 1H), 5.11-5.16 (m, 1H), 5.56 (s, 2H), 7.05-7.09 (m, 2H), 7.21-7.23 (m, 1H), 7.27-7.33 (m, 3H), 7.36-7.37 (m, 1H), 7.66-7.68 (s, 1H), 7.79-7.80 (m, 1H), 8.12 (s, 2H), 8.58 (s, 1H).

Example 305



[0001091] To a solution of Compound **304A** (50 mg, 0.167 mmol) in dichloromethane (3 mL) was added Intermediate **C** (59 mg, 0.201 mmol) and HATU (95 mg, 0.25 mmol). The mixture was stirred at room temperature for 2 h. It was purified with prep-HPLC and prep-TLC to afford Compound **305**. LC-MS (ESI) m/z : 577 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.82-1.85 (m, 4H), 2.75-2.84 (m, 4H), 3.01-3.04 (m, 2H), 4.16-4.33 (m, 5H), 5.03 (d, $J = 1.6$ Hz, 1H), 5.57 (s, 2H), 6.69-6.74 (m, 2H), 7.04-7.09 (m, 2H), 7.26-7.32 (m, 2H), 7.42-7.45 (m, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 8.09 (s, 1H), 8.93 (s, 1H).

Example 306

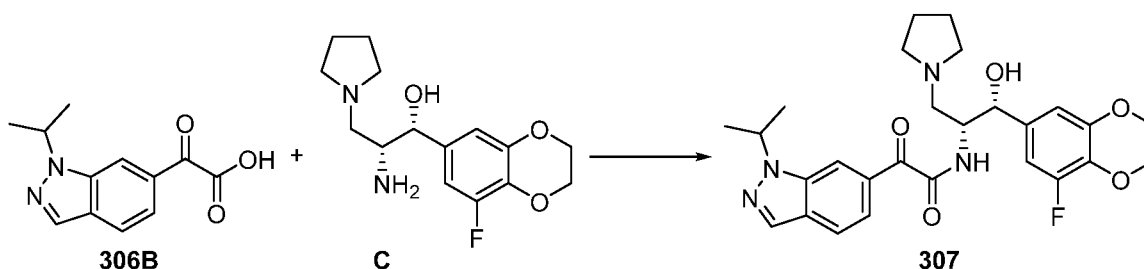


[0001092] To a solution of Compound **256A** (640 mg, 2.69 mmol) in dry THF (10 mL) was added dropwise n -BuLi solution (2.5 M in hexane, 1.1 mL, 2.72 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 30 min and diethyl oxalate (0.91 mL, 6.73 mmol) was added quickly to the above mixture. The mixture was stirred at -78 °C for 30 min, quenched with saturated aqueous ammonium chloride solution (10 mL), and extracted with ethyl acetate (80 mL x 2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 5% v/v) to furnish Compound **306A**.

[0001093] To a solution of Compound **306A** (490 mg, 2.11 mmol) in methanol (5 mL) was added $LiOH \cdot H_2O$ (177 mg, 4.22 mmol) in water (5 mL) and the mixture was stirred at room temperature overnight. After completion of the reaction, the mixture was adjusted to pH 6 with aqueous HCl solution (3 N) and concentrated in *vacuo*. The residue was in lyophilization to afford Compound **306B**.

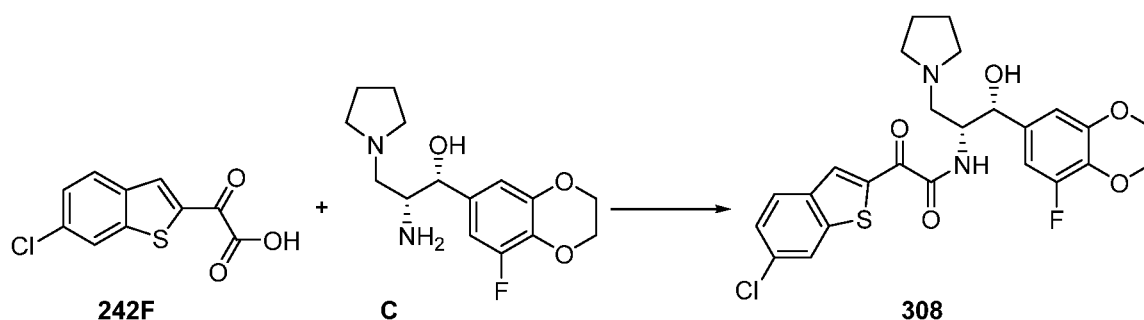
[0001094] A mixture of Compound **306B** (70 mg, 0.30 mmol), HATU (171 mg, 0.45 mmol), and Intermediate **G** (93 mg, 0.30 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to yield Compound **306**. LC-MS (ESI) m/z : 525 [M+H]⁺; ¹H-NMR (*O**M**S**O*-*d*₆, 400 MHz): δ (ppm) 0.59-0.81 (m, 4H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.87-2.04 (m, 4H), 3.06-3.22 (m, 2H), 3.47-3.56 (m, 4H), 3.87-3.91 (m, 1H), 4.54-4.56 (m, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 5.01-5.05 (m, 1H), 6.07 (brs, 1H), 7.33-7.39 (m, 2H), 7.45-7.48 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 8.23 (s, 1H), 8.35 (s, 1H), 8.81 (d, *J* = 9.6 Hz, 1H), 9.34 (brs, 1H).

Example 307



[0001095] A mixture of Compound **306B** (70 mg, 0.30 mmol), HATU (171 mg, 0.45 mmol), and Intermediate **C** (93 mg, 0.30 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to afford Compound **307**. LC-MS (ESI) m/z : 511 [M+H]⁺; ¹H-NMR (*D**M**S**O*-*d*₆, 400 MHz): δ (ppm) 1.49 (d, *J* = 6.8 Hz, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.87-1.89 (m, 2H), 2.02-2.04 (m, 2H), 3.10-3.21 (m, 2H), 3.43-3.55 (m, 4H), 4.21-4.31 (m, 4H), 4.48-4.55 (m, 1H), 4.77 (d, *J* = 3.2 Hz, 1H), 5.02-5.08 (m, 1H), 6.77 (s, 1H), 6.84 (dd, *J* = 11.6, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.24 (s, 1H), 8.38 (s, 1H), 8.79 (d, *J* = 9.6 Hz, 1H), 9.30 (brs, 1H).

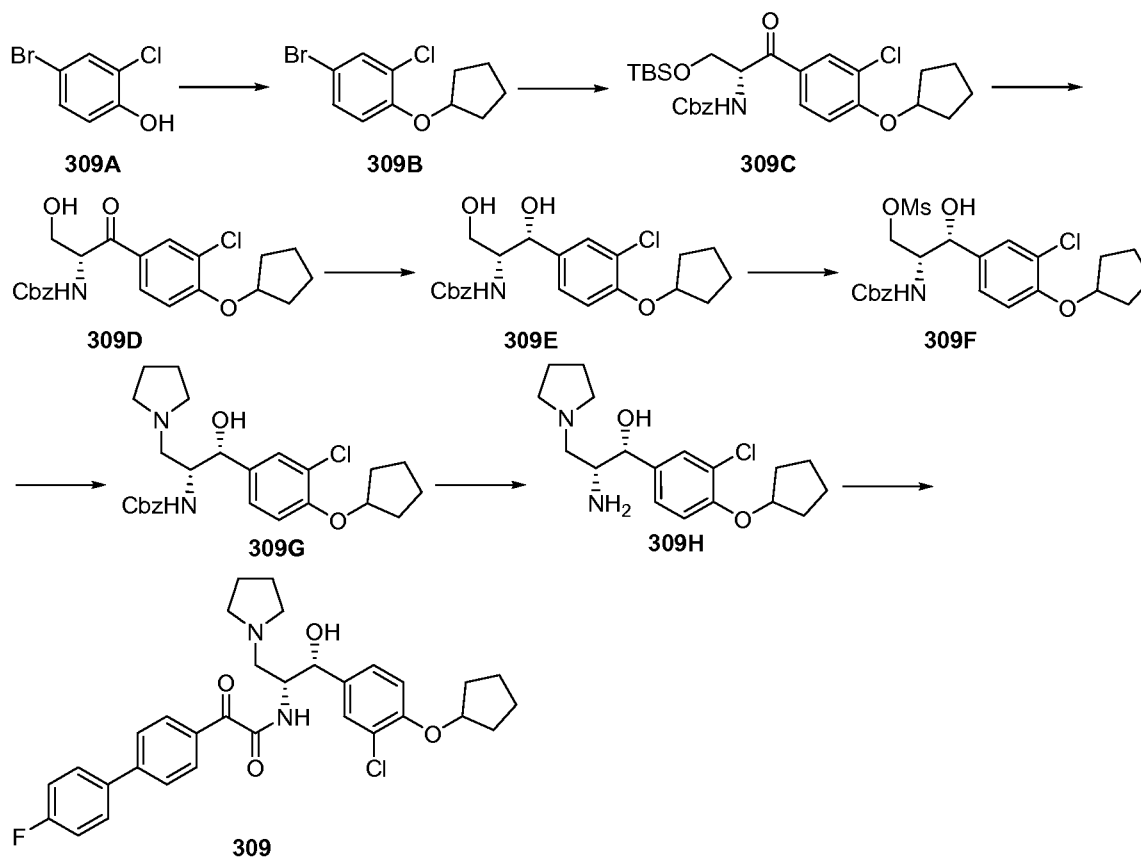
Example 308



[0001096] To a solution of Intermediate **C** (118 mg, 0.40 mmol) in DMF (10 mL) was added Compound **242F** (80 mg, 0.33 mmol), HATU (190 mg, 0.50 mmol), and *N,N*-diisopropylethylamine (129 mg, 1.0 mmol). The mixture was stirred under nitrogen at 25 °C overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate

solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **308**. LC-MS (ESI) m/z : 519 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.00-2.04 (m, 2H), 2.15-2.18 (m, 2H), 3.19-3.29 (m, 2H), 3.46-3.50 (m, 1H), 3.67-3.81 (m, 3H), 4.11-4.23 (m, 4H), 4.29-4.35 (m, 2H), 4.54-4.57 (m, 1H), 4.85 (d, $J = 3.2$ Hz, 1H), 6.76-6.81 (m, 2H), 7.46 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 8.04 (d, $J = 1.6$ Hz, 1H), 8.48 (s, 1H).

Example 309



[0001098] To a solution of Compound **309A** (3.17 g, 154 mmol) in 1-methyl-2-pyrrolidinone (300 mL) was added cesium carbonate (100.4 g, 308 mmol) and bromocyclopentane (68.4 g, 462 mmol). The mixture was stirred for 24 h while keeping inner temperature between 145 °C and 155 °C. After the reaction was cooled to ambient temperature, the dark solution was diluted with water (400 mL) and extracted with a mixture of ethyl acetate in petroleum ether (15% v/v) (300 mL x 3). The combined organic phases were washed with brine (150 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **309B**.

[0001099] To a solution of Compound **309B** (32 g, 116.8 mmol) in dry THF (360 mL) maintained at -70 °C was added n-BuLi (2.5 M in hexane, 46.7 mL) dropwise under nitrogen atmosphere over a period of 20 minutes. After the reaction was stirred for 40 minutes at -70 °C, Compound **A4** (18.5 g, 46.7 mmol) dissolved in dry THF (50 mL) was added slowly to the cold solution at a rate that maintained the internal temperature between -70 °C and -50 °C. After the addition was complete, the solution was left to stir for 1 h. The reaction was quenched with saturated ammonium chloride solution (400 mL), extracted with ethyl acetate (400 mL x 3), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude Compound (**3**). The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 20% v/v) to furnish Compound **309C**.

[0001100] A solution of Compound **309C** (14.1 g, 26.5 mmol) in a mixture of tetrahydrofuran water and glacial acetic acid (450 mL, 1/1/3, v/v/v) was stirred at 25 °C for 30 h. After that, the reaction mixture was concentrated under reduced pressure to remove excess solvent. The reaction residue was poured into ice water (20 g) and adjusted pH 7-8 with aqueous sodium hydroxide (1 N) and saturated aqueous sodium bicarbonate solution. The solution was extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 30% to 50% v/v) to give Compound **309D**.

[0001101] To a solution of Compound **309D** (10.0 g, 24.0 mmol) in dry THF (500 mL) maintained at -78 °C was added diisobutylaluminum hydride (1.0 M in toluene, 96 mL) dropwise under nitrogen atmosphere over a period of 15 minutes. After the reaction was stirred at -70 °C for 1 h, a solution of HCl (2 N, 100 mL) was added to the mixture slowly. The reaction mixture was extracted with ethyl acetate (100 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 50% to 150% v/v) to furnish Compound **309E**.

[0001102] To a solution of Compound **309E** (9.25 g, 24.0 mmol) dissolved in tetrahydrofuran (300 mL) was added triethylamine (7.3 g, 72.0 mmol). The mixture was cooled to -30 °C, and then methanesulfonyl chloride (3 g, 26.4 mmol) was added dropwise over a period of 15 minutes. After the addition was complete, the reaction was stirred at -30 °C for 1.5 h, diluted with water (150 mL), and extracted with ethyl acetate (150 mL x 2). The

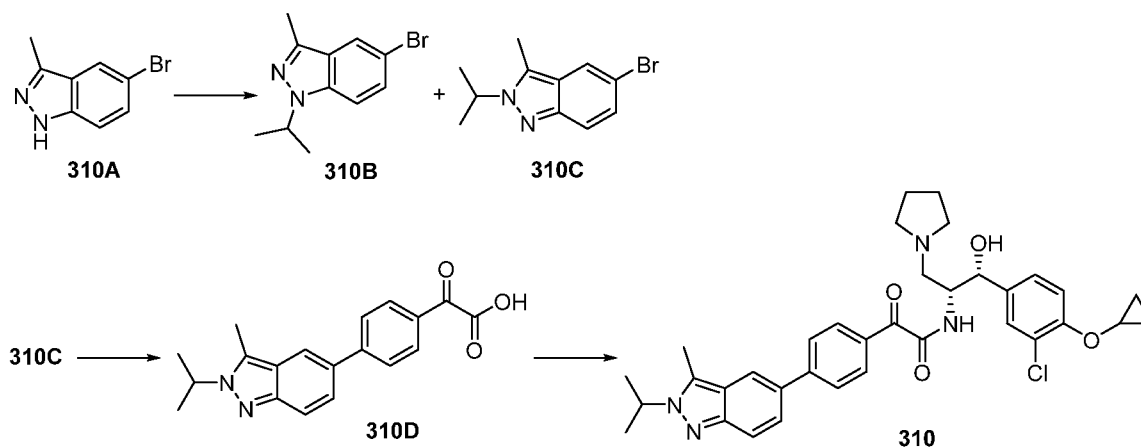
combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford crude Compound **309F**, which was directly used for the next step without further purification.

[0001103] To a solution of Compound **309F** (11.2 g, purity 70%) in tetrahydrofuran (50 mL) was added pyrrolidine (13.5 g, 190 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (100 mL), extracted with ethyl acetate (250 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **309G**.

[0001104] To a solution of Compound **309G** (800 mg, 1.69 mmol) in ethanol (12 mL) and water (2 mL) was added LiOH·H₂O (284 mg, 6.76 mmol). The mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **309H**, which was directly used for the next step without further purification.

[0001105] To a solution of Compound **309H** (200 mg, 0.6 mmol), Intermediate **C** (146 mg, 0.6 mmol), and HATU (456 mg, 1.2 mmol) in *N,N*-dimethylformamide (3 mL) was stirred at room temperature for 1 h. The reaction solution was purified with prep-HPLC to furnish Compound **309**. LC-MS (ESI) *m/z*: 565 [M+H]⁺; ¹H-NMR (*OMSO-d*₆, 400 MHz): δ (ppm) 1.55-1.74 (m, 6H), 1.87-2.02 (m, 6H), 3.05-3.54 (m, 6H), 4.51-4.91 (m, 3H), 6.01 (d, *J* = 4.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.33-7.42 (m, 3H), 7.70-7.81 (m, 6H), 8.81 (d, *J* = 10.0 Hz, 1H), 9.34 (s, 1H).

Example 310

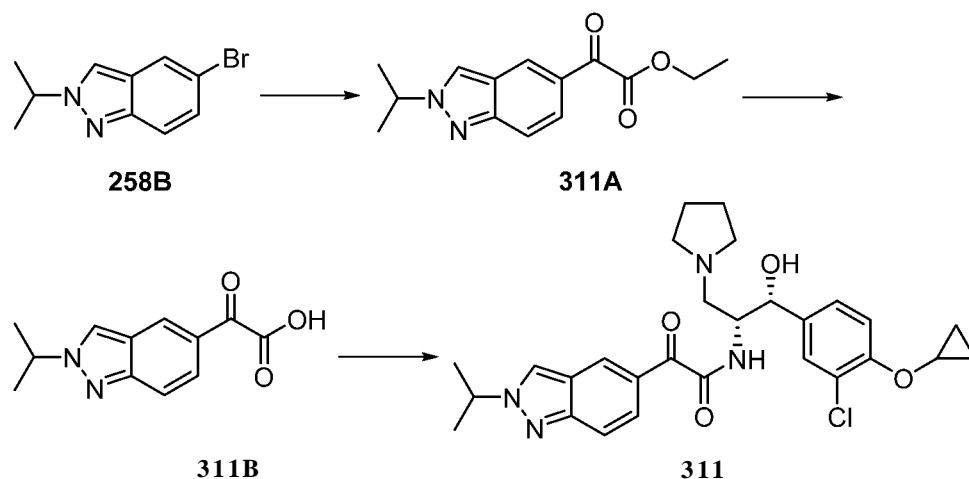


[0001106] A mixture of Compound **310A** (2.11 g, 10 mmol), 2-bromopropane (2.46 g, 20 mmol), and K_2CO_3 in DMF (40 mL) was stirred at 100 °C overnight. The mixture was diluted with ethyl acetate (200 mL), washed with water (200 mL x 4) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to afford Compound **310B** and Compound **310C**.

[0001107] A mixture of Compound **310C** (330 mg, 1.3 mmol), Compound **175B** (594 mg, 1.96 mmol), $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol), and K_2CO_3 (333 mg, 2.6 mmol) in dioxane (6 mL) and water (0.6 mL) was stirred at 80 °C for 2 h. The mixture was cooled down and filtered. The precipitate was dissolved in water and washed with ethyl acetate (50 mL). The aqueous layer was adjusted to pH 2 with concentrated HCl and extracted with ethyl acetate (200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to yield Compound **310D**.

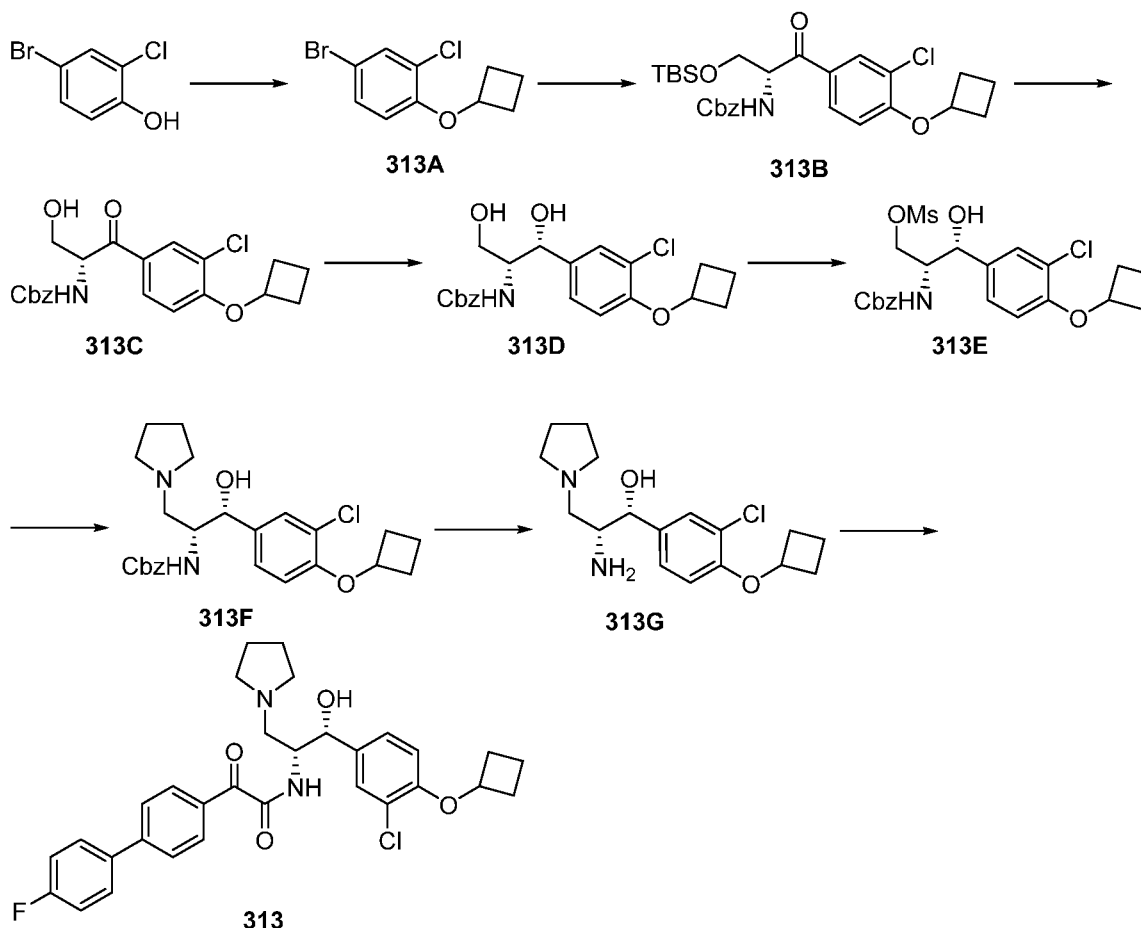
[0001108] A mixture of Compound **310D** (100 mg, 0.31 mmol), Intermediate **C** (96 mg, 0.31 mmol), and HATU (177 mg, 0.465 mmol) in DCM (2 mL) was stirred at room temperature overnight. The mixture was diluted with DCM (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **310**. LC-MS (ESI) m/z : 615 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.64-0.70 (m, 2H), 0.79-0.85 (m, 2H), 1.52 (d, $J = 6.4$ Hz, 6H), 1.86-1.92 (m, 2H), 2.01-2.06 (m, 2H), 2.71 (s, 3H), 3.09-3.24 (m, 2H), 3.46-3.59 (m, 4H), 3.93-3.98 (m, 1H), 4.56-4.60 (m, 1H), 4.86-4.91 (m, 2H), 6.04-6.08 (m, 1H), 7.35-7.46 (m, 3H), 7.60-7.62 (m, 1H), 7.67-7.69 (m, 1H), 7.74-7.76 (m, 2H), 7.81-7.84 (m, 2H), 8.13 (s, 1H), 8.81 (d, $J = 10.0$ Hz, 1H), 9.43 (brs, 1H).

Example 311



2.04 (m, 4H), 3.10-3.20 (m, 2H), 3.43-3.56 (m, 4H), 4.24-4.30 (m, 4H), 4.51-4.55 (m, 1H), 4.77 (d, $J = 2.4$ Hz, 1H), 4.86-4.96 (m, 1H), 6.76 (s, 1H), 6.82 (dd, $J = 11.6, 2.0$ Hz, 1H), 7.45 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H), 8.29 (m, 1H), 8.56 (s, 1H), 8.71 (d, $J = 9.6$ Hz, 1H), 9.29 (brs, 1H).

Example 313



[0001113] To a solution of 4-bromo-2-chlorophenol (5.0 g, 24 mmol) in 1-methyl-2-pyrrolidinone (70 mL) was added cesium carbonate (15.6 g, 48 mmol) and bromocyclobutane (9.7 g, 72 mmol). The mixture was stirred for 24 h while keeping inner temperature between 145 °C and 155 °C. After the reaction mixture was cooled to ambient temperature, the dark solution was diluted with water (100 mL) and extracted with a mixture of ethyl acetate in petroleum ether (15% v/v) (100 mL x 3). The combined organic phases were washed with brine (150 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **313A**.

[0001114] To a solution of Compound **313A** (15.6 g, 60 mmol) in dry THF (500 mL) maintained at -70 °C was added n-BuLi (60 mmol, 2.4 M in hexane, 25 mL) dropwise under

nitrogen atmosphere over a period of 20 minutes. After the reaction mixture was stirred at -70 °C for 40 minutes, Compound **A4** (7.9 g, 20 mmol) dissolved in dry THF (50 mL) was added slowly to the cold solution at a rate that maintained the internal temperature between -70 °C and -50 °C. After the addition was complete, the solution was left to stir for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (100 mL x 3). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude Compound **313B**. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **313B**.

[0001115] A solution of Compound **313B** (8.5 g, 16.4 mmol) in a mixture of tetrahydrofuran, water, and glacial acetic acid (250 mL, 1/1/3, v/v/v) was stirred at 25 °C for 72 h. The reaction mixture was concentrated under reduced pressure to remove excess solvent. The residue was poured into ice water (20 g) and adjusted to pH 7-8 with aqueous sodium hydroxide (1 N) and saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 30% to 50% v/v) to give Compound **313C**.

[0001116] To a solution of Compound **313C** (1.2 g, 2.97 mmol) in dry THF (700 mL) maintained at -78 °C was added diisobutylaluminum hydride (1.0 M in toluene, 11.9 mL) dropwise under nitrogen atmosphere over a period of 15 minutes. After the reaction mixture was stirred at -70 °C for 1 h, a solution of HCl (2 N, 20 mL) was added to the mixture slowly. The reaction mixture was extracted with ethyl acetate (30 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 50% to 150% v/v) to furnish Compound **313D**.

[0001117] To a solution of Compound **313D** (607 mg, 1.50 mmol) dissolved in THF (15 mL) was added triethylamine (454 mg, 4.50 mmol). The mixture was cooled to -30 °C, and then methanesulfonyl chloride (188 mg, 1.65 mmol) was added dropwise over a period of 15 minutes. After the addition was complete, the reaction mixture was stirred at -30 °C for 1.5 h, diluted with water (30 mL), and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate,

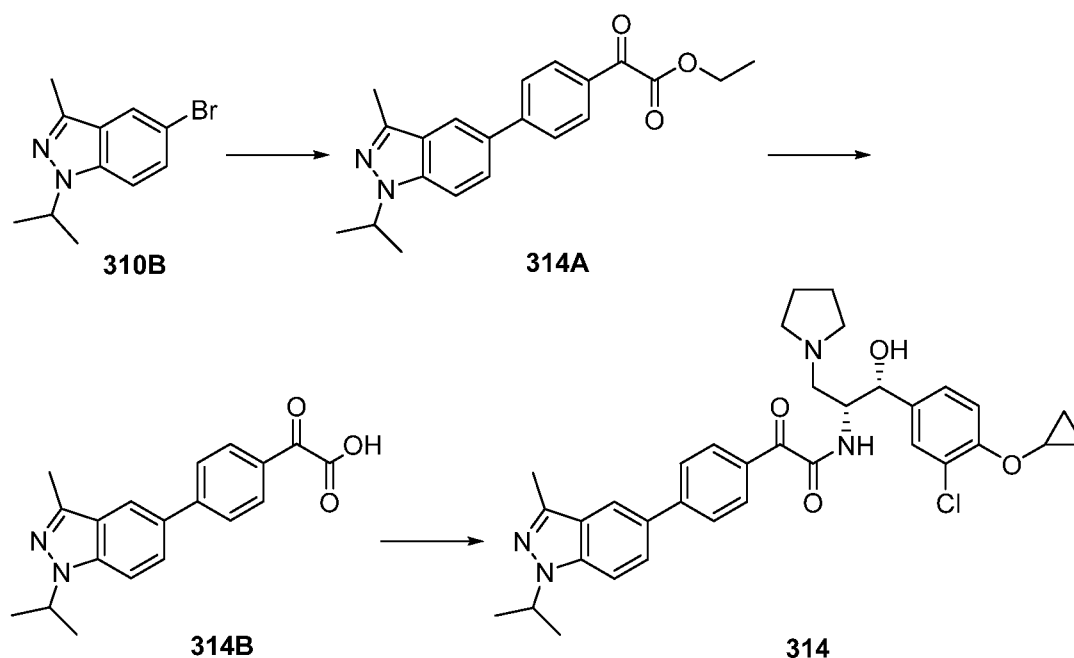
filtered, and concentrated to afford Compound **313E**, which was directly used for the next step without further purification.

[0001118] To a solution of Compound **313E** (690 mg, 1.42 mmol) in THF (30 mL) was added pyrrolidine (1.0 g, 14.2 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (15 mL), extracted with ethyl acetate (75 mL x 2), washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **313F**.

[0001119] To a solution of Compound **313F** (330 mg, 0.72 mmol) in ethanol (6 mL) and water (1 mL) was added LiOH·H₂O (121 mg, 2.88 mmol). The mixture was heated to 80 °C and stirred for 10 h. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (20 mL x 2). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **313G**, which was directly used for the next step without further purification.

[0001120] To a solution of Compound **313G** (75 mg, 0.23 mmol) in dichloromethane (5 mL) was added Intermediate C (56 mg, 0.23 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (131 mg, 0.345 mmol). The reaction mixture was stirred at 20 °C for 5 h. The resulting mixture was washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with prep-HPLC to yield Compound **313**. LC-MS (ESI) m/z: 551 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.60-1.63 (m, 1H), 1.74-1.77 (m, 1H), 1.89-1.91 (m, 2H), 2.00-2.08 (m, 4H), 2.41-2.45 (m, 2H), 3.15-3.22 (m, 2H), 3.45-3.48 (m, 3H), 3.55-3.56 (m, 2H), 4.55-4.56 (m, 1H), 4.71-4.75 (m, 1H), 4.87 (s, 1H), 6.03 (s, 1H), 6.95-6.98 (m, 1H), 7.26-7.29 (m, 1H), 7.36-7.40 (m, 2H), 7.44-7.45 (m, 1H), 7.73-7.76 (m, 3H), 7.80-7.84 (m, 2H), 8.79-8.81 (m, 1H), 9.47 (brs, 1H).

Example 314



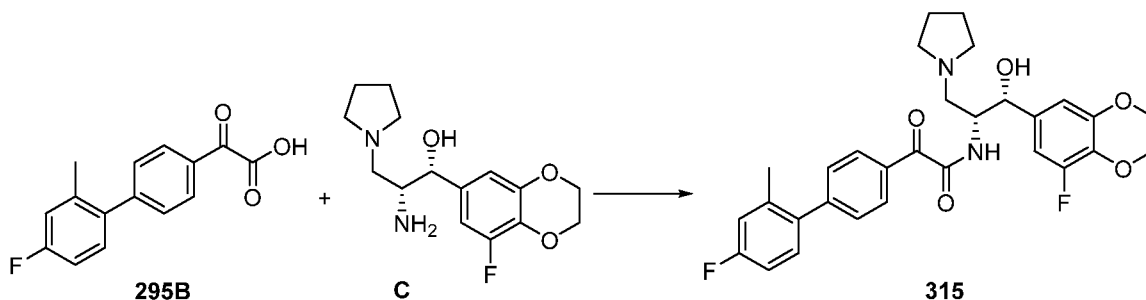
[0001121] A mixture of Compound **310B** (330 mg, 1.3 mmol), Compound **175B** (594 mg, 1.96 mmol), Pd(PPh₃)₂Cl₂ (91 mg, 0.13 mmol), and K₂CO₃ (333 mg, 2.6 mmol) in dioxane (6 mL) and water (0.6 mL) was stirred at 80 °C for 2 h. The mixture was cooled down, diluted with ethyl acetate (200 mL), washed with water (200 mL x 4) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to yield Compound **314A**.

[0001122] A mixture of Compound **314A** (240 mg, 0.68 mmol) and LiOH·H₂O (43 mg, 1.03 mmol) in THF (5 mL) and water (0.5 mL) was stirred at room temperature overnight. The mixture was diluted with water (50 mL), adjusted to pH 2 with concentrated HCl, and extracted with ethyl acetate (200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to yield Compound **314B**.

[0001123] A mixture of Compound **314B** (120 mg, 0.372 mmol), Intermediate **G** (115 mg, 0.372 mmol), and HATU (211 mg, 0.555 mmol) in dichloromethane (3 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **314**. LC-MS (ESI) m/z: 615 [M+H]⁺; ¹H-NMR (OMSO-*d*₆, 400 MHz): δ (ppm) 0.63-0.70 (m, 2H), 0.79-0.86 (m, 2H), 1.48 (d, *J* = 6.4 Hz, 6H), 1.87-1.93 (m, 2H), 2.02-2.07 (m, 2H), 2.57 (s, 3H), 3.13-3.24 (m, 2H), 3.49-3.60 (m, 4H), 3.93-3.98 (m, 1H), 4.52-4.61 (m, 1H), 4.89-5.00

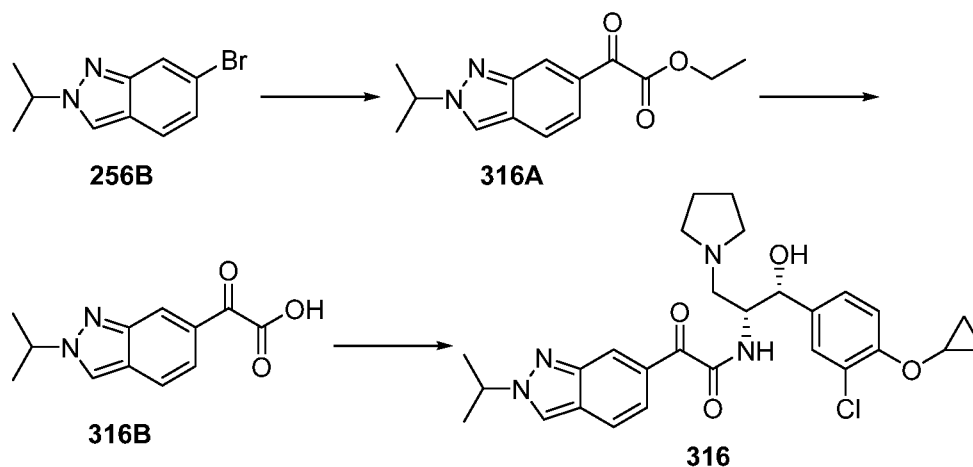
(m, 2H), 6.06-6.07 (m, 1H), 7.35-7.46 (m, 3H), 7.73-7.79 (m, 4H), 7.82-7.86 (m, 2H), 8.11 (d, $J = 7.2$ Hz, 1H), 8.81-8.83 (m, 1H), 9.43 (brs, 1H).

Example 315



[0001124] To a solution of Compound **295B** (78 mg, 0.3 mmol) in DMF (1.5 mL) and dichloromethane (4 mL) was added Intermediate C (100 mg, 0.33 mmol) and HATU (171 mg, 0.45 mmol). The reaction mixture was stirred at 25 °C for 3 hours. The mixture was purified with prep-HPLC to yield Compound **315**. LC-MS (m/z) 537 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.80-1.87 (m, 4H), 2.25 (s, 3H), 3.04-3.15 (m, 2H), 3.44-3.53 (m, 3H), 4.25-4.27 (m, 5H), 4.47-4.52 (m, 1H), 4.76 (s, 1H), 6.05 (s, 1H), 6.76-6.80 (m, 2H), 7.17-7.26 (m, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.88 (d, $J = 8.4$ Hz, 2H), 8.76 (d, $J = 10$ Hz, 1H), 9.30 (brs, 1H).

Example 316



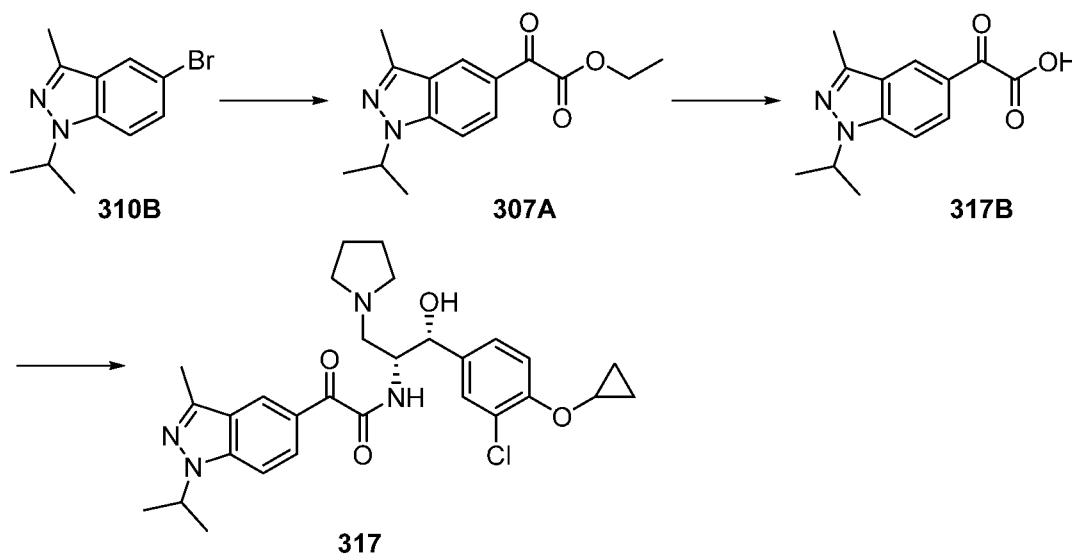
[0001125] To a solution of Compound **256B** (640 mg, 2.69 mmol) in dry THF (10 mL) was added dropwise n -BuLi solution (2.5 M in hexane, 1.1 mL, 2.72 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 30 min and diethyl oxalate (0.91 mL, 6.73 mmol) was added quickly to the above mixture. The mixture was stirred at -78 °C for 30 min, quenched with saturated aqueous ammonium chloride solution (10 mL), and extracted with ethyl acetate (80 mL x 2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified with flash column

chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to furnish Compound **316A**.

[0001126] To a solution of Compound **316A** (180 mg, 0.69 mmol) in methanol (3 mL) was added LiOH·H₂O (44 mg, 1.04 mmol) in water (3 mL) and the mixture was stirred at room temperature overnight. After completion of the reaction, the mixture was adjusted to pH 3 with aqueous HCl solution (3 N) and concentrated in *vacuo*. The residue was in lyophilization to afford Compound **316B**.

[0001127] A mixture of Compound **316B** (70 mg, 0.30 mmol), HATU (171 mg, 0.45 mmol), and Intermediate **G** (93 mg, 0.30 mmol) in DMF (5 mL) was stirred at 10 °C for 18 h. The mixture was directly purified with prep-HPLC to yield Compound **316**. LC-MS (ESI) *m/z*: 525 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.67-0.81 (m, 4H), 1.67 (d, *J* = 6.8 Hz, 6H), 2.04-2.22 (m, 4H), 3.22-3.28 (m, 2H), 3.55-3.61 (m, 1H), 3.68-3.89 (m, 4H), 4.66-4.69 (m, 1H), 4.87-4.90 (m, 1H), 4.95 (d, *J* = 3.2 Hz, 1H), 7.37 (s, 2H), 7.44-7.47 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 8.37 (s, 1H), 8.39 (s, 1H).

Example 317

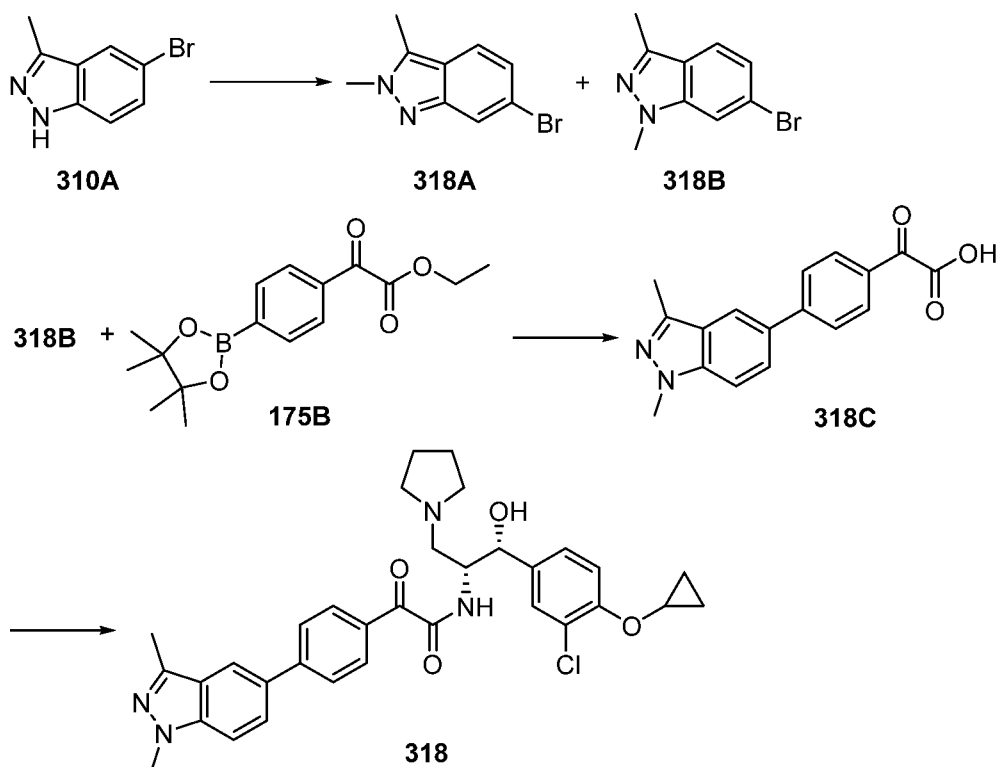


[0001128] To a solution of Compound **310B** (245 mg, 0.97 mmol) in dry THF (12 mL) maintained at -70 °C was added *n*-BuLi (2.5 M in hexane, 0.4 mL) dropwise under nitrogen atmosphere over a period of 5 minutes. After the reaction mixture was stirred at -70 °C for 40 minutes, diethyl oxalate (355 mg, 2.4 mmol) was added in one portion. The mixture was stirred at 60 °C for 2 hours. The solution was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **317A**.

[0001129] To a solution of Compound **317A** (260 mg, 0.96 mmol) in THF (9 mL) was added LiOH \cdot H $_2$ O (70 mg, 1.66 mmol) in water (3 mL) at -5 °C, the mixture was stirred at this temperature for 5 hours. The reaction mixture was treated with ice water (20 mL) and extracted with ethyl acetate (50 mL). The water layer was adjusted to pH 2 with diluted HCl and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resulting solid was washed with petroleum ether and filtered to afford the crude Compound **317B**.

[0001130] A mixture of Compound **317B** (75 mg, (0.3 mmol), HATU (174 mg, 0.46 mmol), and Intermediate **G** (113 mg, 0.36 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. The reaction mixture was treated with water (20 mL), extracted with dichloromethane 50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **317**. LC-MS (ESI) m/z : 539.2 [M+H] $^+$; 1 H-NMR (CD $_3$ OD, 400 MHz): δ (ppm) 0.45-0.75 (m, 4H), 1.53-1.56 (m, 6H), 2.04-2.23 (m, 4H), 2.55 (d, J = 4.0 Hz, 3H), 3.21-3.32 (m, 2H), 3.59-3.60 (m, 1H), 3.70-3.77 (m, 4H), 4.67 (d, J = 10.8 Hz, 1H), 4.90 (s, 1H), 4.98 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.76 (dd, J = 1.6 Hz, 9.2 Hz, 1H), 8.36 (d, J = 0.8 Hz, 1H).

Example 318

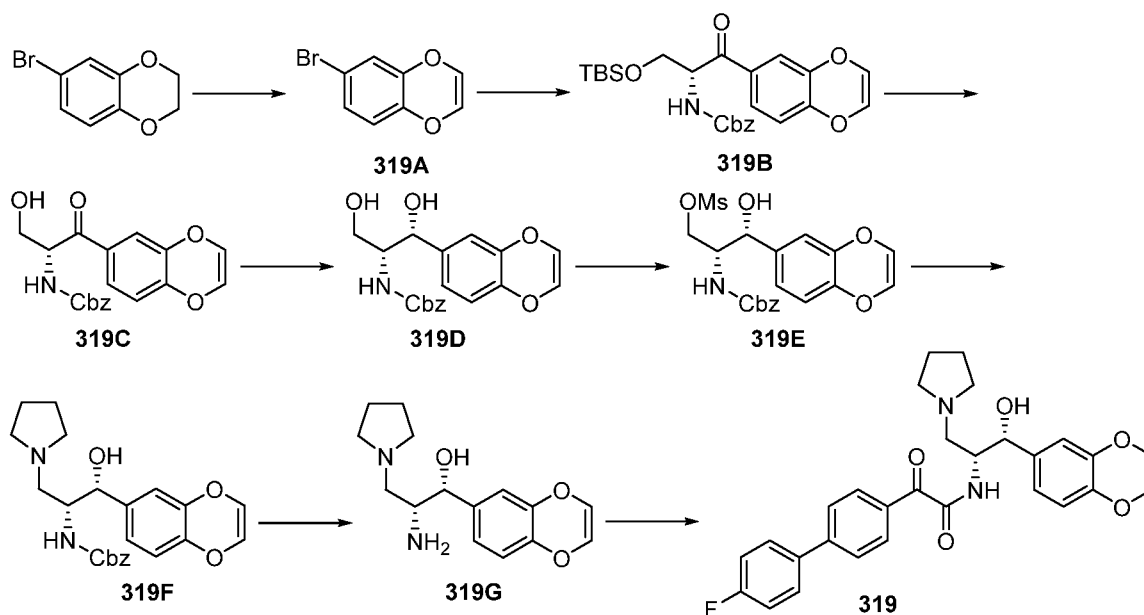


[0001131] To Compound **310A** (1.9 g, 9.05 mmol) in DMF (15 mL) was added sodium hydride (60% in mineral, 398 mg, 9.96 mmol) with ice bath cooling. The mixture was stirred for 30 min at room temperature and iodomethane (0.94 mL, 27.15 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, quenched with ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 90% v/v) to give Compound **318A** and Compound **318B**.

[0001132] A mixture of Compound **318B** (225 mg, 1 mmol), Compound **175B** (477 mg, 1.57 mmol), Pd(PPh₃)₂Cl₂ (70 mg, 0.1 mmol), and K₂CO₃ (256 mg, 2 mmol) in dioxane (5 mL) and water (0.5 mL) was stirred at 80 °C for 2 h. The mixture was cooled down and filtered. The precipitate dissolved with water (10 mL) and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to yield Compound **318C**.

[0001133] A mixture of Compound **318C** (70 mg, 0.238 mmol), Intermediate **G** (74 mg, 0.238 mmol), and HATU (136 mg, 0.357 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **318**. LC-MS (ESI) m/z: 587 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.66-0.70 (m, 2H), 0.80-0.85 (m, 2H), 1.87-1.92 (m, 2H), 2.02-2.07 (m, 2H), 2.55 (s, 3H), 3.11-3.24 (m, 2H), 3.49-3.58 (m, 4H), 3.93-3.98 (m, 1H), 4.00 (s, 3H), 4.55-4.62 (m, 1H), 4.89-4.90 (m, 1H), 6.06-6.07 (m, 1H), 7.35-7.46 (m, 3H), 7.70-7.86 (m, 6H), 8.13 (s, 1H), 8.82 (d, *J* = 9.6 Hz, 1H), 9.44 (brs, 1H).

Example 319



[0001134] A mixture of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxane (1.07 g, 5 mmol), NBS (2.1 g, 12 mmol), and AIBN (20 mg) in CCl_4 (60 mL) was refluxed under nitrogen for 18 h. The mixture was cooled down to room temperature and filtered. The filtrate was washed with water (50 mL x 2) and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in acetone (50 mL) and refluxed under nitrogen for 3 h with NaI (3.75 g, 25 mmol). The mixture was cooled down to room temperature and evaporated. The residue was diluted with water (100 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with aqueous $\text{Na}_2\text{S}_2\text{C}_3$ solution (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **319A**.

[0001135] To a solution of Compound **A4** (5.7 g, 26.8 mmol) in THF (120 mL) was added n-BuLi (2.5 M in hexane, 14.4 mL, 36 mmol) under nitrogen at -78°C . The mixture was stirred at -78°C for 0.5 h and a solution of Compound **319A** (3.6 g, 9 mmol) in THF (30 mL) was added. The mixture was stirred at -78°C for 5 min, quenched with saturated aqueous ammonium chloride solution (100 mL), and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 9% v/v) to furnish Compound **319B**.

[0001136] A mixture of Compound **319B** (100 mg) in AcOH (5 mL), THF (2 mL), and water (2 mL) was stirred at 40°C overnight. The mixture was cooled down to room temperature, diluted with brine (20 mL), and extracted with ethyl acetate (20 mL x 3). The

organic layer was adjusted to pH 8 with saturated aqueous sodium bicarbonate solution (30 mL) and separated. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **319C**.

[0001137] To a solution of Compound **319C** (1.5 g, 4.2 mmol) in THF (30 mL) was added dropwise DIBAL-H (1.5 N in toluene, 12 mL, 17 mmol) under nitrogen at -80 °C. The mixture was stirred under nitrogen at -70 °C for 0.5 h, quenched with aqueous hydrogen chloride solution (1 N, 50 mL), and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 55% v/v) to give Compound **319D**.

[0001138] To a solution of Compound **319D** (1.48 g, 4 mmol) and triethylamine (1.2 g, 12 mmol) in THF (30 mL) was added dropwise MsCl (0.52 g, 4.6 mmol) under nitrogen at -20 °C. The mixture was stirred under nitrogen at -15 °C for 1 h, quenched with water (100 mL), and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **319E**.

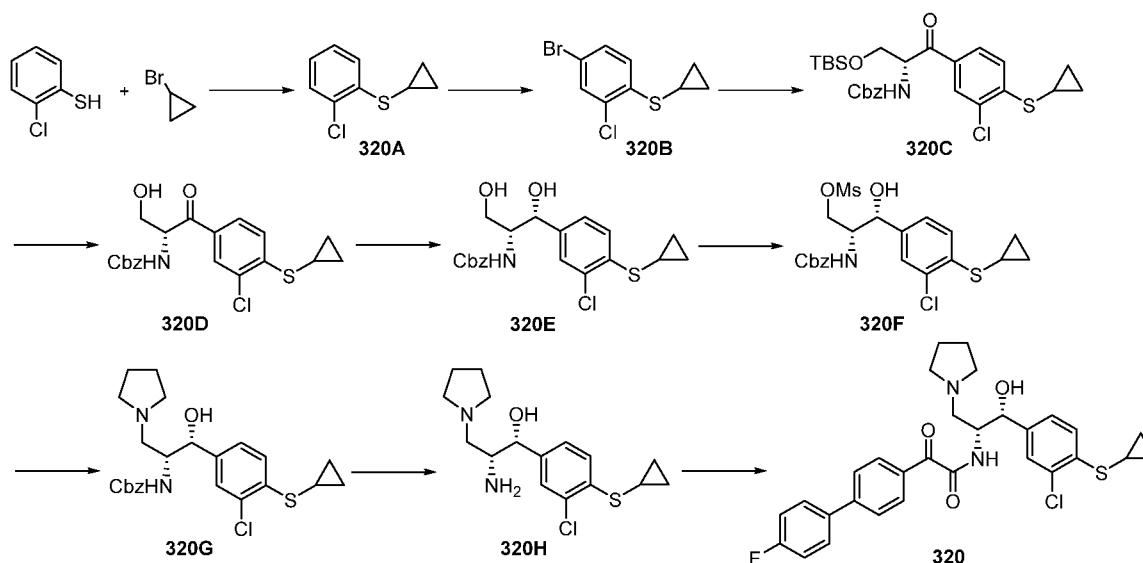
[0001139] To a solution of Compound **319E** (1.74 g, 4 mmol) in THF (50 mL) was added pyrrolidine (2.8 g, 40 mmol). The mixture was stirred at 50 °C overnight. The mixture was cooled down to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to afford Compound **319F**.

[0001140] To a solution of Compound **319F** (550 mg, 1.34 mmol) in ethanol (20 mL) was added a solution of LiOH·H₂O (225 mg, 5.37 mmol) in water (5 mL). The mixture was stirred at 100 °C overnight. After removal of ethanol, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **319G**.

[0001141] A mixture of Compound **319G** (100 mg, 0.36 mmol), Compound **133D** (88 mg, 0.36 mmol), and HATU (275 mg, 0.72 mmol) in DMF (3 mL) was stirred at room temperature overnight. The mixture was directly purified with prep-HPLC to yield Compound **319**. LC-MS (ESI) m/z: 503 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.86-1.93 (m, 2H), 2.02-2.03 (m, 2H), 3.10-3.22 (m, 2H), 3.44-3.47 (m, 2H), 3.53-3.56 (m, 2H), 4.47-4.54 (m, 1H), 4.76 (s, 1H), 5.99 (s, 1H), 6.19 (d, *J* = 4.0 Hz, 1H), 6.22 (d, *J* = 3.6

Hz, 1H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.74 (d, $J = 2.0$ Hz, 1H), 6.89-6.92 (m, 1H), 7.35-7.40 (m, 2H), 7.82-7.90 (m, 6H), 8.79 (d, $J = 10.0$ Hz, 1H), 9.34 (s, 1H).

Example 320



[0001143] To a solution of 2-chlorobenzenethiol (7.2 g, 50 mmol) in DMSO (20 mL) was added potassium *tert*-butoxide (6.7 g, 60 mmol) in portions under nitrogen at 5 °C. The reaction mixture was stirred at 25 °C for 15 min. To the above solution was added bromocyclopropane (12 g, 100 mmol) in DMSO (10 mL) dropwise. The reaction mixture was stirred under nitrogen at 80 °C. After the reaction mixture was cooled to ambient temperature, the dark solution was diluted with water (400 mL) and extracted with a mixture of ethyl acetate (60 mL x 3). The combined organic phases were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **320A**.

[0001144] To a solution of Compound **320A** (36 g, 195.6 mmol) in dry dichloromethane (600 mL) was added Br₂ (37.6 g, 235 mmol) at 5 °C dropwise. The reaction mixture was stirred at 25 °C for 22 hours. It was washed with water (200 mL), saturated sodium thiosulfate (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **320B**.

[0001145] To a solution of Compound **320B** (23.6 g, 90 mmol) in dry THF (400 mL) maintained at -70 °C was added *n*-BuLi (2.5 *Min* hexane, 36.4 mL) dropwise under nitrogen atmosphere over a period of 20 minutes. After the reaction mixture was stirred at -70 °C for 40 minutes, Compound **A4** (11.9 g, 30 mmol) dissolved in dry THF (20 mL) was added

slowly to the cold solution at a rate that maintained the internal temperature between $-70\text{ }^{\circ}\text{C}$ and $-50\text{ }^{\circ}\text{C}$. After the addition was complete, the solution was left to stir for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (200 mL) and extracted with ethyl acetate (200 mL x 3). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude Compound **320C**. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish the pure Compound **320C**.

[0001146] A solution of Compound **320C** (7.0 g, 13.5 mmol) in a mixture of tetrahydrofuran, water, and glacial acetic acid (145 mL, 1/1/3, v/v/v) was stirred at $25\text{ }^{\circ}\text{C}$ for 30 h. The reaction mixture was concentrated under reduced pressure to remove excess solvent. The residue was poured into ice water (20 g) and adjusted to pH 7-8 with aqueous sodium hydroxide (1 N) and saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 30% to 50% v/v) to give Compound **320D**.

[0001147] To a solution of Compound **320D** (2.4 g, 5.9 mmol) in dry THF (50 mL) maintained at $-78\text{ }^{\circ}\text{C}$ was added diisobutylaluminum hydride (1.5 M in toluene, 16 mL) dropwise under nitrogen atmosphere over a period of 15 minutes. After the reaction mixture was stirred at $-70\text{ }^{\circ}\text{C}$ for 1 h, a solution of HCl (2 N) was added to the mixture slowly. The reaction mixture was extracted with ethyl acetate (20 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 50% to 67% v/v) to furnish Compound **320E**.

[0001148] To a solution of Compound **320E** (1.69 g, 4.15 mmol) dissolved in THF (30 mL) was added triethylamine (1.26 g, 12.5 mmol). The mixture was cooled to $-30\text{ }^{\circ}\text{C}$, and then methanesulfonyl chloride (526 mg, 4.57 mmol) was added dropwise over a period of 15 minutes. After the addition was complete, the reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 1.5 h, diluted with water (50 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **320F**, which was directly used for the next step without further purification.

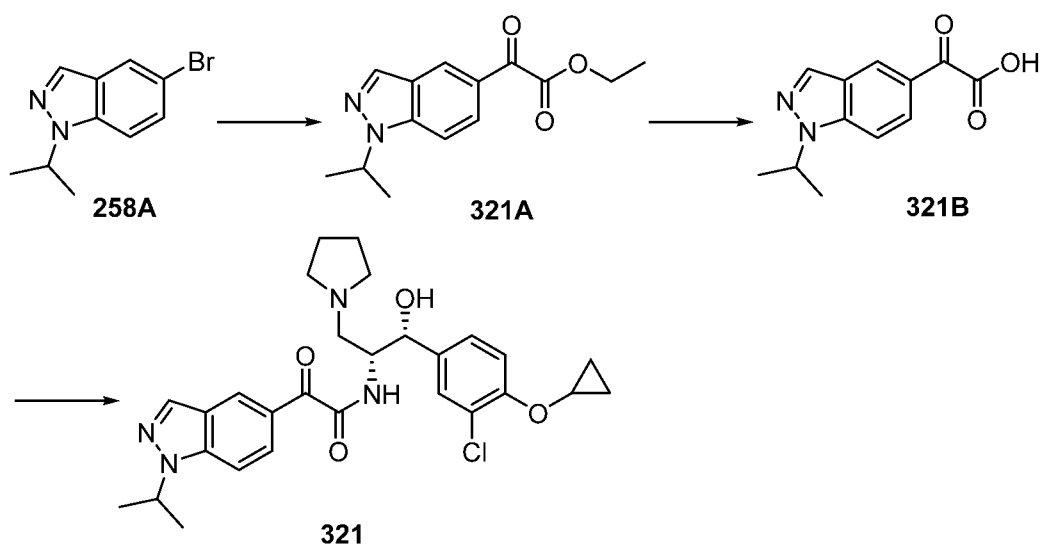
[0001149] To a solution of Compound **320F** (910 mg, 1.88 mmol) in THF (60 mL) was added pyrrolidine (1.33 g, 18.8 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (30 mL), extracted with ethyl acetate (60 mL x 2), washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 7% v/v) to give Compound **320G**.

[0001150] To a solution of Compound **320G** (548 mg, 1.19 mmol) in ethanol (14 mL) and water (2 mL) was added LiOH·H₂O (200 mg, 4.77 mmol). The mixture was heated to 80 °C and stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **320H**, which was directly used for the next step without further purification.

[0001151]

[0001152] To a solution of Compound **320H** (100 mg, 0.3 mmol) in dichloromethane (10 mL) was added Compound **133D** (56 mg, 0.23 mmol) and HATU (131 mg, 0.35 mmol). The reaction mixture was stirred at 25 °C for 3 hours. The mixture was purified with prep-HPLC to yield Compound **320**. LC-MS (m/z) 553 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.57 (s, 2H), 1.15 (d, *J* = 7.6 Hz, 2H), 1.88-1.90 (m, 2H), 2.04 (s, 2H), 2.24-2.26 (m, 1H), 3.12-3.23 (m, 2H), 3.42-3.56 (m, 4H), 4.59-4.61 (m, 1H), 4.92 (s, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 7.36-7.46 (m, 4H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.71-7.81 (m, 6H), 8.85 (d, *J* = 10.0 Hz, 1H), 9.36 (s, 1H).

Example 321



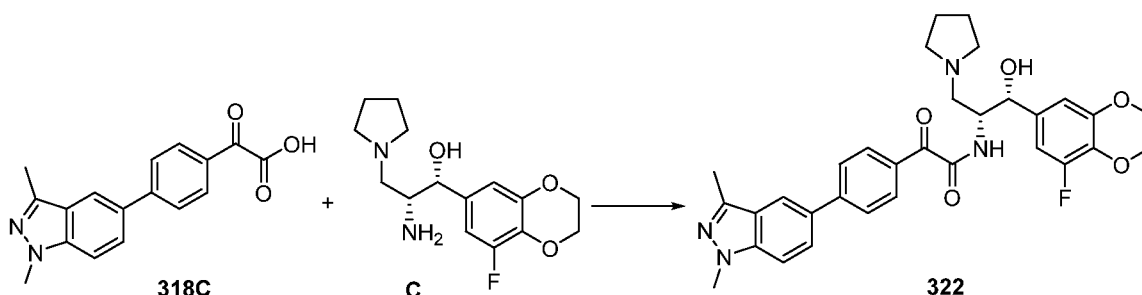
[0001153] To a solution of Compound **258A** (960 mg, 4.0 mmol) in THF (30 mL) was added dropwise *n*-BuLi (1.6 mL, 2.5 *M* in hexane, 4.0 mmol) under nitrogen atmosphere at -60 °C. The reaction mixture was stirred at the same temperature for 30 minutes. Compound diethyl oxalate (1.75 g, 12.0 mmol) was added. The resulting mixture was stirred at -60 °C for an additional 30 minutes. The reaction mixture was quenched with saturated ammonium chloride solution (40 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, filtered, evaporated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **321A**.

[0001154] To a solution of Compound **321A** (160 mg, 0.61 mmol) in MeOH (5 mL) was added LiOH·H₂O (51 mg, 1.22 mmol) and water (1.0 mL). The reaction mixture was stirred at 15 °C for 4 h. The reaction mixture was neutralized with HCl (1 *N*). The resulting mixture was evaporated. The residue was dissolved in water (5 mL). The mixture was extracted with ethyl acetate (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and evaporated to give Compound **321B**.

[0001155] To a solution of Compound **321B** (70 mg, 0.30 mmol) in DMF (4 mL) was added Intermediate **G** (93 mg, 0.30 mmol) and HATU (81 mg, 0.45 mmol). The reaction mixture was stirred at 20 °C for 5 h. The mixture was purified with prep-HPLC to yield Compound **321**. LC-MS (*m/z*) 525 [M+H]⁺; ¹H-NMR (acetone-*d*₆, 400 MHz): δ (ppm) 0.57-0.59 (m, 1H), 0.67-0.68 (m, 1H), 0.76-0.81 (m, 2H), 1.57 (d, *J* = 6.8 Hz, 6H), 2.09-2.11 (m, 2H), 2.27 (s, 2H), 3.47-3.51 (m, 2H), 3.82-3.86 (m, 2H), 3.99-4.02 (m, 3H), 4.91-4.92 (m,

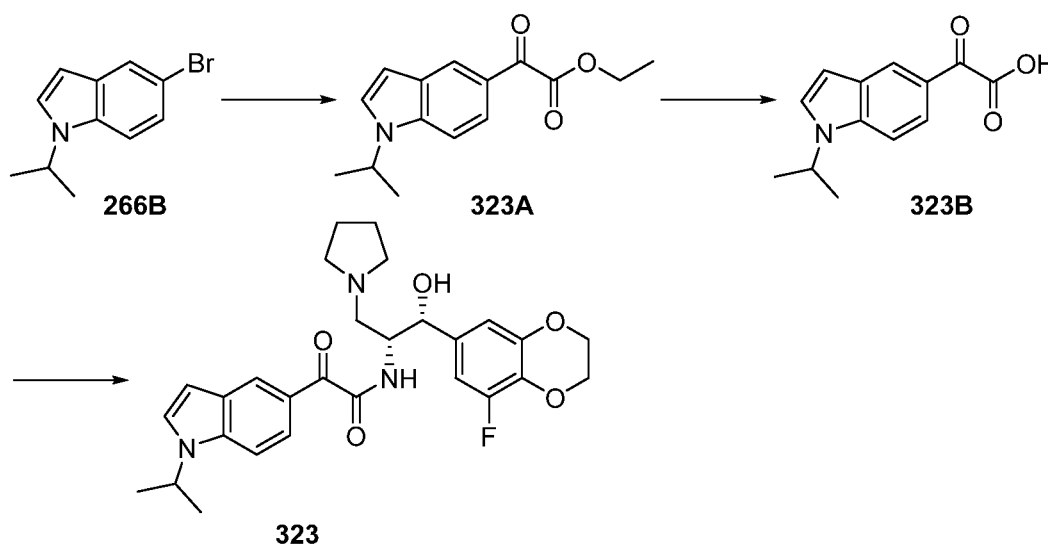
1H), 5.04-5.07 (m, 1H), 5.19 (s, 1H), 1.27 (m, 1H), 7.41-7.43 (m, 1H), 7.50 (s, 1H), 7.69-7.71 (m, 1H), 7.93-7.96 (m, 1H), 8.12-8.14 (m, 1H), 8.21 (s, 1H), 8.55 (s, 1H), 9.01 (brs, 1H).

Example 322



[0001157] A mixture of Compound **318C** (80 mg, 0.272 mmol), Intermediate **C** (81 mg, 0.272 mmol), and HATU (155 mg, 0.408 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **322**. LC-MS (ESI) m/z : 573 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.84-1.93 (m, 2H), 1.99-2.08 (m, 2H), 2.55 (s, 3H), 3.11-3.21 (m, 2H), 3.43-3.56 (m, 4H), 4.00 (s, 3H), 4.25-4.29 (m, 4H), 4.49-4.56 (m, 1H), 4.78-4.80 (m, 1H), 6.05-6.06 (m, 1H), 6.77 (s, 1H), 6.83 (d, $J = 11.2$ Hz, 1H), 7.69-7.72 (m, 1H), 7.79-7.82 (m, 1H), 8.02-8.04 (m, 4H), 8.17 (s, 1H), 8.74 (d, $J = 10.0$ Hz, 1H), 9.40 (brs, 1H).

Example 323



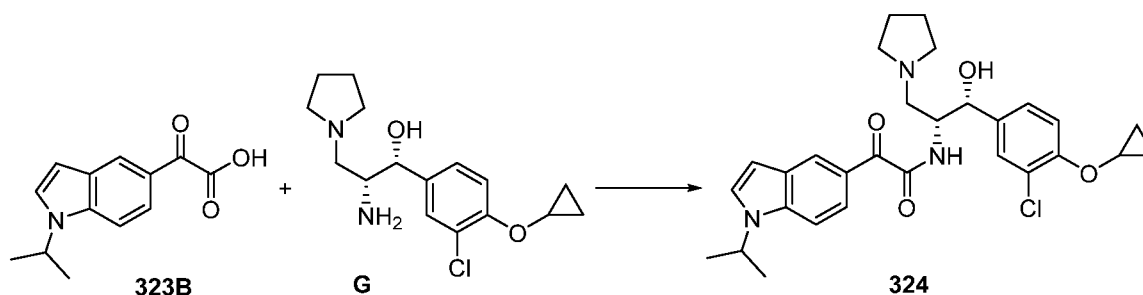
[0001159] To a solution of Compound **266B** (1.6 g, 6.7 mmol) in THF (70 mL) was added *n*-BuLi (2.5 M in hexane, 3.2 mL, 8 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 0.5 h and diethyl oxalate (1.96 g, 13.4 mmol) was added at this temperature. The mixture was stirred at -78 °C for 0.5 h, quenched with saturated aqueous

ammonium chloride solution (100 mL), and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **323A**.

[0001160] To a solution of Compound **323A** (259 mg, 1 mmol) in THF (10 mL) was added a solution of LiOH·H₂O (84 mg, 2 mmol) in water (3 mL). The mixture was stirred at room temperature overnight. After removal of THF, the mixture was acidified to pH 1 with aqueous HCl solution (1 N) and extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous sodium sulfate and used directly for the next step as a dichloromethane solution.

[0001161] A mixture of Compound **323B** in dichloromethane solution (115 mg, 0.5 mmol), Intermediate **C** (150 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in dichloromethane (10 mL) and DMF (3 mL) was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to yield Compound **323**. LC-MS (ESI) m/z: 510 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.47 (d, *J* = 6.8 Hz, 6H), 1.87-1.90 (m, 2H), 2.01-2.03 (m, 2H), 3.09-3.21 (m, 2H), 3.37-3.43 (m, 2H), 3.53-3.59 (m, 2H), 4.22-4.32 (m, 4H), 4.52-4.56 (m, 1H), 4.78-4.79 (m, 1H), 4.82-4.87 (m, 1H), 6.00 (s, 1H), 6.65 (d, *J* = 2.8 Hz, 1H), 6.77 (s, 1H), 6.82 (d, *J* = 13.2 Hz, 1H), 7.60-7.69 (m, 3H), 8.10 (s, 1H), 8.67 (d, *J* = 9.6 Hz, 1H), 9.34 (s, 1H).

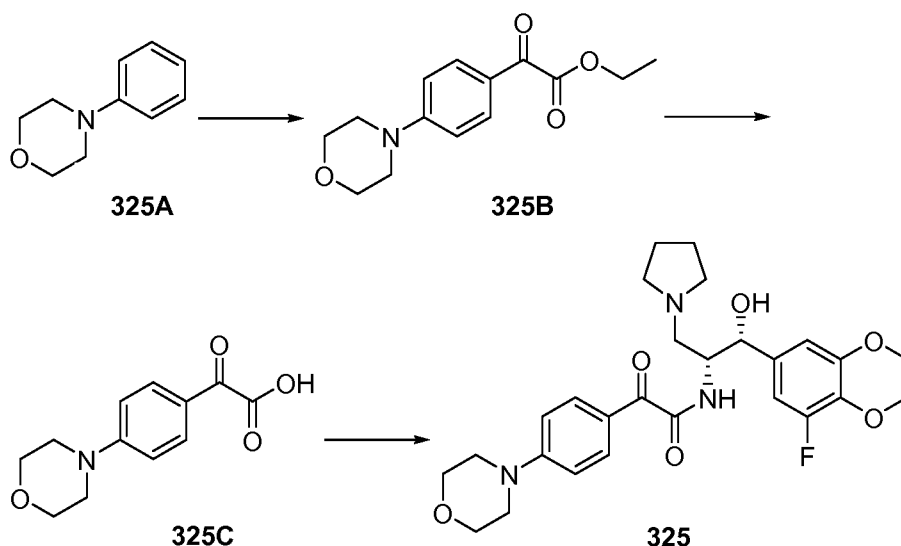
Example 324



[0001162] A mixture of Compound **323B** in dichloromethane solution (115 mg, 0.5 mmol), Intermediate **G** (155 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in dichloromethane (10 mL) and DMF (3 mL) was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to yield Compound **324**. LC-MS (ESI) m/z: 524 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.59-0.69 (m, 2H), 0.80-0.81 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.87-1.89 (m, 2H), 2.03 (s, 2H), 3.12-3.20 (m, 2H), 3.43-3.57 (m, 4H), 3.89-3.90 (m, 1H), 4.57-4.62 (m, 1H), 4.80-4.83 (m, 1H), 4.88 (s, 1H), 6.01 (d, *J* = 4.0 Hz, 1H), 6.62 (d, *J* = 3.2 Hz, 1H), 7.34-7.40 (m, 2H),

7.45 (s, 1H), 7.58 (s, 2H), 7.68 (d, $J = 3.6$ Hz, 1H), 8.04 (s, 1H), 8.68 (d, $J = 9.2$ Hz, 1H), 9.38 (s, 1H).

Example 325

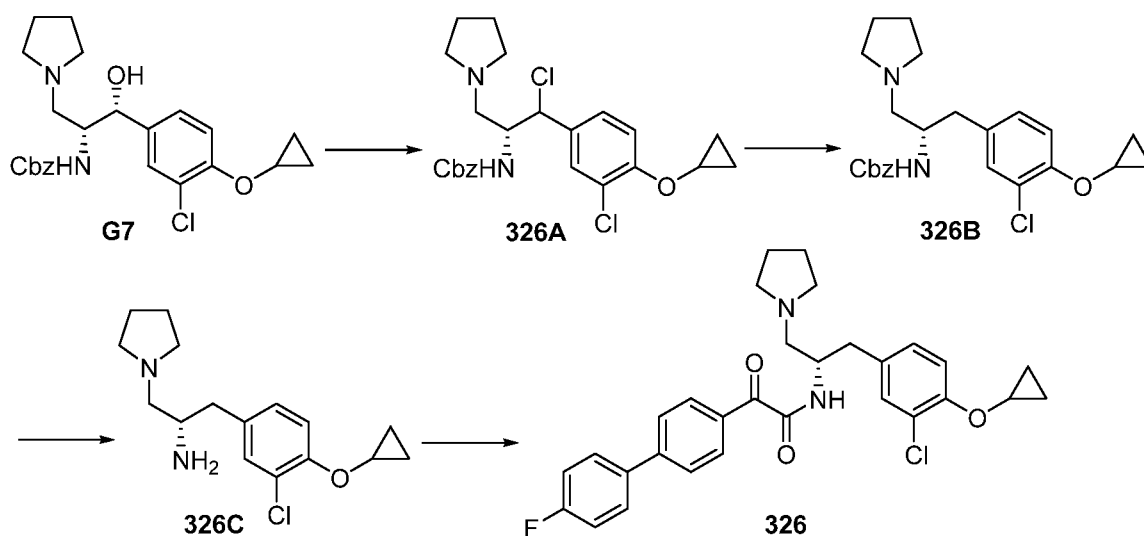


[0001163] To a solution of Compound **325A** (1.63 g, 10.0 mmol) and ethyl 2-chloro-2-oxoacetate (1.49 g, 11.0 mmol) in dichloromethane (50 mL) was added dropwise titanium chloride solution (1 M in dichloromethane, 20 mL, 20.0 mmol) at -10° C. The mixture was stirred for 4 hours while keeping the temperature at -10° C. The mixture was poured into ice water, and then extracted with diethyl ether (50 mL x 3). The resulting product was concentrated under reduced pressure and purified with silica gel column chromatography (ethyl acetate in petroleum ether, 30% v/v) to give Compound **325B**.

[0001164] To a solution of Compound **325B** (263 mg, 1.00 mmol) in MeOH (5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (63 mg, 1.50 mmol) and water (1.0 mL). The reaction mixture was stirred at 15° C for 4 h. The reaction mixture was neutralized with HCl (1 N). The resulting mixture was evaporated. The residue was dissolved in water (5 mL). The mixture was extracted with ethyl acetate (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and evaporated to give Compound **325C**.

[0001165] To a solution of Compound **325C** (71 mg, 0.31 mmol) in DMF (4 mL) was added Intermediate **C** (92 mg, 0.31 mmol) and HATU (81 mg, 0.45 mmol). The reaction mixture was stirred at 20° C for 5 h. The mixture was purified with prep-HPLC to yield Compound **325**. LC-MS (m/z) 514 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (acetone- d_6 , 400 MHz): δ (ppm) 2.06-2.12 (m, 2H), 2.26-2.28 (m, 2H), 3.55-3.64 (m, 5H), 3.82-3.85 (m, 1H), 3.93-4.10 (m, 7H), 4.23-4.31 (m, 5H), 4.80-4.87 (m, 1H), 5.05-5.06 (m, 1H), 6.78-6.84 (m, 2H), 7.33-7.34 (m, 2H), 8.04-8.06 (m, 1H), 8.11-8.14 (m, 2H), 8.56 (brs, 1H).

Example 326



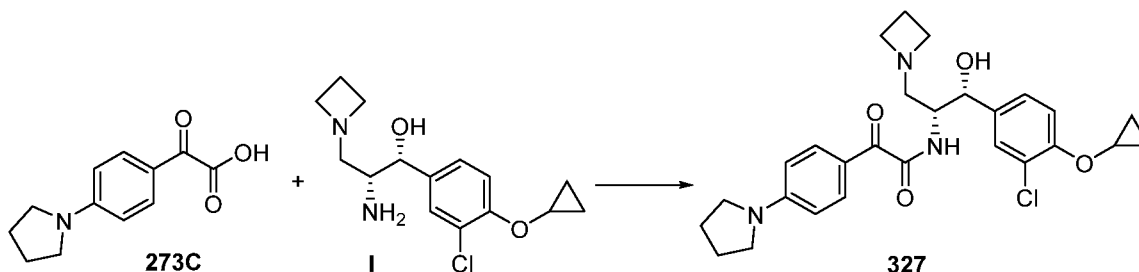
[0001166] To a solution of Compound **G7** (3.8 g, 8.6 mmol) in dichloromethane (20 mL) was added dropwise SOCl_2 (3.05 g, 25.7 mmol) under nitrogen at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The mixture was adjusted to pH 8 with sat. sodium bicarbonate solution, extracted with dichloromethane (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to furnish Compound **326A**.

[0001167] To a solution of Compound **326A** (600 mg, 1.30 mmol) in methanol (20 mL) was added K_2CO_3 (89 mg, 0.65 mmol) and Pt/C (60 mg). The resulting mixture was stirred under H_2 at 25 °C for 12 h. The mixture was filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to furnish Compound **326B**.

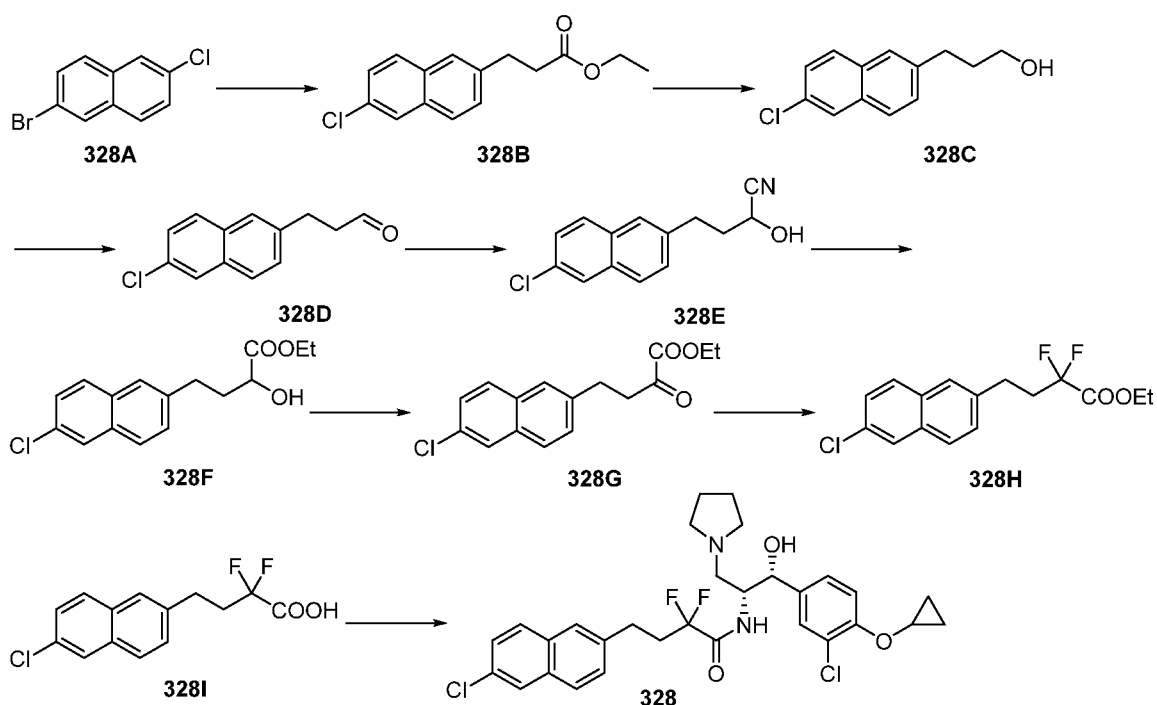
[0001168] To a solution of Compound **326B** (288 mg, 0.67 mmol) in dichloromethane (15 mL) was added PdCl_2 (30 mg). The resulting mixture was stirred under H_2 at room temperature for 12 h. The mixture was filtered. The filtrate was treated with water (20 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (20 mL). The mixture was stirred at room temperature for 10 min, extracted with dichloromethane (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford Compound **326C**.

[0001169] A mixture of Compound **326C** (90 mg, 0.3 mmol), Intermediate **C** (75 mg, 0.3 mmol), and HATU (170 mg, 0.47 mmol) in dichloromethane (20 mL) was stirred at room temperature for 4 h. The mixture was treated with water (50 mL), extracted with dichloromethane (20 mL x 2), washed with water (20 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound

326. LC-MS (ESI) m/z : 521 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.73-0.75 (m, 4H), 2.07 (s, 4H), 2.85-3.05 (m, 4H), 3.19-3.24 (m, 1H), 3.66-3.77 (m, 3H), 3.91 (s, 1H), 4.67 (s, 1H), 7.09-7.11 (m, 3H), 7.14-7.16 (m, 1H), 7.18-7.24 (m, 1H), 7.50-7.54 (m, 4H), 7.85 (d, $J = 9.2$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 8.94 (s, 1H).

Example 327

[0001170] A mixture of Compound **273C** (90 mg, 0.41 mmol), HATU (234 mg, 0.62 mmol), and Intermediate **I** (121 mg, 0.41 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **327**. LC-MS (ESI) m/z : 498 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.67-0.68 (m, 2H), 0.82-0.84 (m, 2H), 1.97-2.00 (m, 4H), 2.25-2.30 (m, 1H), 2.38-2.46 (m, 1H), 3.47-4.19 (m, 11H), 4.35-4.40 (m, 1H), 4.79 (s, 1H), 5.96 (s, 1H), 6.49 (d, $J = 8.8$ Hz, 2H), 7.28-7.31 (m, 1H), 7.38-7.40 (m, 2H), 7.56 (d, $J = 8.8$ Hz, 2H), 8.47 (d, $J = 9.6$ Hz, 1H), 9.62 (s, 1H).

Example 328

[0001171] To a mixture of Compound **328A** (2.4 g, 10 mmol), 3,3-diethoxyprop-1-ene (4 g, 30 mmol), and TBAC (2.7 g, 10 mmol) in DMF (80 mL) was added Pd(OAc)₂ (224 mg, 1 mmol). The reaction mixture was stirred under nitrogen at 90 °C overnight. After the completion of reaction, the resulting mixture was cooled down to room temperature, washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **328B**.

[0001172] To a solution of Compound **328B** (2.64 g, 10 mmol) in anhydrous THF (30 mL) was added lithium aluminum hydride (458 mg, 12 mmol) in portions under nitrogen at 0 °C. The mixture was stirred at room temperature for 0.5 h and quenched with addition of water (2 mL). The resulting precipitation was filtered. The filtrate was dried over anhydrous sodium sulfate and evaporated to dryness in *vacuo* to afford Compound **328C**.

[0001173] To a solution of Compound **328C** (2.2 g, 0.01 mol) in dichloromethane (40 mL) was Dess-Martin periodinane (845 mg, 0.02 mol). After 4 hours, the reaction mixture was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to yield Compound **328D**.

[0001174] To a suspension of Compound **328D** (218 mg, 1 mmol) and NaCN (74 mg, 1.5 mmol) in methanol (5 mL) was carefully added dropwise AcOH (1 mL). The reaction mixture was stirred at room temperature overnight. After removal of methanol, the residue was dissolved in dichloromethane (40 mL), washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **328E**.

[0001175] A solution of Compound **328E** (2.5 g, 10 mmol) in methanol (50 mL) was stirred under HCl gas at room temperature for 6 h. The reaction mixture was quenched with water (30 mL) and stirred at room temperature for 1 h. After removal of solvent, the residue was dissolved in ethyl acetate (200 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **328F**.

[0001176] A solution of Compound **328F** (2.9 g, 10 mmol) and Dess-Martin periodinane (6.3 g, 15 mmol) in dichloromethane (50 mL) was stirred at room temperature for 2 h. After the completion of reaction, the reaction mixture was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The crude product was purified

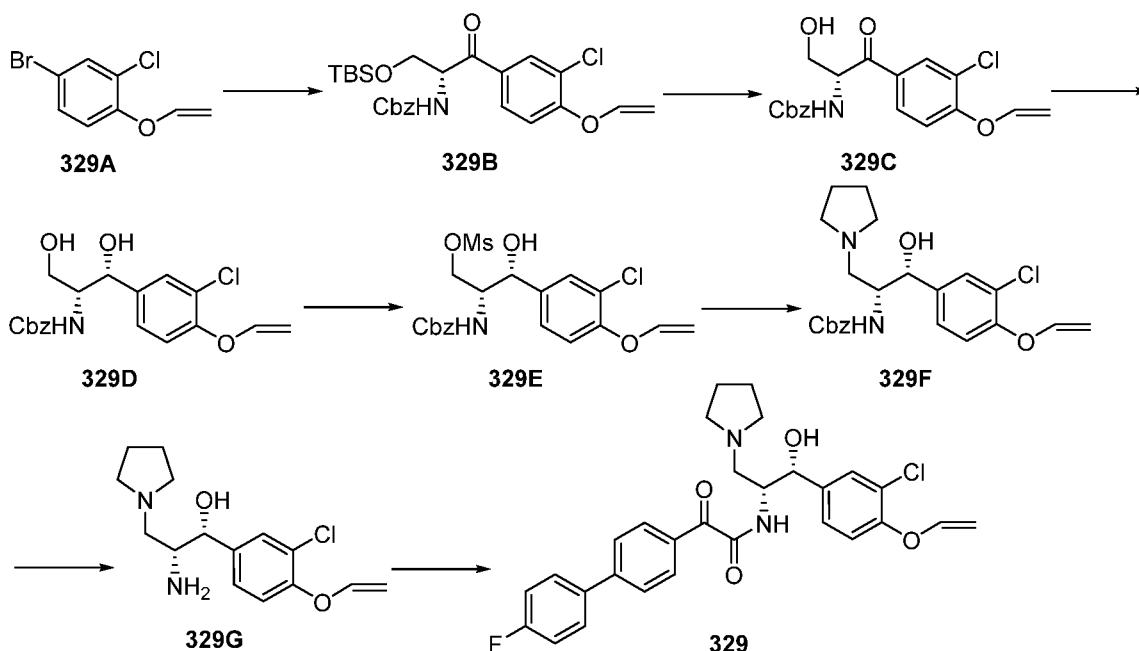
with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 20% to 30% v/v) to afford Compound **328G**.

[0001177] To a solution of Compound **328G** (2.9 g, 10 mmol) in dichloromethane (50 mL) was added DAST (3 mL, 41.3 mmol) at room temperature. The mixture was stirred at room temperature overnight. After the completion of the reaction, the reaction mixture was washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford a residue. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 20% to 40% v/v) to give Compound **328H**.

[0001178] A mixture of Compound **328H** (3.1 g, 10 mmol) and LiOH·H₂O (1.2 g, 28.4 mmol) in ethanol/water (40 mL/4 mL) was stirred at room temperature overnight. After the completion of the reaction, the reaction mixture was adjusted to pH 6 with aqueous HCl solution (2 N, 1.5 mL). After removal of solvent, the residue was dissolved in ethyl acetate (200 mL), washed with water (50 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **328I**.

[0001179] To a mixture of Compound **328I** (142 mg, 0.5 mmol) and Intermediate **G** (232 mg, 0.75 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight and the resulting solution was diluted with ethyl acetate (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with reverse phase chromatography using eluent (methanol in water, from 10% to 55% v/v) to furnish Compound **328**. LC-MS (ESI) m/z: 577 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.28-0.29 (m, 2H), 0.41-0.51 (m, 2H), 2.01-2.23 (m, 6H), 2.39-2.65 (m, 2H), 3.18-3.35 (m, 3H), 3.51-3.59 (m, 1H), 3.63-3.84 (m, 3H), 3.61-3.65 (m, 1H), 4.94 (s, 1H), 7.19-7.21 (m, 1H), 7.31-7.38 (m, 2H), 7.42-7.51 (m, 2H), 7.61 (s, 1H), 7.76-7.89 (m, 3H).

Example 329



[0001180] To a solution of Compound **329A** (19.8 g, 85.4 mmol) in dry THF (600 mL) maintained at $-70\text{ }^{\circ}\text{C}$ was added *n*-BuLi (2.5 M in hexane, 34.5 mL) dropwise under nitrogen atmosphere over a period of 20 minutes. After the reaction mixture was stirred at $-70\text{ }^{\circ}\text{C}$ for 40 minutes, Compound **A4** (12 g, 30.4 mmol) dissolved in dry THF (50 mL) was added slowly to the cold solution at a rate that maintained the internal temperature between $-70\text{ }^{\circ}\text{C}$ and $-50\text{ }^{\circ}\text{C}$. After the addition was complete, the solution was left to stir for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (400 mL) and extracted with ethyl acetate (300 mL x 3). The organic phase was washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish the crude Compound **329B**. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to furnish Compound **329B**.

[0001181] A solution of Compound **329B** (7.4 g, 15.1 mmol) in a mixture of tetrahydrofuran, water, and glacial acetic acid (153 mL, 1/1/3, v/v/v) was stirred at $25\text{ }^{\circ}\text{C}$ for 30 h. The reaction mixture was concentrated under reduced pressure to remove excess solvent. The residue was poured into ice water (20 g) and adjusted to pH 7-8 with aqueous sodium hydroxide (1 N) and saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the

crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 30% to 50% v/v) to give Compound **329C**.

[0001182] To a solution of Compound **329C** (3.0 g, 8 mmol) in dry THF (140 mL) maintained at -78 °C was added diisobutylaluminum hydride (1.5 M in toluene, 25 mL) dropwise under nitrogen atmosphere over a period of 15 minutes. After the reaction mixture was stirred at -70 °C for 1 h, a solution of HCl (2 N, 40 mL) was added to the mixture slowly. The reaction mixture was extracted with ethyl acetate (30 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound, which was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 50% to 150% v/v) to furnish Compound **329D**.

[0001183] To a solution of Compound **329D** (2.30 g, 6.10 mmol) dissolved in THF (100 mL) was added triethylamine (1.90 g, 18.81 mmol). The mixture was cooled to -30 °C, and then methanesulfonyl chloride (0.80 g, 6.98 mmol) was added dropwise over a period of 15 minutes. After the addition was complete, the reaction mixture was stirred at -30 °C for 1.5 h, diluted with water (100 mL), and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **329E**, which was directly used for the next step without further purification.

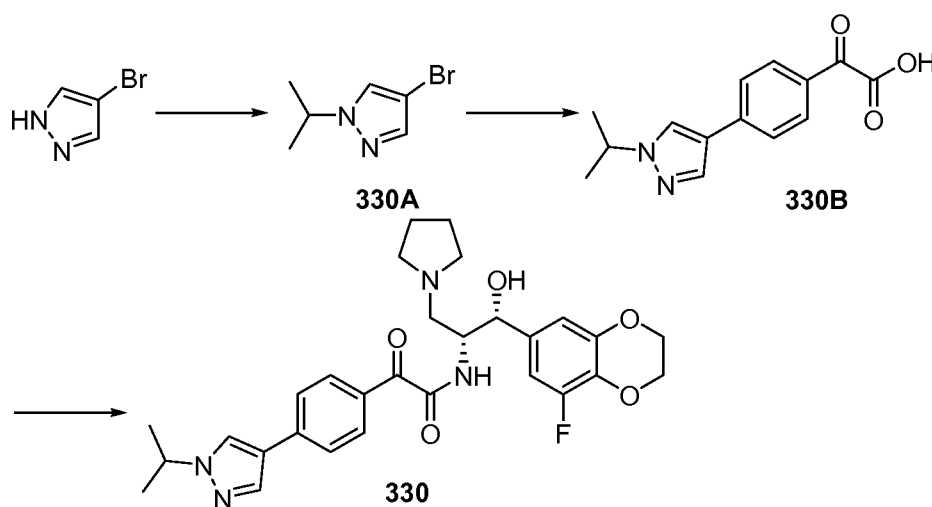
[0001184] To a solution of Compound **329E** (3.81 g, 6.10 mmol) in THF (100 mL) was added pyrrolidine (11 g, 154 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (100 mL), extracted with ethyl acetate (150 mL x 2), washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **329F**.

[0001185] To a solution of Compound **329F** (1.33 g, 3.08 mmol) in ethanol (30 mL) and water (7 mL) was added LiOH·H₂O (570 mg, 13.51 mmol). The mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **329G**, which was directly used for the next step without further purification.

[0001186] A mixture of Intermediate **C** (80 mg, 0.32 mmol), Compound **329G** (116 mg, 0.39 mmol), and HATU (187 mg, 0.49 mmol) in dichloromethane (20 mL) was stirred at

room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **329**. LC-MS (ESI) m/z : 523 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.05-2.23 (m, 4H), 3.20-3.37 (m, 2H), 3.60-3.77 (m, 4H), 4.48-4.50 (m, 1H), 4.68-4.74 (m, 2H), 5.04 (s, 1H), 6.73-6.78 (m, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.22-7.27 (m, 2H), 7.42 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.58 (d, $J = 1.6$ Hz, 1H), 7.65-7.76 (m, 6H).

Example 330



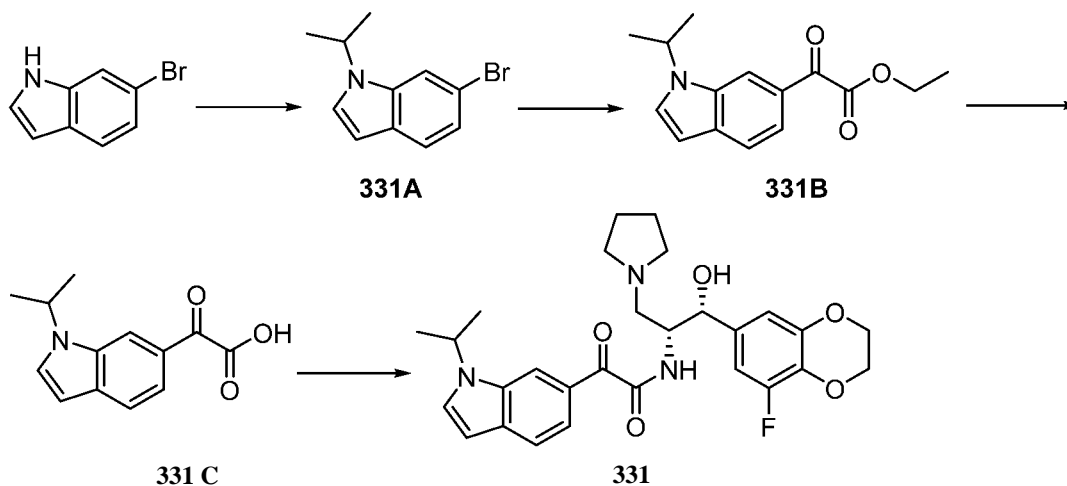
[0001187] To a solution of 4-bromo-1H-pyrazole (2.92 g, 20.0 mmol) in anhydrous DMF (50 mL) was added 2-bromopropane (3.69 g, 30.0 mmol) and potassium carbonate (6.90 g, 50 mmol) at room temperature. The reaction mixture was stirred for 10 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic extracts were washed with brine (150 mL x 2) and dried over anhydrous sodium sulfate. After filtration, the solvent was removed in *vacuo* and the residue was purified with flash column chromatography on silica gel to give Compound **330A**.

[0001188] To a solution of Compound **330A** (189 mg, 1.0 mmol) in 1,4-dioxane (10 mL) was added Intermediate **175B** (304 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (35 mg, 0.05 mmol), sodium carbonate (318 mg, 3.0 mmol), and water (1 mL) under nitrogen. The reaction mixture was stirred at 110 °C for 2 hours. The resulting mixture was cooled to 25 °C. The precipitated solid was filtered and dried to afford Compound **330B**.

[0001189] To a solution of Compound **330B** (25 mg, 0.10 mmol) in DMF (2 mL) was added Intermediate **C** (30 mg, 0.10 mmol) and HATU (57 mg, 0.15 mmol). The reaction mixture was stirred at 20 °C for 2 h. The mixture was purified with prep-HPLC to yield Compound **330**. LC-MS (ESI) m/z : 537 $[M+H]^+$; 1H -NMR (acetone- d_6 , 400 MHz): δ (ppm)

1.61 (d, $J = 6.4$ Hz, 6H), 2.09-2.12 (m, 1H), 2.25-2.31 (m, 2H), 2.86 (s, 1H), 3.03 (s, 1H), 3.46-3.54 (m, 2H), 3.82-3.85 (m, 1H), 3.95-4.07 (m, 3H), 4.24-4.30 (m, 4H), 5.07-5.08 (m, 1H), 6.81-6.87 (m, 2H), 7.79-7.81 (m, 2H), 8.06-8.10 (m, 3H), 8.30 (s, 1H), 8.56 (s, 1H), 8.69 (brs, 1H).

Example 331



[0001190] To a solution of 6-bromo-1H-indole (6 g, 30 mmol) in DMF (150 mL) was added sodium hydride (60% suspend in oil, 2.4 g, 60 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and 2-iodopropane (7.6 g, 45 mmol) was added at 0 °C. The resultant mixture was stirred at room temperature overnight and diluted with ethyl acetate (300 mL). The organic layer was washed with water (100 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **331A**.

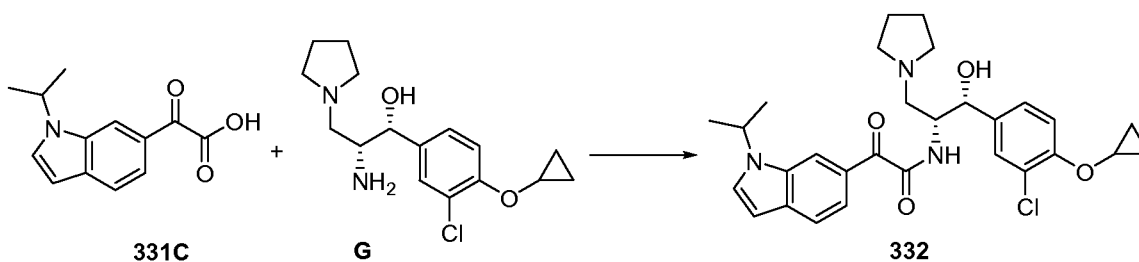
[0001191] To a solution of Compound **331A** (476 mg, 2 mmol) in THF (20 mL) was added n-BuLi (2.5 M in hexane, 1 mL, 2.4 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 0.5 h and diethyl oxalate (584 mg, 4 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 0.5 h, quenched with saturated aqueous ammonium chloride solution (50 mL), and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **331B**.

[0001192] To a solution of Compound **331B** (368 mg, 1.42 mmol) in THF (10 mL) was added a solution of LiOH·H₂O (120 mg, 2.84 mmol) in water (3 mL). The mixture was stirred at room temperature overnight. After removal of THF, the mixture was acidified to pH 1 with aqueous HCl solution (1 N) and extracted with dichloromethane (20 mL). The organic layer

was dried over anhydrous sodium sulfate and used directly for the next step as a dichloromethane solution.

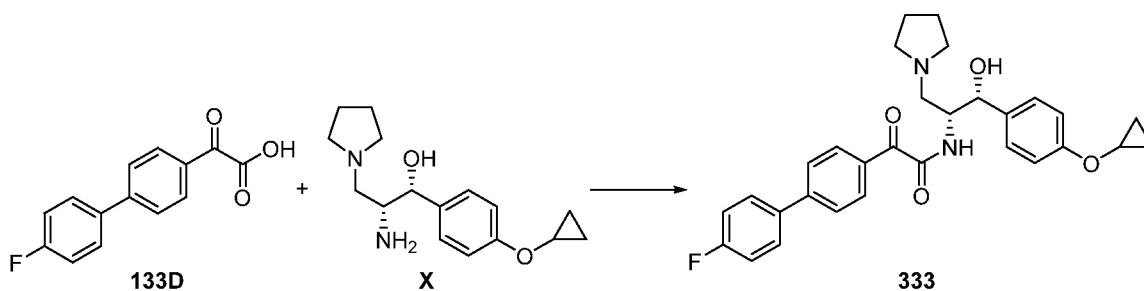
[0001193] A mixture of Compound **331C** in dichloromethane solution (115 mg, 0.5 mmol), Intermediate **C** (150 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in dichloromethane (10 mL) and DMF (3 mL) was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to yield Compound **331**. LC-MS (ESI) m/z : 510 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.46 (d, $J = 6.8$ Hz, 3H), 1.50 (d, $J = 6.4$ Hz, 3H), 1.85-1.88 (m, 2H), 2.02-2.03 (m, 2H), 3.09-3.20 (m, 2H), 3.41-3.44 (m, 2H), 3.52-3.56 (m, 2H), 4.23-4.25 (m, 4H), 4.50-4.55 (m, 1H), 4.76-4.81 (m, 2H), 6.02 (s, 1H), 6.60 (d, $J = 3.2$ Hz, 1H), 6.76 (s, 1H), 6.82-6.85 (m, 1H), 7.45-7.47 (m, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 3.2$ Hz, 1H), 8.27 (s, 1H), 8.66 (d, $J = 9.2$ Hz, 1H), 9.33 (s, 1H).

Example 332



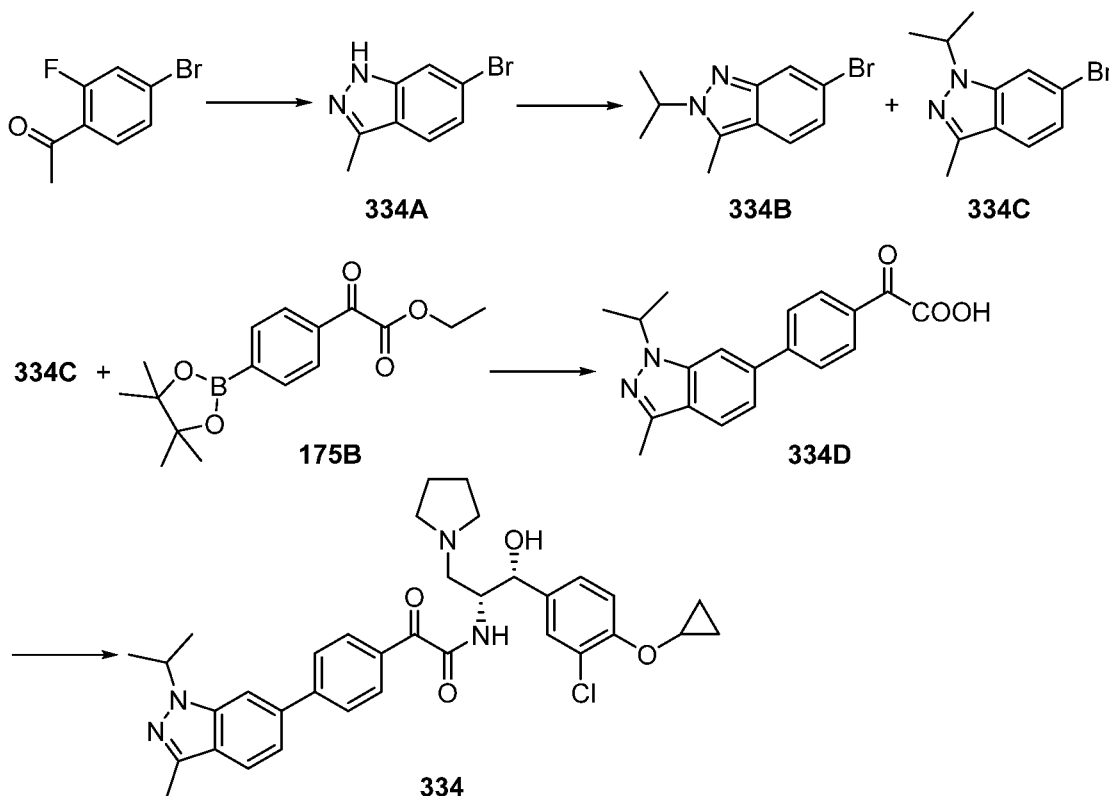
[0001194] A mixture of Compound **331C** in dichloromethane solution (115 mg, 0.5 mmol), Intermediate **G** (155 mg, 0.5 mmol), and HATU (380 mg, 1 mmol) in dichloromethane (10 mL) and DMF (3 mL) was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to yield Compound **332**. LC-MS (ESI) m/z : 524 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.62-0.65 (m, 2H), 0.79-0.81 (m, 2H), 1.45 (d, $J = 6.8$ Hz, 3H), 1.49 (d, $J = 6.8$ Hz, 3H), 1.86-1.88 (m, 2H), 2.00-2.03 (m, 2H), 3.12-3.20 (m, 2H), 3.45-3.47 (m, 4H), 3.87-3.90 (m, 1H), 4.54-4.58 (m, 1H), 4.74-4.80 (m, 1H), 4.85 (s, 1H), 6.05 (s, 1H), 6.59 (d, $J = 3.2$ Hz, 1H), 7.32-7.38 (m, 2H), 7.41-7.45 (m, 2H), 7.58 (d, $J = 8.8$ Hz, 1H), 7.84 (d, $J = 3.2$ Hz, 1H), 8.24 (s, 1H), 8.67 (d, $J = 9.2$ Hz, 1H), 9.39 (s, 1H).

Example 333



[0001195] To a solution of Intermediate **X** (80 mg, 0.29 mmol) in a mixture of dichloromethane (3 mL) and DMF (3 mL) was added Compound **133D** (72 mg, 0.29 mmol) and HATU (165 mg, 0.43 mmol). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and the resulting residue was purified with prep-HPLC to furnish Compound **333**. LC-MS (ESI) m/z : 503 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.64-0.65 (m, 2H), 0.74-0.77 (m, 2H), 1.29 (s, 1H), 2.02-2.07 (m, 2H), 2.17-2.21 (m, 2H), 3.23-3.26 (m, 1H), 3.56 (dd, $J = 13.3, 2.8$ Hz, 1H), 3.67-3.80 (m, 3H), 3.81-3.83 (m, 1H), 4.66-4.70 (m, 1H), 4.98 (d, $J = 3.1$ Hz, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 7.22-7.26 (m, 2H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.68 (d, $J = 8.5$ Hz, 2H), 7.71-7.75 (m, 2H), 7.78 (d, $J = 8.5$ Hz, 2H).

Example 334



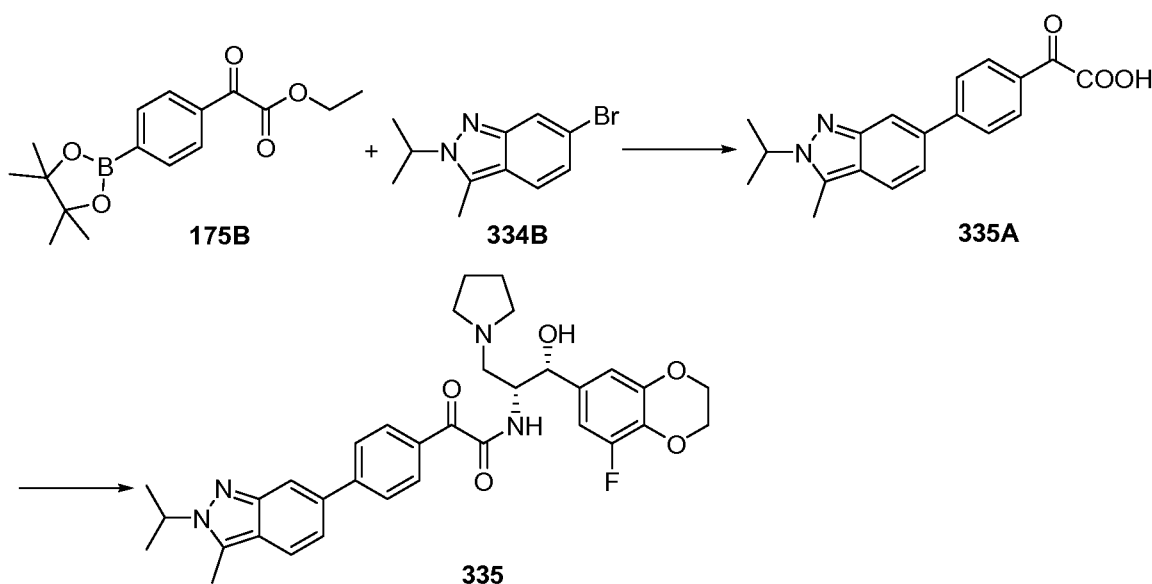
[0001196] To a solution of 1-(4-bromo-2-fluorophenyl)ethan-1-one (1.0 g, 3.89 mmol) in 1,2-ethanediol (12 mL) was added 80% of hydrazine monohydrate (0.6 mL, 7.78 mmol) at room temperature. The reaction mixture was stirred at 200 °C in a microwave for 4.5 h, cooled down to room temperature, and quenched with water (50 mL). The solid precipitated was filtered, washed with water (20 mL), and dried under *vacuo* to afford Compound **334A**.

[0001197] To Compound **334A** (1.9 g, 9.05 mmol) in DMF (15 mL) was added sodium hydride (60% in mineral, 398 mg, 9.96 mmol) with ice bath cooling. The mixture was stirred at room temperature for 30 min and 2-iodopropane (2.7 mL, 27.15 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20% v/v) to give Compound **334B** and Compound **334C**.

[0001198] A mixture of Compound **334C** (400 mg, 1.59 mmol), Compound **175B** (483 mg, 1.59 mmol), Pd(dppf)Cl₂ (65 mg, 0.08 mmol), and K₂CO₃ (658 mg, 4.77 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled down to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to yield Compound **334D**.

[0001199] A mixture of Compound **334D** (80 mg, 0.25 mmol), HATU (143 mg, 0.37 mmol), and Intermediate **G** (78 mg, 0.25 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **334**. LC-MS (ESI) *m/z*: 615 [M+H]⁺; ¹H-NMR (*OMSO-d*₆, 400 MHz): δ (ppm) 0.65-0.85 (m, 4H), 1.48-1.51 (m, 6H), 1.89-2.08 (m, 4H), 2.53 (s, 3H), 3.14-3.25 (m, 2H), 3.45-3.49 (m, 4H), 3.94-3.97 (m, 1H), 4.57-4.62 (m, 1H), 4.92 (s, 1H), 5.03-5.09 (m, 1H), 6.10 (brs, 1H), 7.37-7.49 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 5.6 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.01 (s, 1H), 8.86 (d, *J* = 10.0 Hz, 1H), 9.57 (brs, 1H).

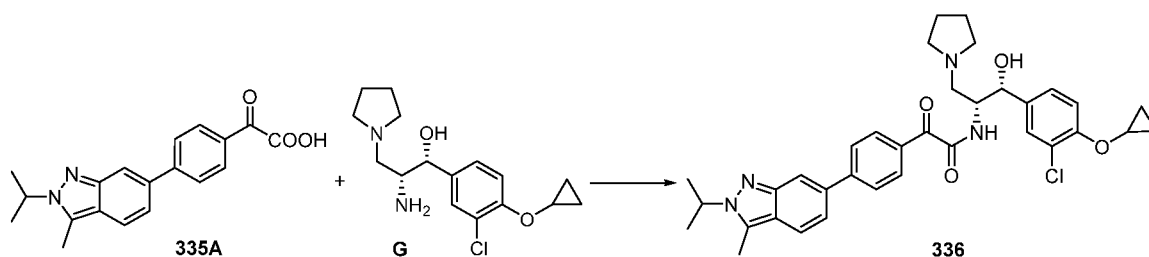
Example 335



[0001200] A mixture of Compound **334B** (460 mg, 1.82 mmol), Compound **175B** (553 mg, 1.82 mmol), Pd(dppf)Cl₂ (73 mg, 0.09 mmol), and K₂CO₃ (753 mg, 5.46 mmol) in dioxane (5 mL) and water (5 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled down to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with water (100 mL x 3), dried over anhydrous sodium sulfate, and concentrated to give Compound **335A**.

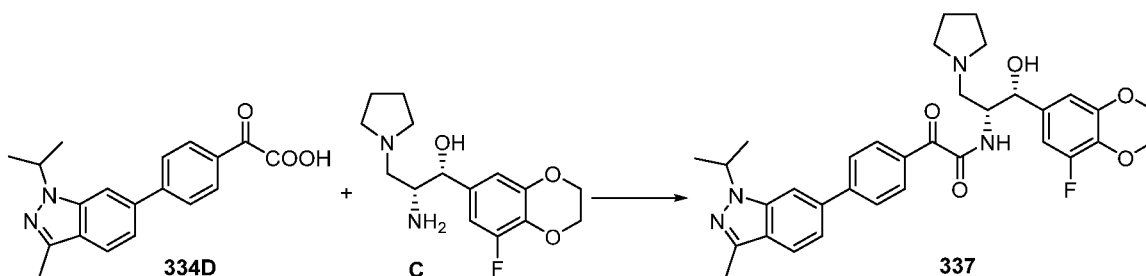
[0001201] A mixture of Compound **335A** (80 mg, 0.25 mmol), HATU (143 mg, 0.37 mmol), and Intermediate **C** (74 mg, 0.25 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **335**. LC-MS (ESI) m/z: 601 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.52 (d, *J* = 6.4 Hz, 6H), 1.88-2.05 (m, 4H), 2.67 (s, 3H), 3.10-3.22 (m, 2H), 3.43-3.55 (m, 4H), 4.24-4.29 (m, 4H), 4.49-4.54 (m, 1H), 4.78 (d, *J* = 2.8 Hz, 1H), 4.86-4.92 (m, 1H), 5.99 (brs, 1H), 6.77 (s, 1H), 6.84 (dd, *J* = 11.6, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.88-8.01 (m, 5H), 8.75 (d, *J* = 9.6 Hz, 1H), 9.33 (brs, 1H).

Example 336



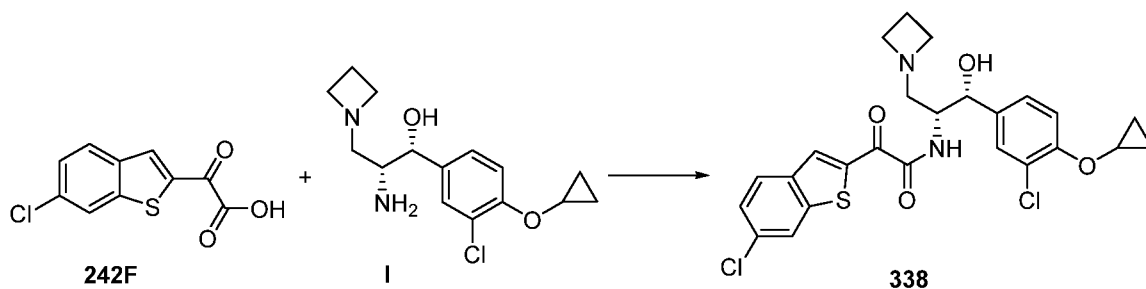
[0001202] A mixture of Compound **335A** (80 mg, 0.25 mmol), HATU (143 mg, 0.37 mmol), and Intermediate **G** (78 mg, 0.25 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **336**. LC-MS (ESI) m/z : 615 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.69-0.85 (m, 4H), 1.52 (d, $J = 6.8$ Hz, 6H), 1.89-2.08 (m, 4H), 2.67 (s, 3H), 3.1 1-3.24 (m, 2H), 3.45-3.57 (m, 4H), 3.93-3.97 (m, 1H), 4.55-4.59 (m, 1H), 4.86-4.93 (m, 2H), 5.99 (brs, 1H), 7.36 (d, $J = 8.8$ Hz, 2H), 7.42-7.46 (m, 2H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.80-7.85 (m, 3H), 7.95 (s, 1H), 8.82 (d, $J = 10.0$ Hz, 1H), 9.34 (brs, 1H).

Example 337



[0001203] A mixture of Compound **334D** (80 mg, 0.25 mmol), HATU (143 mg, 0.37 mmol), and Intermediate **C** (74 mg, 0.25 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **337**. LC-MS (ESI) m/z : 601 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.48 (d, $J = 6.4$ Hz, 6H), 1.88-2.08 (m, 4H), 2.53 (s, 3H), 3.1 1-3.22 (m, 2H), 3.39-3.55 (m, 4H), 4.20-4.29 (m, 4H), 4.51-4.55 (m, 1H), 4.79 (d, $J = 2.8$ Hz, 1H), 5.03-5.09 (m, 1H), 6.03 (brs, 1H), 6.78 (s, 1H), 6.84 (d, $J = 11.6$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.92-7.97 (m, 4H), 8.02 (s, 1H), 8.77 (d, $J = 9.6$ Hz, 1H), 9.31 (brs, 1H).

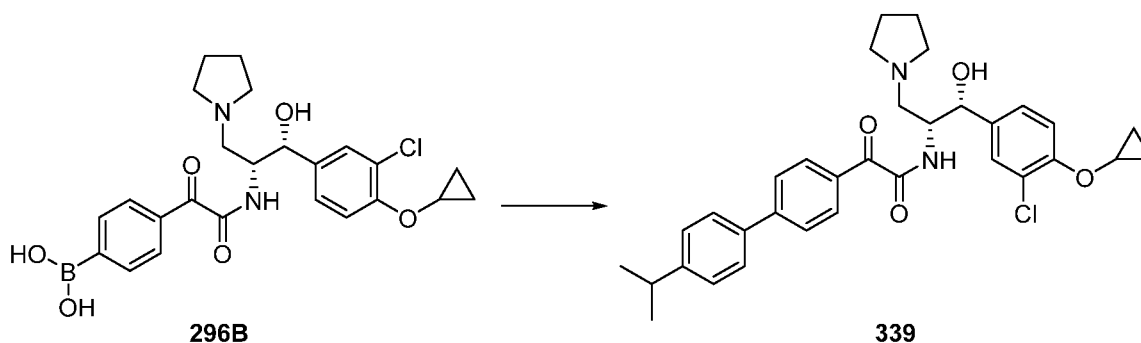
Example 338



[0001204] To a solution of Intermediate **I** (172 mg, 0.58 mmol) in dichloromethane (10 mL) was added Compound **242F** (140 mg, 0.58 mmol) and HATU (332 mg, 0.87 mmol). The mixture was stirred under nitrogen at room temperature overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and

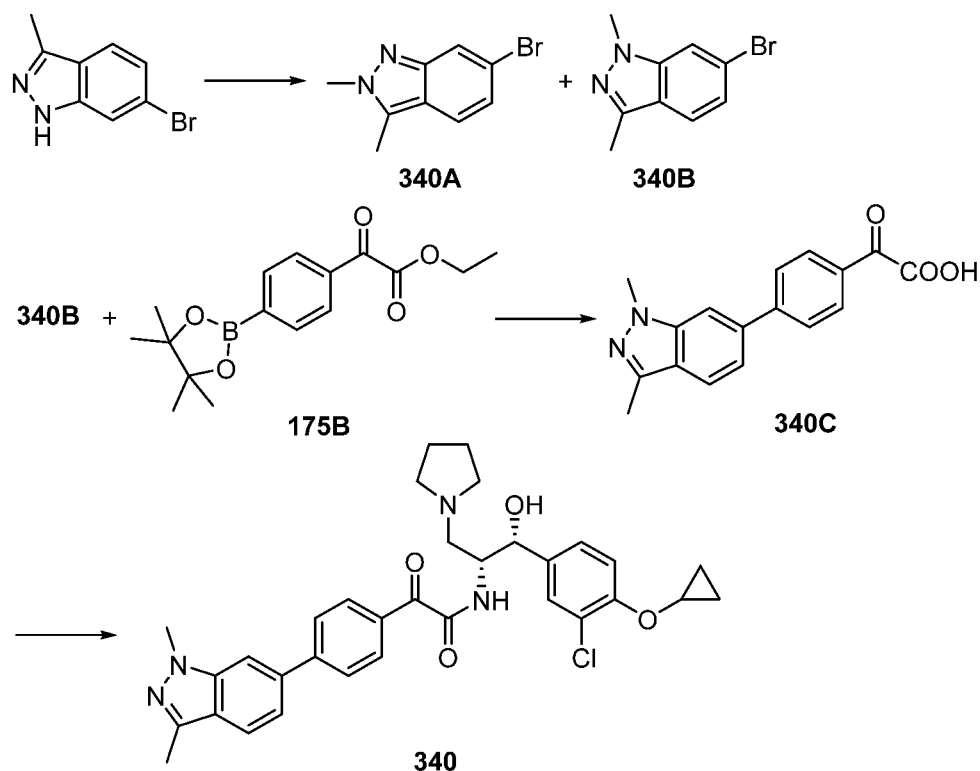
brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **338**. LC-MS (ESI) m/z : 519 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.62-0.64 (m, 2H), 0.78-0.79 (m, 2H), 2.22-2.28 (m, 1H), 2.33-2.42 (m, 1H), 3.30-3.31 (m, 1H), 3.86-3.90 (m, 1H), 4.02-4.30 (m, 6H), 4.78 (d, $J = 2.4$ Hz, 1H), 6.04 (s, 1H), 7.29 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 2.4$ Hz, 1H), 7.55 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 8.30 (d, $J = 1.6$ Hz, 1H), 8.49 (s, 1H), 8.57 (d, $J = 10.0$ Hz, 1H), 9.49 (s, 1H).

Example 339



[0001205] A mixture of 1-bromo-4-isopropylbenzene (44 mg, 0.22 mmol), Compound **296B** (110 mg, 0.22 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6 mg, 8.2 μmol), sodium carbonate (47 mg, 0.44 mmol), water (0.5 mL), and 1,4-dioxane (5 mL) was stirred under nitrogen atmosphere at 80 °C for 2 h. After cooling, the reaction mixture was treated with water (5 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a black oil. The oil was purified with prep-HPLC to furnish Compound **339**. LC-MS (ESI) m/z : 561 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.60-0.66 (m, 2H), 0.76-0.84 (m, 2H), 1.23 (d, $J = 7.2$ Hz, 6H), 1.82-1.92 (m, 2H), 1.97-2.07 (m, 2H), 2.91-3.00 (m, 1H), 3.08-3.27 (m, 2H), 3.41-3.61 (m, 4H), 3.86-3.95 (m, 1H), 4.42-4.61 (m, 1H), 4.85-4.91 (m, 1H), 6.04 (d, $J = 4.8$ Hz, 1H), 7.33-7.44 (m, 5H), 7.64 (d, $J = 12.4$ Hz, 2H), 7.69-7.80 (m, 4H), 8.77 (d, $J = 10.0$ Hz, 1H), 9.34 (s, 1H).

Example 340

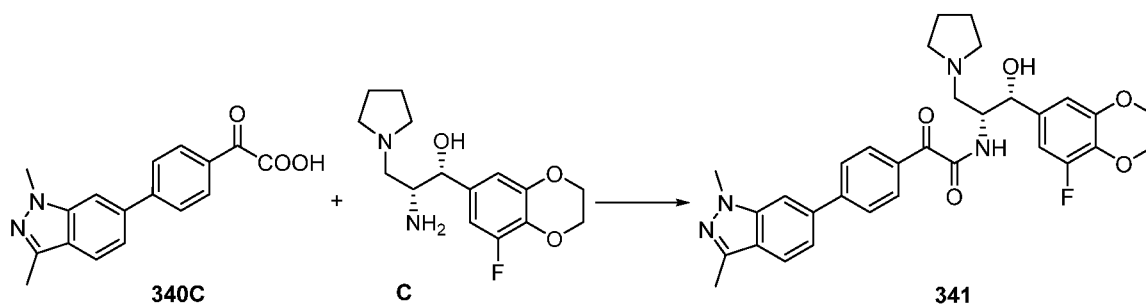


[0001206] To 6-bromo-3-methyl-1H-indazole (1.9 g, 9.05 mmol) in DMF (15 mL) was added sodium hydride (60% in mineral, 398 mg, 9.96 mmol) with ice bath cooling. The mixture was stirred for 30 min at room temperature and iodomethane (0.94 mL, 27.15 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, quenched with ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 90% v/v) to give Compound **340A** and Compound **340B**.

[0001207] A mixture of Compound **340B** (500 mg, 2.23 mmol), Compound **175B** (678 mg, 2.23 mmol), Pd(dppf)Cl₂ (90 mg, 0.11 mmol), and K₂CO₃ (923 mg, 6.69 mmol) in dioxane (10 mL) and water (10 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **340C**.

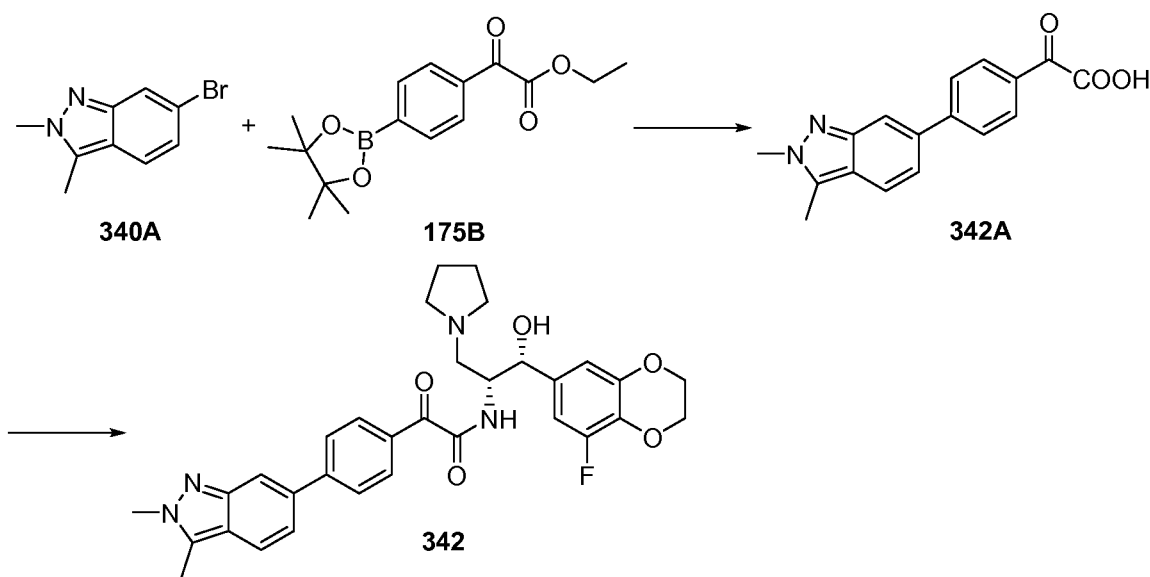
[0001208] A mixture of Compound **340C** (70 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), and Intermediate **G** (75 mg, 0.24 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **340**. LC-MS (ESI) m/z : 587 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.65-0.87 (m, 4H), 1.85-2.04 (m, 4H), 2.53 (s, 3H), 3.10-3.24 (m, 2H), 3.44-3.58 (m, 4H), 3.93-3.98 (m, 1H), 4.04 (s, 3H), 4.55-4.59 (m, 1H), 4.89 (d, $J = 2.0$ Hz, 1H), 6.06 (brs, 1H), 7.36 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.42-7.50 (m, 3H), 7.80-7.86 (m, 3H), 7.89 (d, $J = 8.4$ Hz, 2H), 7.96 (s, 1H), 8.83 (d, $J = 9.6$ Hz, 1H), 9.35 (brs, 1H).

Example 341



[0001209] A mixture of Compound **340C** (70 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), and Intermediate **C** (71 mg, 0.24 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **341**. LC-MS (ESI) m/z : 573 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.88-2.08 (m, 4H), 2.50 (s, 3H), 3.13-3.19 (m, 2H), 3.50-3.51 (m, 4H), 4.04 (s, 3H), 4.26-4.29 (m, 4H), 4.51-4.53 (m, 1H), 4.79 (d, $J = 2.4$ Hz, 1H), 6.06 (brs, 1H), 6.78 (s, 1H), 6.84 (d, $J = 10.8$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.95-7.97 (m, 5H), 8.77 (d, $J = 9.6$ Hz, 1H), 9.31 (brs, 1H).

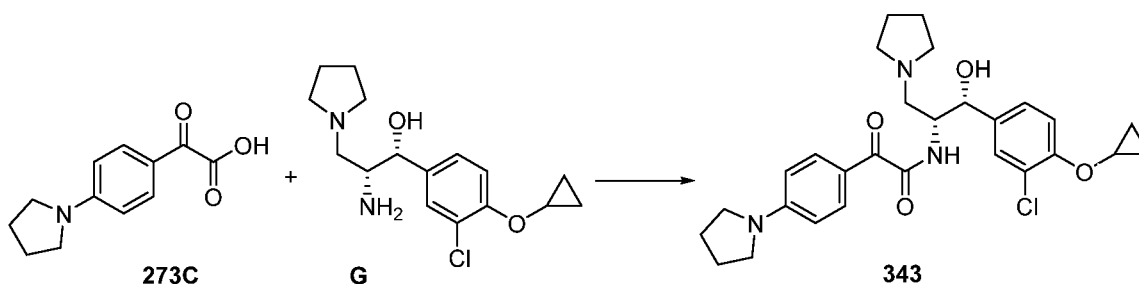
Example 342



[0001210] A mixture of Compound **340A** (500 mg, 2.23 mmol), Compound **175B** (678 mg, 2.23 mmol), Pd(dppf)Cl₂ (90 mg, 0.11 mmol), and K₂CO₃ (923 mg, 6.69 mmol) in dioxane (10 mL) and water (10 mL) was stirred under nitrogen at 100 °C for 3 h. The reaction mixture was cooled down to room temperature and filtered through celite. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **342A**.

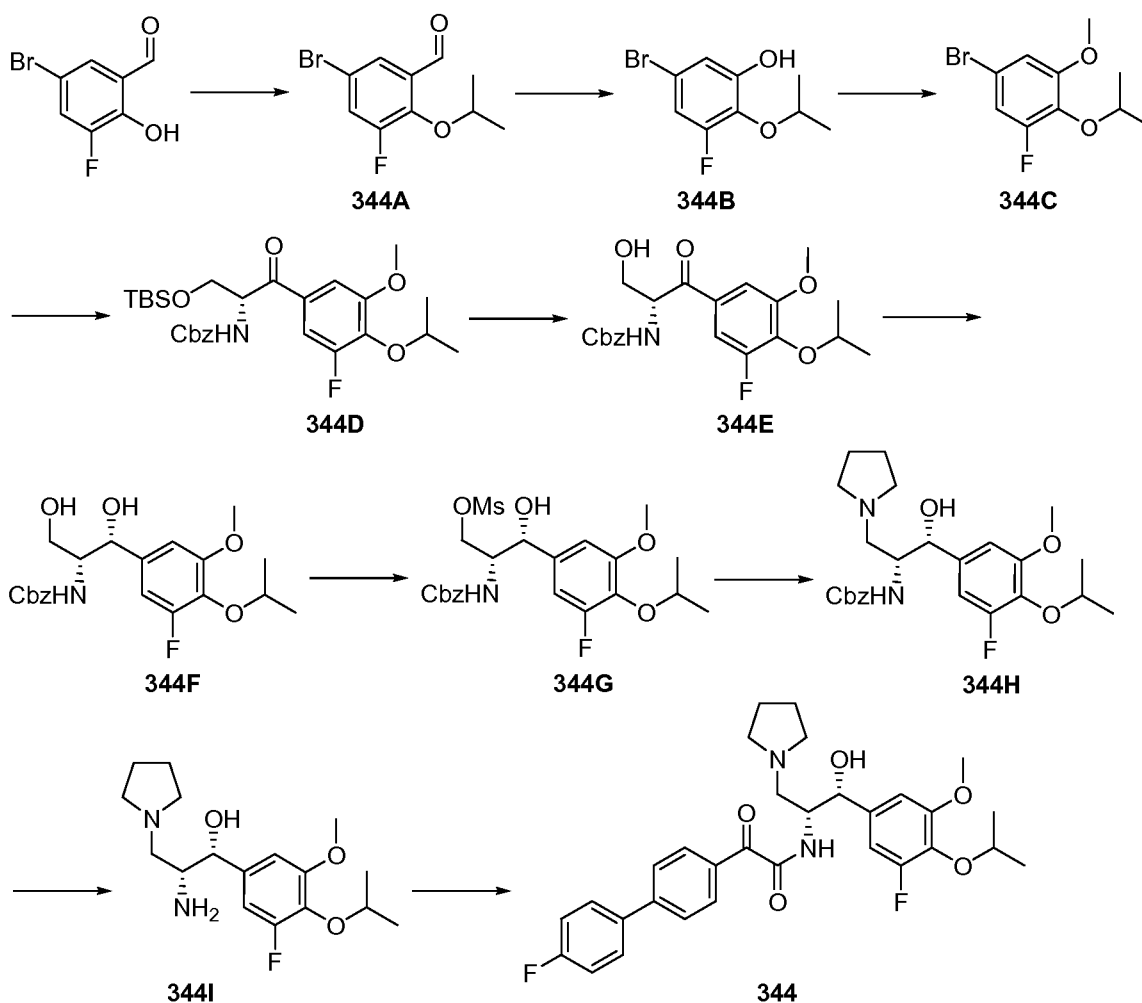
[0001211] A mixture of Compound **342A** (70 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), and Intermediate **C** (71 mg, 0.24 mmol) in DMF (5 mL) was stirred at 20 °C for 18 h. The mixture was directly purified with prep-HPLC to furnish Compound **342**. LC-MS (ESI) *m/z*: 573 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.88-2.03 (m, 4H), 2.65 (s, 3H), 3.13-3.21 (m, 2H), 3.41-3.55 (m, 4H), 4.09 (s, 3H), 4.27-4.29 (m, 4H), 4.48-4.53 (m, 1H), 4.78 (d, *J* = 2.0 Hz, 1H), 6.77 (s, 1H), 6.83 (d, *J* = 12.8 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.82-7.93 (m, 6H), 7.76 (d, *J* = 9.6 Hz, 1H), 9.29 (brs, 1H).

Example 343



[0001212] A mixture of Compound **273C** (90 mg, 0.41 mmol), HATU (234 mg, 0.62 mmol), and Intermediate **G** (127 mg, 0.41 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **343**. LC-MS (ESI) m/z : 512 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.65-0.67 (m, 2H), 0.82-0.83 (m, 2H), 1.85-1.87 (m, 2H), 1.97-2.01 (m, 6H), 3.09-3.20 (m, 2H), 3.48-3.54 (m, 8H), 3.89-3.94 (m, 1H), 4.50-4.55 (m, 1H), 4.84 (d, $J = 2.4$ Hz, 1H), 5.97-6.04 (m, 1H), 6.51 (d, $J = 9.2$ Hz, 2H), 7.30-7.32 (m, 1H), 7.37-7.41 (m, 2H), 7.64 (d, $J = 9.2$ Hz, 2H), 8.47 (d, $J = 9.6$ Hz, 1H), 9.32 (s, 1H).

Example 344



[0001213] To a mixture of 5-bromo-3-fluoro-2-hydroxybenzaldehyde (21.8 g, 100 mol) and K_2CO_3 (110 g, 800 mol) in DMF (400 mL) was added 2-iodopropane (20 mL, 200 mol). The mixture was stirred at 70 °C for 4 h. It was cooled to room temperature and filtered. The cake was washed with ethyl acetate (50 mL). The filtrate was diluted with water (900 mL) and extracted with ethyl acetate (400 mL x 3). The organic layer was washed with water (900 mL x 5) and brine (900 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel on silica (ethyl acetate in petroleum, 10% v/v) to afford Compound **344A**.

[0001214] A mixture of Compound **344A** (4.3 g, 16.5 mol) and m-chloroperoxybenzoic acid (5.7 g, 33 mole) in methylene chloride (40 mL) was refluxed under nitrogen overnight. The cooled mixture was filtered and the precipitate was washed with methylene chloride. The combined filtrate and washing were washed with aq. sodium bicarbonate (40 mL x 3) and NaCl (40 mL) and concentrated to give a solid. The solid was dissolved in MeOH (27 mL). A solution of 10% NaOH (9 mL) was added with cooling. After stirring for 45 min at room

temperature, the mixture was concentrated and 5% NaOH (100 mL) was added. The solution was washed with ether (80 mL x 2). The basic solution was acidified with con. HCl and extracted with ether (80 mL x 2). The ether extracts were washed with aq. sodium bicarbonate (100 mL x 3), dried over $MgSO_4$, and concentrated to give the crude Compound **344B**.

[0001215] To a mixture of Compound **344B** (4.2 g, 17 mol) and K_2CO_3 (3.5 g, 26 mol) in DMF (60 mL) was added iodomethane (1.27 mL, 20 mol). The mixture was stirred at 25 °C overnight. It was filtered. The cake was washed with ethyl acetate (10 mL). The filtrate was diluted with water (120 mL) and extracted with ethyl acetate (40 mL x 3). The organic layer was washed with water (100 mL x 5) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel on silica (ethyl acetate in petroleum, 5% v/v) to afford Compound **344C**.

[0001216] To a solution of Compound **344C** (6.37 g, 24 mmol) in THF (70 mL) was added n-BuLi (2.4 M, 10 mL, 24 mmol) under nitrogen at -60 °C. It was stirred at -60 °C for 0.5 h. And then it was added a solution of Compound **A4** (3.21 g, 8 mmol) in THF (20 mL). The mixture was stirred at -60 °C for 0.5 h, quenched with saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (60 mL x 3), washed with brine (100 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **344D**.

[0001217] To a solution of Compound **344D** (3.89 g, 7.5 mmol) in THF (30 mL) was added TBAF (1 M, 2.2 mL) which had been adjusted to pH 6-7 with CH_3COOH . The mixture was stirred at 35 °C for 16 h. Water (50 mL) was added. It was extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to yield Compound **344E**.

[0001218] To a solution of Compound **344E** (1.54 g, 3.70 mmol) in dry THF (35 mL) was added DIBAL-H (1.5 M, 5 mL, 7.5 mmol) slowly dropwise under nitrogen at -60 °C. It was stirred at -65 °C for 0.5 h. And then DIBAL-H (1.5 M, 5 mL, 7.5 mmol) was added to the reaction. It was stirred at -65 °C for another 0.5 h. A solution of HCl (2 M) was added to quench the reaction. It was extracted with ethyl acetate (50 mL), washed with brine (40 mL x 2), dried over anhydrous sodium sulfate, and concentrated to yield a crude product. It was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to yield Compound **344F**.

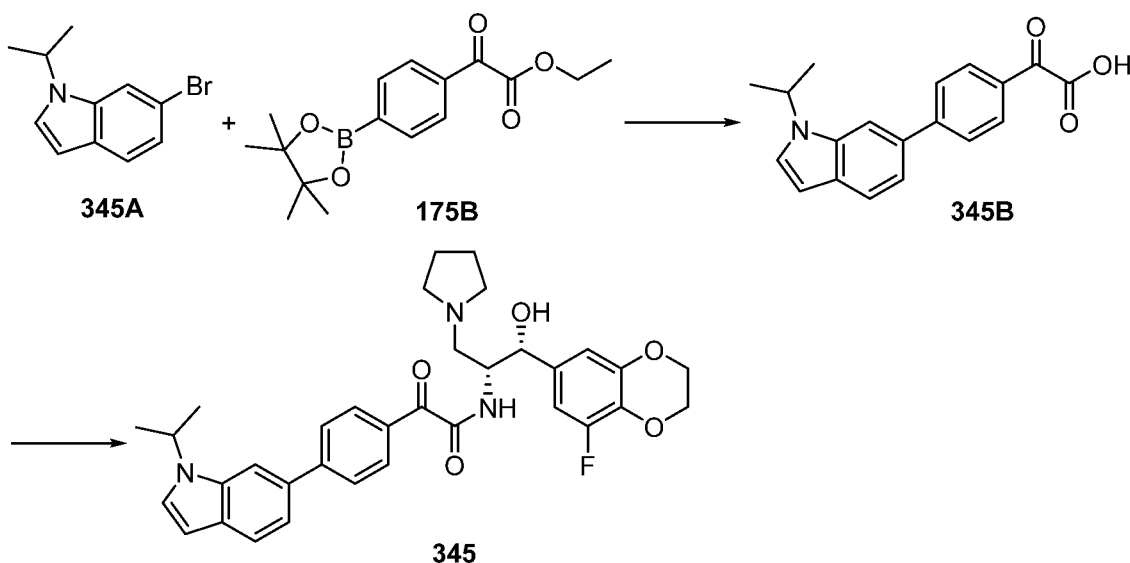
[0001219] To a solution of Compound **344F** (1.04 g, 2.56 mmol) and triethylamine (0.7 mL, 5.12 mmol) in dichloromethane (30 mL) was added MsCl (0.22 mL, 2.81 mmol) at -30 °C and the resultant mixture was stirred at -30 °C for 2 h. It was treated with water (20 mL). The organic layer was washed with water (40 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **344G**.

[0001220] To a solution of Compound **344G** (1.2 g, 2.5 mmol) in THF (20 mL) was added pyrrolidine (2.3 mL, 25 mmol). The mixture was stirred at 50 °C overnight. It was treated with water (20 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (30 mL x 1), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give a crude product. It was purified with flash column chromatography on silica gel (methanol in dichloromethane, 20% v/v) to yield Compound **344H**.

[0001221] To a solution of Compound **344H** (840 mg, 1.8 mmol) in MeOH (30 mL) was added 10% Pd(OH)₂ (150 mg). The solution was stirred under H₂ atmosphere at 25 °C for 24 h. The solution was filtered. The filtrate was concentrated to yield the crude Compound **344I**.

[0001222] A mixture of Compound **344I** (72 mg, 0.22 mmol), Compound **133D** (49 mg, 0.20 mmol), and HATU (91 mg, 0.24 mmol) in DMF (4 mL) was stirred at 20 °C for 15 h. It was purified with prep-HPLC to give Compound **344**. LC-MS (ESI) m/z: 553 [M+H]⁺; ¹H-NMR ((CD₃)₂CO, 400 MHz): δ (ppm) 1.22 (t, *J* = 6.4 Hz, 6H), 2.08-2.17 (m, 2H), 2.25 (s, 2H), 2.49 (s, 3H), 3.74 (s, 3H), 3.85 (s, 1H), 3.90-4.03 (m, 3H), 4.32-4.38 (m, 1H), 4.91 (s, 1H), 5.23 (s, 1H), 6.90 (dd, *J*₁ = 11.2 Hz, *J*₂ = 1.6 Hz, 1H), 7.01 (s, 1H), 7.29 (t, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.80-7.84 (m, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 10 Hz, 1H), 9.52 (brs, 1H).

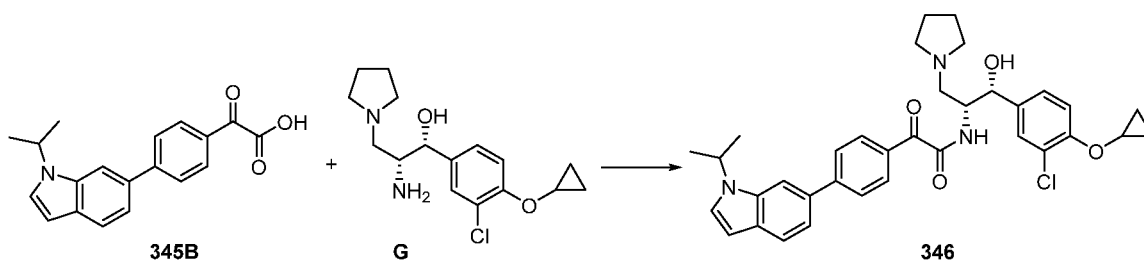
Example 345



[0001223] A mixture of Compound **345A** (500 mg, 2.1 mmol), Pd(dppf)Cl₂ (86 mg, 0.1 mmol), ethyl 2-oxo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate **175B** (638 mg, 2.1 mmol), and K₂CO₃ (668 mg, 6.3 mmol) in 1,4-dioxane (15 mL) and water (2 mL) was stirred under nitrogen at 100 °C overnight. The mixture was cooled down to room temperature, concentrated, diluted with water (50 mL), and extracted with ethyl acetate (30 mL x 3). The aqueous layer was acidified to pH 2 with aqueous HCl solution (1 N) and extracted with dichloromethane (10 mL x 3). The dichloromethane layer was dried over anhydrous sodium sulfate, filtered to afford Compound **345B**/dichloromethane solution. The solution of Compound **345B** in dichloromethane was directly used for the next step without further purification.

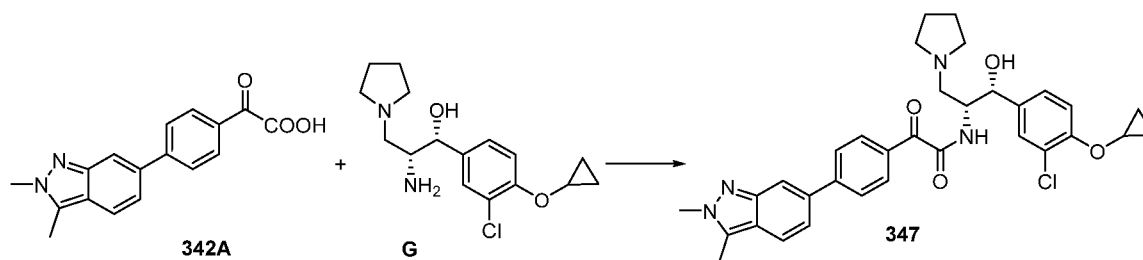
[0001224] To a solution of Compound **345B** in dichloromethane (15 mL, from previous step) and DMF (3 mL) was added Intermediate **C** (155 mg, 0.5 mmol) and HATU (380 mg, 1 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to furnish Compound **345**. LC-MS (ESI) m/z: 586 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.49-1.51 (m, 6H), 1.88-1.89 (m, 2H), 2.02-2.03 (m, 2H), 3.12-3.21 (m, 2H), 3.60-3.62 (m, 4H), 4.25-4.29 (m, 4H), 4.50-4.54 (m, 1H), 4.79 (s, 1H), 4.90-4.97 (m, 1H), 6.04 (s, 1H), 6.52-6.52 (m, 1H), 6.78 (s, 1H), 6.82-6.85 (m, 1H), 7.43-7.45 (m, 1H), 7.61-7.62 (m, 1H), 7.66-7.68 (m, 1H), 7.88-7.94 (m, 5H), 8.74-8.76 (m, 1H), 9.32 (brs, 1H).

Example 346



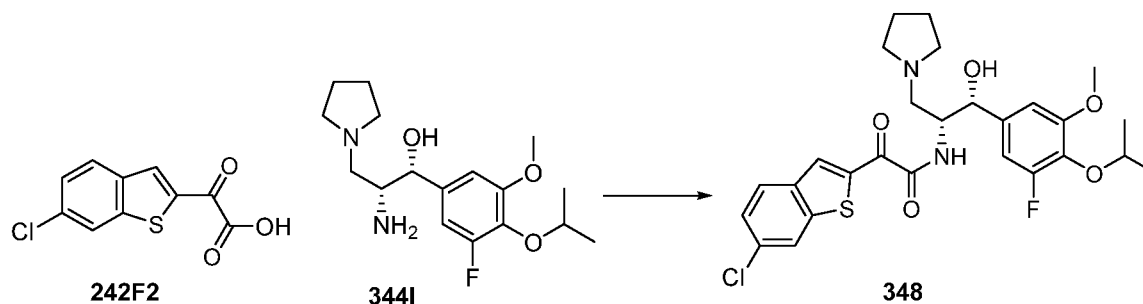
[0001225] To a solution of Compound **346B** in dichloromethane (15 mL, from the previous step) was added Intermediate **G** (155 mg, 0.5 mmol) and HATU (380 mg, 1 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated and the resulting residue was purified with prep-HPLC to furnish Compound **346**. LC-MS (ESI) m/z: 600 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.82-0.83 (m, 2H), 1.49-1.52 (m, 6H), 1.89-1.90 (m, 2H), 2.03-2.04 (m, 2H), 3.13-3.22 (m, 2H), 3.55-3.59 (m, 4H), 3.94-3.98 (m, 1H), 4.57-4.62 (m, 1H), 4.91-4.95 (m, 2H), 6.06-6.07 (m, 1H), 6.52-6.53 (m, 1H), 7.36-7.46 (m, 4H), 7.62-7.73 (m, 4H), 7.84-7.86 (m, 2H), 7.92 (s, 1H), 8.82-8.84 (m, 1H), 9.52 (brs, 1H).

Example 347



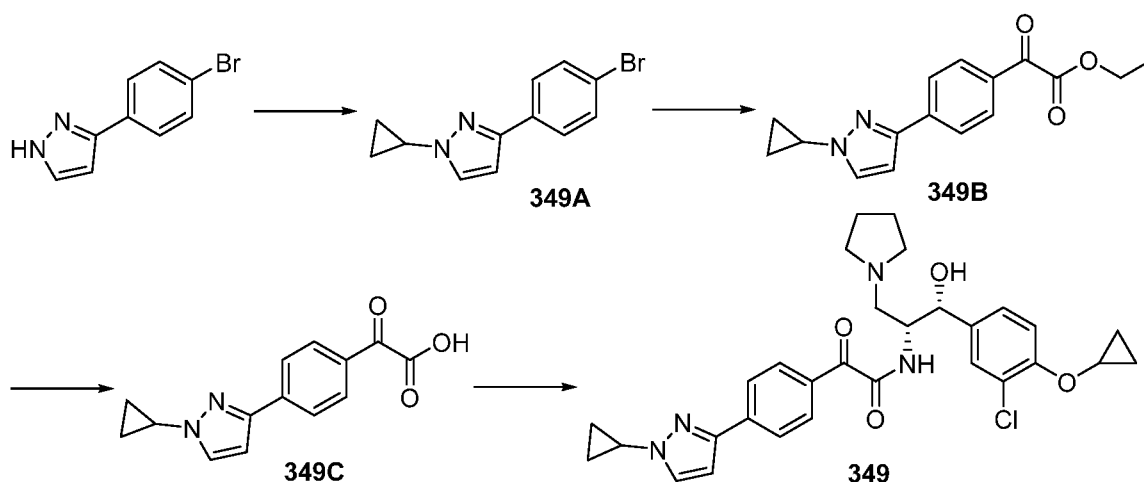
[0001226] A mixture of Compound **342A** (70 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), DIPEA (0.04 mL, 0.24 mmol), and Intermediate **G** (75 mg, 0.24 mmol) in DMF (5 mL) was stirred at 25 °C for 2 h. The mixture was directly purified with prep-HPLC to furnish Compound **347**. LC-MS (ESI) m/z : 587 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 0.68-0.85 (m, 4H), 1.89-2.04 (m, 4H), 2.65 (s, 3H), 3.11-3.24 (m, 2H), 3.47-3.57 (m, 4H), 3.92-3.97 (m, 1H), 4.09 (s, 3H), 4.56-4.60 (m, 1H), 4.88 (s, 1H), 7.35-7.39 (m, 2H), 7.42-7.46 (m, 2H), 7.75-7.84 (m, 5H), 7.89 (s, 1H), 8.82 (d, $J = 9.6$ Hz, 1H), 9.34 (brs, 1H).

Example 348



[0001227] A mixture of Compound **344I** (72 mg, 0.22 mmol), Compound **242F** (48 mg, 0.20 mmol), and HATU (91 mg, 0.24 mmol) in DMF (4 mL) was stirred at 20 °C for 15 h. It was purified with prep-HPLC to give Compound **348**. LC-MS (ESI) m/z : 549 $[M+H]^+$; $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$, 400 MHz): δ (ppm) 1.34 (dd, $J_1 = 15.2$ Hz, $J_2 = 10.4$ Hz, 6H), 2.22 (s, 2H), 2.97 (s, 3H), 3.45 (s, 2H), 3.78-3.81 (m, 4H), 3.95 (s, 3H), 4.23-4.29 (m, 1H), 4.86 (s, 1H), 5.17 (s, 1H), 6.86 (dd, $J_1 = 10.8$ Hz, $J_2 = 1.6$ Hz, 1H), 6.98 (s, 1H), 7.51 (dd, $J_1 = 8.8$ Hz, $J_2 = 2$ Hz, 1H), 8.09-8.17 (m, 3H), 8.60 (s, 1H), 9.83 (brs, 1H).

Example 349



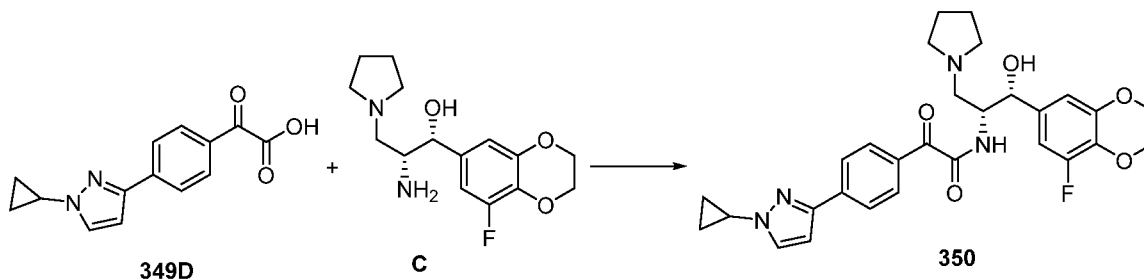
[0001228] A mixture of 3-(4-bromophenyl)-1H-pyrazole (1.0 g, 4.5 mmol), cyclopropylboronic acid (0.8 g, 9 mmol), $\text{Cu}(\text{OAc})_2$ (1.6 g, 9 mmol), Na_2CO_3 (0.9 g, 9 mmol), bipyridine (1.4 g, 9 mmol), and 4 Å molecular sieve powder (5 g) in 1,2-dichloroethane (20 mL) was stirred at 30 °C for 72 h. After filtration, the mixture was diluted with dichloromethane (50 mL), washed with water (30 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound **349A**.

[0001229] To a solution of Compound **349A** (342 mg, 1.3 mmol) in dry THF (10 mL) was added n-BuLi (2.5 N in hexane, 0.6 mL, 1.5 mmol) under nitrogen at -78 °C. The resulting solution was stirred at -78 °C for 30 min and transferred into a stirred solution of diethyl oxalate (0.97 g, 6.6 mmol) in dry THF (5 mL) at this temperature. The solution was stirred at -78 °C for 1 h, quenched with addition of saturated aqueous ammonium chloride solution (10 mL), poured into water (50 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give Compound 349B, which was used for the next step without further purification.

[0001230] A mixture of Compound **349B** (0.26 g, 0.9 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (77 mg, 1.8 mmol) in THF (5 mL) and water (2 mL) was stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to afford Compound **349C**.

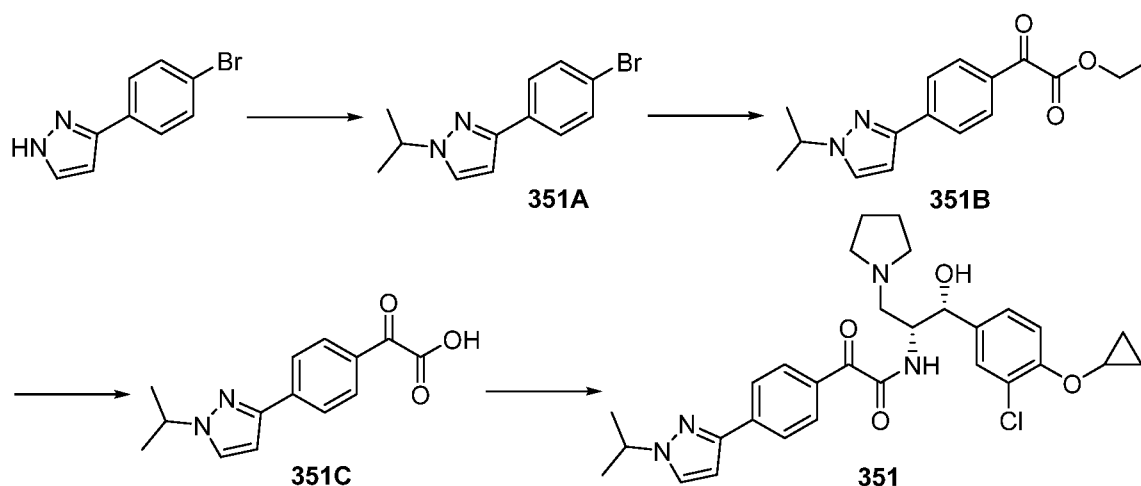
[0001231] A mixture of Compound **349D** (77 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate G (93 mg, 0.3 mmol) in dichloromethane (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude compound. The crude product was purified with prep-HPLC to furnish Compound **349**. LC-MS (ESI) m/z : 549 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.69-0.71 (m, 2H), 0.83-0.84 (m, 2H), 1.01-1.03 (m, 2H), 1.11-1.12 (m, 2H), 1.88-1.89 (m, 2H), 2.02-2.04 (m, 2H), 3.12-3.21 (m, 2H), 3.48-3.55 (m, 4H), 3.77-3.84 (m, 1H), 3.92-3.97 (m, 1H), 4.57 (s, 1H), 4.87 (s, 1H), 6.01-6.10 (m, 1H), 6.82-6.83 (m, 1H), 7.35-7.45 (m, 3H), 7.72-7.74 (m, 2H), 7.87-7.91 (m, 3H), 8.77 (d, $J = 10$ Hz, 1H), 9.32 (s, 1H).

Example 350



[0001232] A mixture of Compound **349D** (77 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate C (89 mg, 0.3 mmol) in dichloromethane (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude compound. The crude product was purified with prep-HPLC to furnish Compound **350**. LC-MS (ESI) m/z : 535 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.01-1.03 (m, 2H), 1.10-1.11 (m, 2H), 1.87-1.88 (m, 2H), 2.02-2.03 (m, 2H), 3.10-3.20 (m, 2H), 3.43-3.45 (m, 2H), 3.53-3.56 (m, 2H), 3.78-3.83 (m, 1H), 4.27-4.30 (m, 4H), 4.51-4.53 (m, 1H), 4.77 (s, 1H), 6.76-6.85 (m, 3H), 7.83-7.85 (m, 2H), 7.90-7.93 (m, 3H), 8.73 (d, $J = 9.6$ Hz, 1H), 9.29 (s, 1H).

Example 351



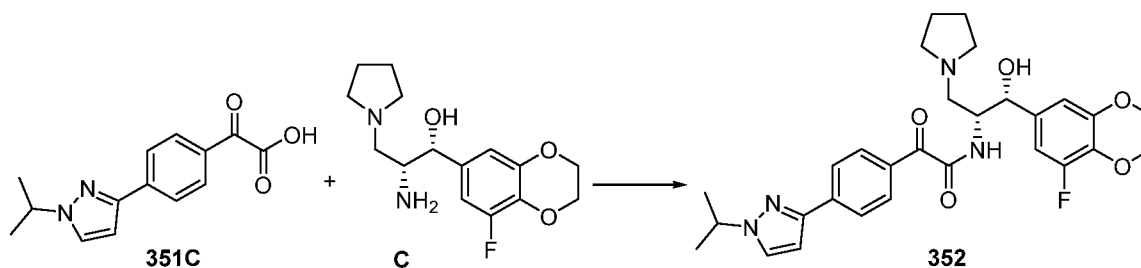
[0001233] To a solution of 3-(4-bromophenyl)-1H-pyrazole (1.0 g, 4.5 mmol) in DMF (20 mL) was added NaH (198 mg, 5 mmol). The mixture was stirred at 25 °C for 0.5 h and 2-iodopropane (1.53 g, 9 mmol) was added. The mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to afford Compound **351A**.

[0001234] To a solution of Compound **351A** (343 mg, 1.3 mmol) in dry THF (10 mL) was added n-BuLi (2.5 N in hexane, 0.6 mL, 1.5 mmol) under nitrogen at -78 °C. The resulting solution was stirred at -78 °C for 30 min and transferred into a stirred solution of diethyl oxalate (0.97 g, 6.6 mmol) in dry THF (5 mL) at this temperature. The solution was stirred at -78 °C for 1 h, quenched with addition of saturated aqueous ammonium chloride solution (10 mL), poured into water (50 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give Compound **351B**, which was used for the next step without further purification.

[0001235] A mixture of Compound **351B** (0.27 g, 0.9 mmol) and LiOH·H₂O (77 mg, 1.8 mmol) in THF (5 mL) and water (2 mL) was stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to afford Compound **351C**.

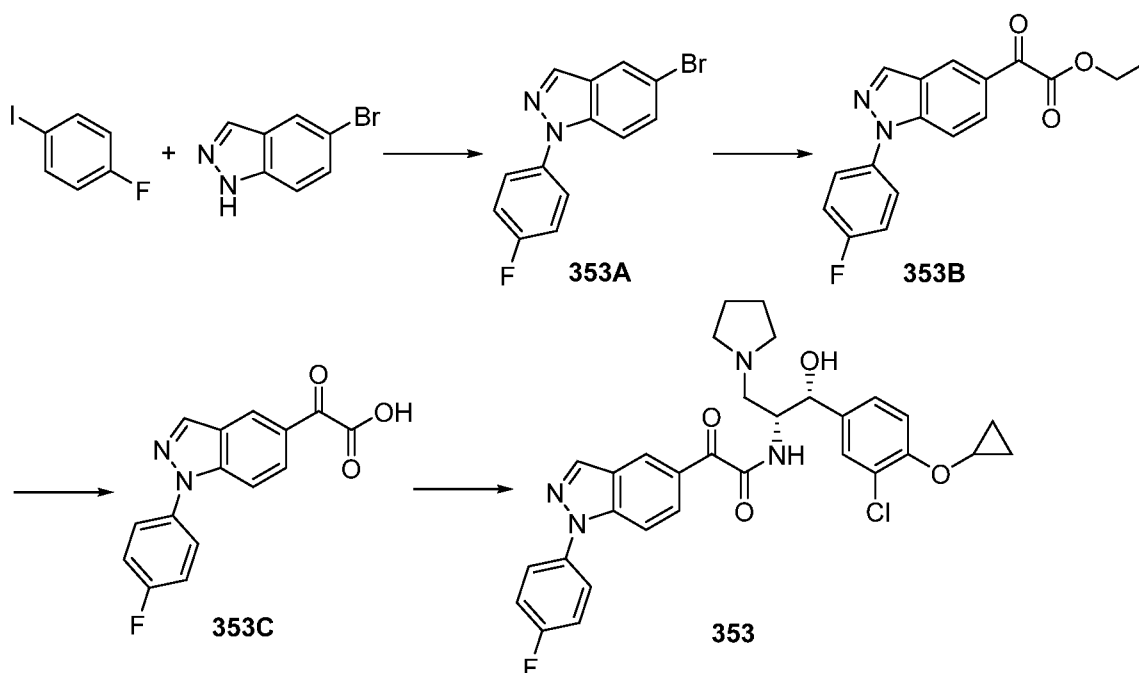
[0001236] A mixture of Compound **351C** (77 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate **G** (93 mg, 0.3 mmol) in dichloromethane (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude compound. The crude product was purified with prep-HPLC to furnish Compound **351**. LC-MS (ESI) m/z : 551 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.70-0.71 (m, 2H), 0.83-0.84 (m, 2H), 1.47 (s, 3H), 1.48 (s, 3H), 1.89-1.90 (m, 2H), 2.04-2.05 (m, 2H), 3.12-3.21 (m, 2H), 3.48-3.51 (m, 4H), 3.94 (s, 1H), 4.56-4.58 (m, 2H), 4.88 (s, 1H), 6.05-6.07 (m, 1H), 6.82-6.83 (m, 1H), 7.35-7.45 (m, 3H), 7.71-7.73 (m, 2H), 7.88-7.90 (m, 3H), 8.78 (d, $J = 9.2$ Hz, 1H), 9.41 (s, 1H).

Example 352



[0001237] A mixture of Compound **351C** (77 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate **C** (89 mg, 0.3 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude compound. The crude product was purified with prep-HPLC to furnish Compound **352**. LC-MS (ESI) m/z : 537 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.47 (s, 3H), 1.48 (s, 3H), 1.87-1.88 (m, 2H), 2.02-2.03 (m, 2H), 3.12-3.21 (m, 2H), 3.43-3.45 (m, 2H), 3.54-3.56 (m, 2H), 4.27-4.30 (m, 4H), 4.52-4.58 (m, 2H), 4.78 (s, 1H), 6.77-6.85 (m, 3H), 7.83-7.85 (m, 2H), 7.90-7.94 (m, 3H), 8.74 (d, $J = 9.6$ Hz, 1H), 9.29 (s, 1H).

Example 353



[0001238] A mixture of 1-fluoro-4-iodobenzene (5 g, 23 mmol), 5-bromo-1H-indazole (4.4 g, 23 mmol), CuI (428 mg, 2.3 mmol), L-proline (518 mg, 4.5 mmol), and K_3PO_4 (9.55 g, 45 mmol) in 1,4-dioxane (200 mL) was stirred under nitrogen at reflux for 24 h. The resulting mixture was cooled to room temperature. The mixture was treated with water (200 mL), extracted with ethyl acetate (100 mL x 2), washed with sat. sodium bicarbonate (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **353A**.

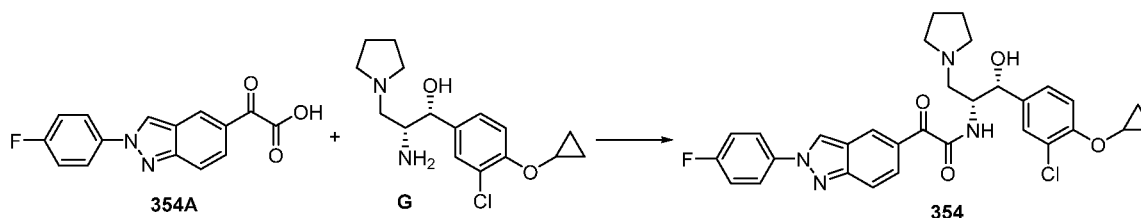
[0001239] To a solution of Compound **353A** (650 mg, 2.2 mmol) in THF (50 mL) was added dropwise n-BuLi (1.1 mL, 2.7 mmol) under nitrogen at $-78^\circ C$. The resulting mixture was stirred at $-78^\circ C$ for 15 min. To the resulting mixture was added diethyl oxalate (1.6 g, 11.2 mmol) as soon as a quickly. The mixture was stirred at $-78^\circ C$ for 1 h, quenched with sat. ammonium chloride solution, treated with water (50 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **353B**.

[0001240] To a solution of Compound **353B** (130 mg, 0.42 mmol) in THF (5 mL) was added dropwise $LiOH \cdot H_2O$ (35 mg, 0.83 mmol) in water (2 mL) at $-20^\circ C$. The resulting mixture was stirred at $-20^\circ C$ for 1 h. The mixture was adjusted pH to 1 with diluted HCl. The

resulting mixture was extracted with ethyl acetate (50 mL x 2), and then the organic layer was dried over anhydrous sodium sulfate and concentrated to furnish Compound **353C**.

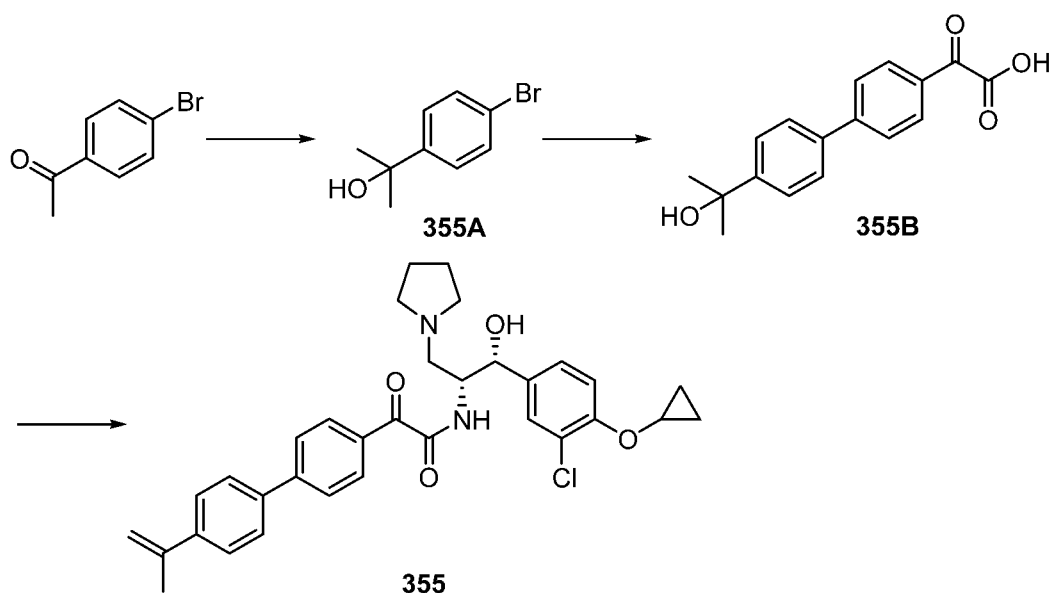
[0001241] A mixture of Compound **353C** (100 mg, 0.35 mmol), Intermediate **353G** (109 mg, 0.35 mmol), and HATU (210 mg, 0.53 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The mixture was treated with water (50 mL), extracted with dichloromethane (20 mL x 2), washed with water (20 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **353**. LC-MS (ESI) m/z : 577 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 0.59-0.81 (m, 4H), 1.86-2.05 (m, 4H), 3.13-3.22 (m, 2H), 3.50-3.57 (m, 4H), 3.89-3.92 (m, 1H), 4.56-4.62 (m, 1H), 4.89 (s, 1H), 6.05-6.06 (m, 1H), 7.34-7.51 (m, 5H), 7.79-7.85 (m, 4H), 7.43 (s, 1H), 8.56 (s, 1H), 8.01 (d, $J = 9.6$ Hz, 1H), 9.39 (s, 1H).

Example 354



[0001242] A mixture of Compound **354A** (100 mg, 0.35 mmol), Intermediate **G** (109 mg, 0.35 mmol), and HATU (210 mg, 0.53 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The mixture was treated with water (50 mL), extracted with dichloromethane (20 mL x 2), washed with water (20 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **354**. LC-MS (ESI) m/z : 577 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.61-0.79 (m, 4H), 1.86-2.02 (m, 4H), 3.11-3.18 (m, 2H), 3.45-3.53 (m, 4H), 3.85-3.89 (m, 1H), 4.45-4.50 (m, 1H), 4.81 (s, 1H), 6.01 (s, 1H), 6.93 (d, $J = 9.2$ Hz, 1H), 7.25-7.39 (m, 7H), 7.73-7.76 (m, 1H), 8.27-8.28 (d, $J = 2.0$ Hz, 1H), 8.63 (d, $J = 9.6$ Hz, 1H), 9.21 (s, 1H), 9.30 (s, 1H).

Example 355



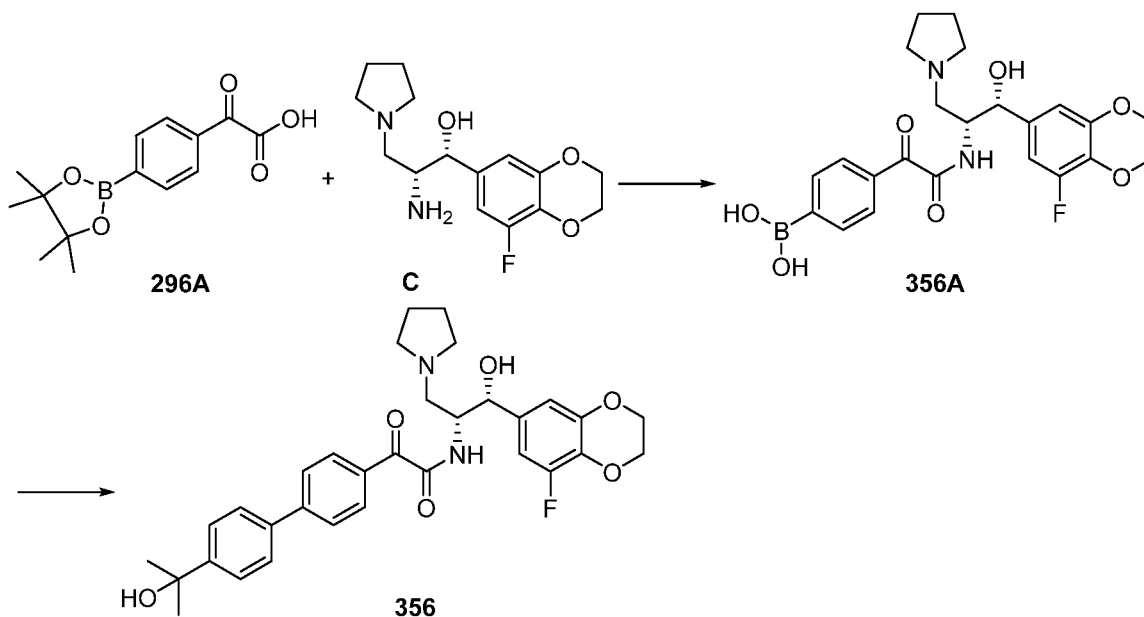
[0001243] A mixture of 1-(4-bromophenyl)ethan-1-one (2.0 g, 10 mmol) in tetrahydrofuran (30 mL) was maintained at -70°C , and methylmagnesium bromide (3 M, 6.7 mL) was added at -70°C . The reaction mixture was stirred at -78°C for 0.5 h. The reaction mixture was treated with water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The remaining residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 25% v/v) to furnish Compound **355A**.

[0001244] A mixture of Compound **175B** (616 mg, 2 mmol), Compound **355A** (428 mg, 2 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (168 mg, 0.2 mol), sodium carbonate (424 mg, 4 mmol), water (0.5 mL), and 1,4-dioxane (5 mL) was stirred under nitrogen atmosphere at 80°C for 2 h. After cooling, the reaction mixture was treated with water (30 mL), washed with ethyl acetate (30 mL x 3), adjusted pH to 2.0 with hydrochloric acid (1 M), extracted with ethyl acetate (20 mL x 3), washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **355B**.

[0001245] A mixture of Compound **355B** (100 mg, 0.35 mmol), Intermediate **G** (108 mg, 0.35 mmol), and HATU (266 mg, 0.70 mmol) in DMF (3.5 mL) was stirred at 25°C for 2 h. The mixture was purified with prep-HPLC directly to furnish Compound **355**. LC-MS (ESI) m/z : 559 $[\text{M}+\text{H}]^{+}$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.68-0.76 (m, 2H), 0.77-0.88 (m, 2H), 1.68-1.92 (m, 1H), 2.07-2.21 (m, 2H), 2.22 (s, 3H), 2.23-2.28 (m, 1H), 3.33-3.50 (m, 2H), 3.76-3.97 (m, 6H), 4.84-4.90 (m, 1H), 5.18-5.26 (m, 2H), 5.53 (s, 1H), 7.28-7.43 (m,

2H), 7.45-7.57 (m, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.75-7.81 (m, 4H), 7.92-8.01 (m, 2H), 8.21 (d, $J = 6.0$ Hz, 1H), 10.84 (brs, 1H).

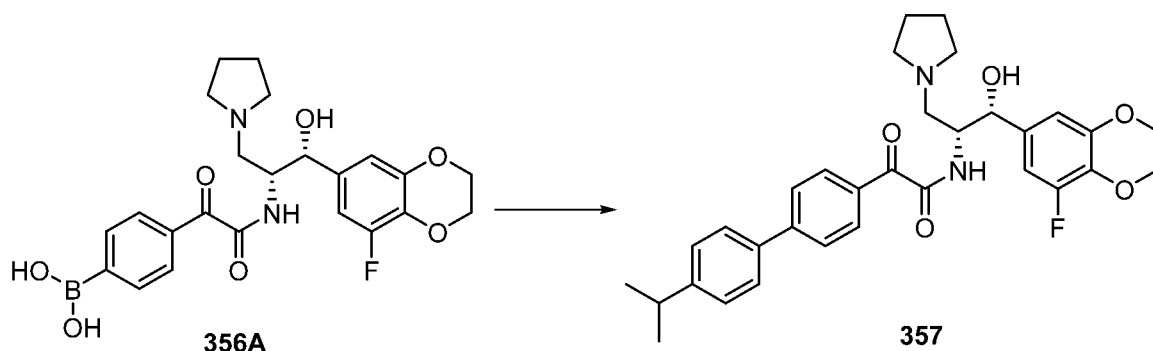
Example 356



[0001246] A mixture of Compound **296A** (150 mg, 0.54 mmol), Intermediate **C** (175 mg, 0.59 mmol), and HATU (308 mg, 0.81 mmol) in dichloromethane (5 mL) was stirred at 25 °C overnight. The mixture was quenched with water (10 mL), extracted with dichloromethane (5 mL x 2), washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with prep-HPLC to furnish Compound **356A**.

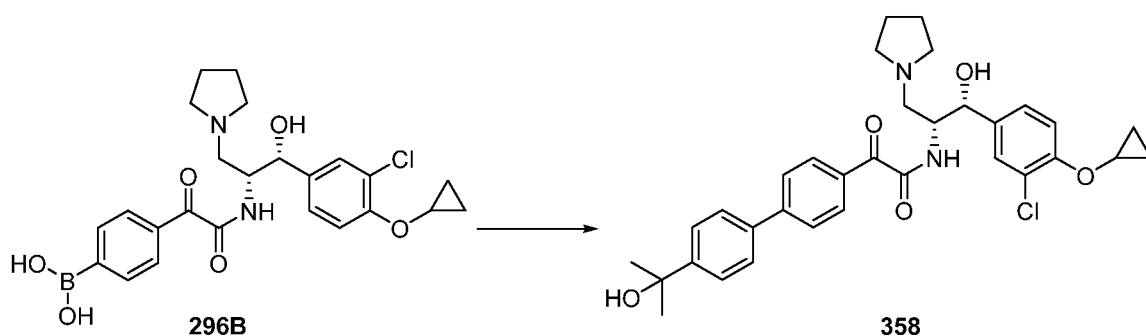
[0001247] A mixture of 2-(4-bromophenyl)propan-2-ol (34 mg, 0.15 mmol), Compound **356A** (75 mg, 0.15 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7 mg, 8.2 μmol), sodium carbonate (44 mg, 0.30 mmol), water (0.5 mL), and 1,4-dioxane (5 mL) was stirred under nitrogen atmosphere at 80 °C for 2 h. After cooling, the reaction mixture was treated with water (5 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC. The solution was adjusted to pH = 8.0 with sodium bicarbonate solution, extracted with ethyl acetate (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **356**. LC-MS (ESI) m/z : 563 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.42-1.75 (m, 6H), 1.79-1.86 (m, 4H), 2.74-2.81 (m, 4H), 2.96-3.04 (m, 2H), 4.24-4.31 (m, 6H), 5.05 (d, $J = 2.4$ Hz, 1H), 6.70-6.76 (m, 2H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.75-7.64 (m, 5H), 7.68 (d, $J = 9.2$ Hz, 2H), 8.31 (d, $J = 8.8$ Hz, 2H).

Example 357



[0001248] A mixture of 1-bromo-4-isopropylbenzene (30 mg, 0.15 mmol), Compound **356A** (75 mg, 0.15 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7 mg, 8.2 μmol), sodium carbonate (32 mg, 0.30 mmol), water (0.5 mL), and 1,4-dioxane (5 mL) was stirred under nitrogen atmosphere at 80 °C for 2 h. After cooling, the reaction mixture was treated with water (5 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC to furnish Compound **357**. LC-MS (ESI) m/z : 547 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$, 400 MHz): δ (ppm) 1.64 (m, 6H), 2.08-2.11 (m, 3H), 2.17-2.23 (m, 1H), 2.96-3.043 (m, 4H), 3.17-3.82 (m, 4H), 4.21-4.33 (m, 3H), 4.37 (d, 1H), 4.69-5.75 (m, 2H), 6.85-7.07 (m, 2H), 7.35-7.43 (m, 2H), 7.46-7.79 (m, 3H), 7.81-7.87 (m, 1H), 7.89-7.98 (m, 1H), 8.02-8.14 (m, 1H).

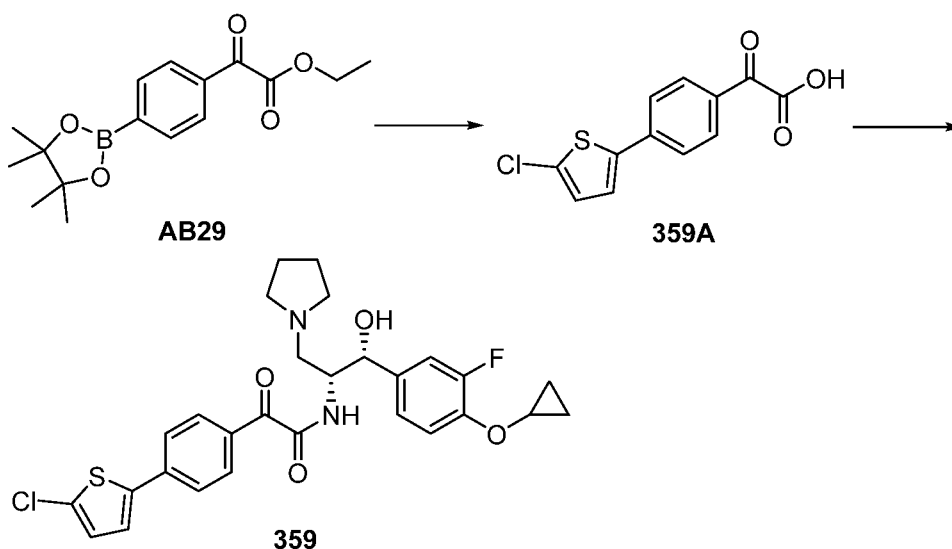
Example 358



[0001250] A mixture of 2-(4-bromophenyl)propan-2-ol (49 mg, 0.23 mmol), Compound **296B** (110 mg, 0.23 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (8.4 mg, 10 μmol), potassium carbonate (49 mg, 0.46 mmol), water (1 mL), and 1,4-dioxane (5 mL) was heated under nitrogen atmosphere at 100 °C for 2 h. After cooling, water (5 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a black

oil. The oil was purified with prep-HPLC. The solution was adjusted to pH = 8.0 with sodium bicarbonate solution, extracted with ethyl acetate (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **358**. LC-MS (ESI) m/z : 577 $[M+H]^+$; 1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.76-0.88 (m, 4H), 1.23-1.30 (m, 1H), 1.63 (s, 6H), 1.83-1.88 (m, 4H), 2.01 (s, 1H), 2.73-2.81 (m, 5H), 2.97-3.03 (m, 2H), 3.74-3.79 (m, 1H), 4.33 (d, $J = 4.4$ Hz, 1H), 5.11 (d, $J = 2.4$ Hz, 1H), 7.21-7.28 (m, 1H), 7.35-7.51 (m, 3H), 7.57-7.63 (m, 4H), 7.68 (d, $J = 7.2$ Hz, 2H), 8.26 (d, $J = 8.8$ Hz, 1H).

Example 359

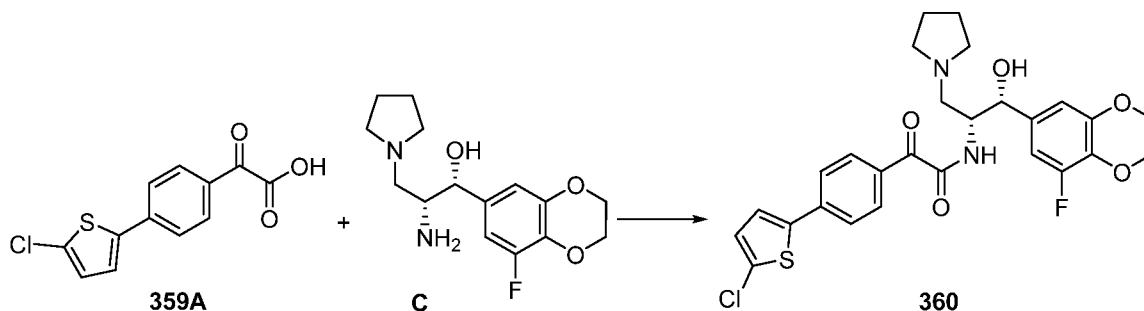


[0001251] To a stirred solution of Compound **175B** (1.29 g, 4.24 mmol) in DMF (20 mL) and water (20 mL) was added Na_2CO_3 (1.12 g, 10.6 mmol), $Pd(PPh_3)_4$ (247 mg, 0.21 mmol), and 2-bromo-5-chlorothiophene (838 mg, 4.24 mmol). The mixture was stirred under nitrogen at 90 °C for 16 h. The reaction mixture was cooled to room temperature and purified with reverse phase chromatography using eluent (methanol in water (include 0.05% of $NH_3 \cdot H_2O$), from 0% to 40% v/v) to afford Compound **359A**.

[0001252] To a solution of Intermediate **S** (55 mg, 0.22 mmol) in dichloromethane (10 mL) was added Compound **359A** (50 mg, 0.18 mmol) and HATU (107 mg, 0.28 mmol). The mixture was stirred under nitrogen at room temperature overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **359**. LC-MS (ESI) m/z : 543 $[M+H]^+$; 1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.79-0.81 (m, 2H), 1.87-1.90 (m, 2H), 2.02-2.04 (m, 2H), 3.12-3.18 (m, 2H), 3.45-3.55

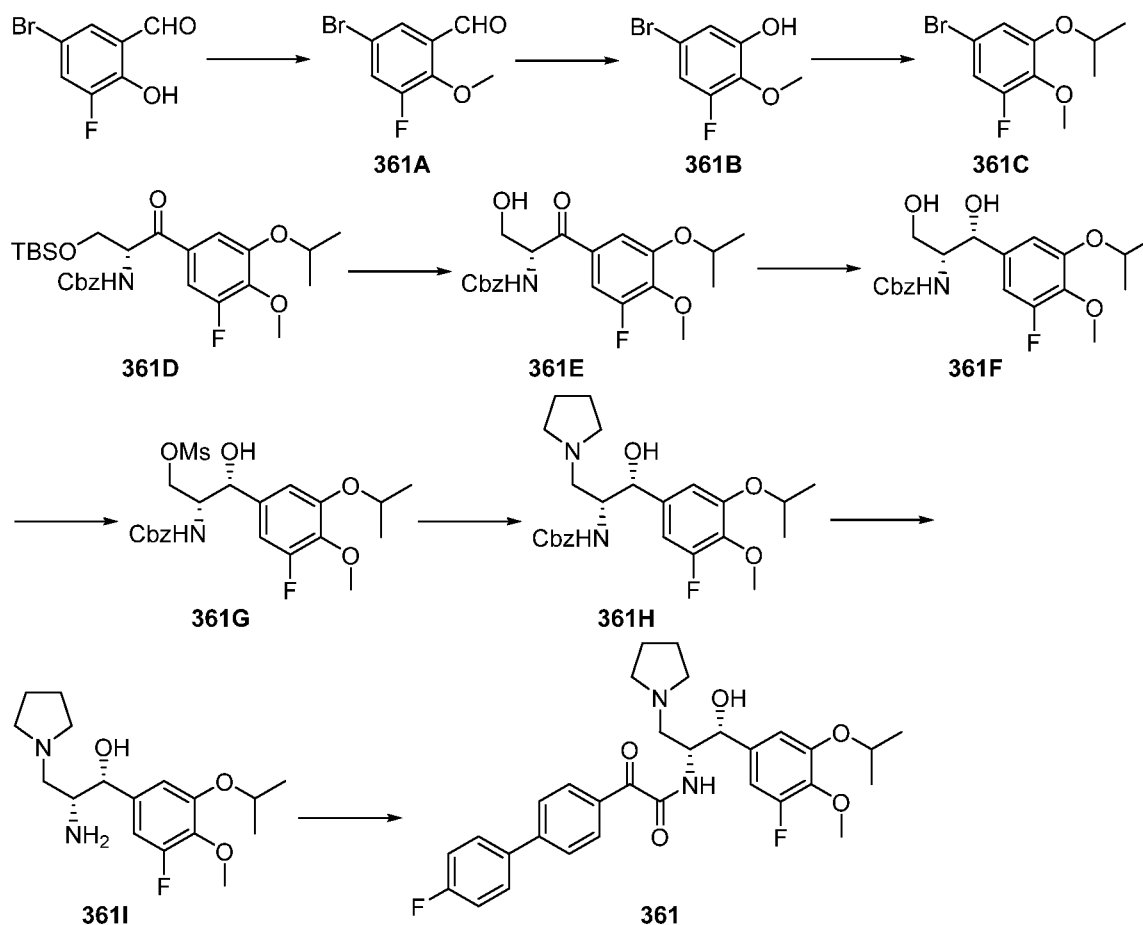
(m, 4H), 3.92-3.95 (m, 1H), 4.51-4.53 (m, 1H), 4.85 (d, $J = 2.4$ Hz, 1H), 6.05 (d, $J = 4.4$ Hz, 1H), 7.19 (t, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 4.0$ Hz, 1H), 7.39 (t, $J = 8.8$ Hz, 1H), 7.63 (d, $J = 4.0$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 9.6$ Hz, 1H), 9.31 (s, 1H).

Example 360



[0001253] To a solution of Intermediate **C** (100 mg, 0.34 mmol) in dichloromethane (10 mL) was added Compound **359A** (75 mg, 0.28 mmol) and HATU (160 mg, 0.42 mmol). The mixture was stirred under nitrogen at room temperature overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **360**. LC-MS (ESI) m/z : 545 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.86-1.88 (m, 2H), 2.01-2.04 (m, 2H), 3.11-3.18 (m, 2H), 3.52-3.54 (m, 4H), 4.28-4.29 (m, 4H), 4.48-4.50 (m, 1H), 4.76 (s, 1H), 6.03 (s, 1H), 6.75 (s, 1H), 6.81 (d, $J = 11.6$ Hz, 1H), 7.27 (d, $J = 2.0$ Hz, 1H), 7.65 (d, $J = 3.6$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.87 (d, $J = 8.4$ Hz, 2H), 8.73 (d, $J = 9.6$ Hz, 1H), 9.28 (s, 1H).

Example 361



[0001255] To a mixture of 5-bromo-3-fluoro-2-hydroxybenzaldehyde (21 g, 97 mol) and K_2CO_3 (20 g, 145 mmol) in DMF (200 mL) was added iodomethane (16.3 g, 115 mmol). The mixture was stirred at room temperature overnight. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (400 mL x 3). The organic layer was washed with water (500 mL x 3) and brine (200 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **361A**.

[0001256] A mixture of Compound **361A** (15.6 g, 66.9 mmol) and *m*-chloroperoxybenzoic acid (23 g, 133.9 mmol) in methylene chloride (200 mL) was stirred at 40 °C overnight. The mixture was filtered and the precipitate was washed with methylene chloride. The combined filtrate and washing were washed with aq. sodium bicarbonate (100 mL x 3) and brine (100 mL) and concentrated to give a yellow oil. The crude Compound was dissolved in MeOH (300 mL). A solution of 33% NaOH (30 mL) was added with cooling. After stirring for 2 h at room temperature, the mixture was acidified with concentrated HCl and extracted with ethyl acetate (200 mL x 2). The extract was washed with aqueous sodium

bicarbonate (100 mL x 3), dried over anhydrous sodium sulfate, and concentrated to give the crude Compound **361B**.

[0001257] To a mixture of Compound **361B** (10.3 g, 46.6 mmol) and K_2CO_3 (12.9 g, 93.2 mmol) in DMF (100 mL) was added 2-bromopropane (11.5 g, 93.2 mmol). The mixture was stirred at 80 °C overnight. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (200 mL x 2). The organic layer was washed with water (300 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 5% v/v) to give Compound **361C**.

[0001258] To a solution of Compound **361C** (8.43 g, 32 mmol) in THF (100 mL) was added n-BuLi (2.4 M, 13.2 mL, 33.1 mmol) under nitrogen at -78 °C. It was stirred at -78 °C for 10 min. A solution of Compound **A4** (4.2 g, 10.68 mmol) in THF (10 mL) was added. The mixture was stirred at -78 °C for 0.5 h, quenched with saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (200 mL), washed with brine (100 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **361D**.

[0001259] A solution of Compound **361D** (5 g, 9.62 mmol) in THF (25 mL), water (25 mL), and acetic acid (75 mL) was stirred at 35 °C overnight. The solvent was removed with evaporation under reduced pressure and the residue was diluted with water (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to yield Compound **361E**.

[0001260] To a solution of Compound **361E** (1.6 g, 3.95 mmol) in dry THF (70 mL) was added DIBAL-H (1 M, 15.8 mL, 15.8 mmol) slowly dropwise under nitrogen at -78 °C. It was stirred at -78 °C for 1 h. A solution of HCl (2 M, 20 mL) was added to quench the reaction. It was extracted with ethyl acetate (50 mL), washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude product. It was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **361F**.

[0001261] To a solution of Compound **361F** (1.44 g, 3.53 mmol) and triethylamine (1.07 g, 10.6 mmol) in dichloromethane (30 mL) was added MsCl (445 mg, 3.89 mmol) at -30 °C and the resultant mixture was stirred at -30 °C for 1 h. It was treated with water (100 mL) and

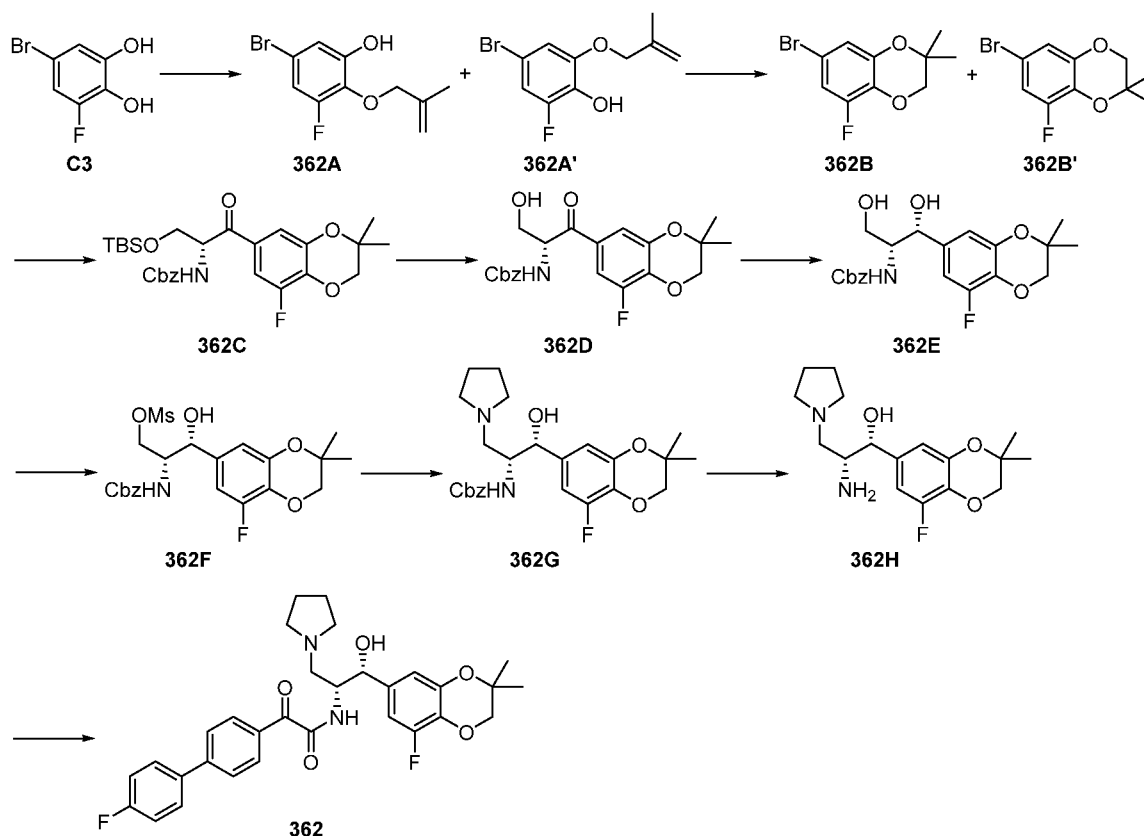
dichloromethane (100 mL). The organic layer was washed with water (40 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to furnish Compound **361G**.

[0001262] To a solution of Compound **361G** (1.71 g, 3.6 mmol) in THF (40 mL) was added pyrrolidine (2.61 g, 36 mmol). The mixture was stirred at 50 °C overnight. It was treated with water (100 mL), extracted with ethyl acetate (100 mL x 3), washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated in *vacuo* to give a crude product. It was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **361H**.

[0001263] To a solution of Compound **361H** (1.25 g, 2.71 mmol) in ethanol (24 mL) was added LiOH·H₂O (456 mg, 10.86 mmol). The solution was stirred at 80 °C overnight. The mixture was diluted with ethyl acetate (100 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to yield the crude Compound **361I**.

[0001264] A mixture of Compound **361I** (100 mg, 0.306 mmol), Intermediate C (69 mg, 0.306 mmol), and HATU (174 mg, 0.459 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (50 mL), washed with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to give Compound **361**. LC-MS (ESI) m/z: 553 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.17 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.87-1.93 (m, 2H), 2.01-2.05 (m, 2H), 3.11-3.24 (m, 2H), 3.45-3.57 (m, 4H), 3.77 (s, 3H), 4.49-4.57 (m, 2H), 4.84-4.85 (m, 1H), 6.09 (d, *J* = 4.0 Hz, 1H), 6.85 (d, *J* = 11.6 Hz, 1H), 6.89 (s, 1H), 7.38 (t, *J* = 8.8 Hz, 2H), 7.78-7.87 (m, 6H), 8.77 (d, *J* = 10.0 Hz, 1H), 9.38 (brs, 1H).

Example 362



[0001265] To a mixture of Compound C3 (31 g, 150 mol) and Li_2CO_3 (22.4 g, 310 mol) in DMF (250 mL) was added 3-bromo-2-methylprop-1-ene (31.9 mL, 310 mol). The mixture was stirred at 55 °C for 48 h, cooled down to room temperature, and filtered. The cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (500 mL) and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with saturated aqueous LiCl solution (100 mL x 5), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel on silica gel (ethyl acetate in petroleum ether, 5% v/v) to give a mixture of Compound 362A and Compound 362A'.

[0001266] A solution of Compound 362A and Compound 362A' (23 g, 88.5 mmol) in formic acid (200 mL) was stirred and heated to reflux for 2 h. After removal of the solvent, the residue was diluted with dichloromethane (200 mL). The mixture was carefully adjusted pH to 9 with saturated aqueous sodium bicarbonate solution at 0 °C and extracted with dichloromethane (100 mL x 3). The combined organic phases were washed with water (50 mL x 2) and brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with flash column

chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish a mixture of Compound **362B** and Compound **362B'**.

[0001267] To a solution of Compound **362B** and Compound **362B'** (3.8 g, 14.6 mmol) in dry THF (80 mL) maintained at -60 °C was dropwise added n-BuLi (2.5 M in hexane, 6.0 mL, 15.1 mmol) under nitrogen atmosphere over a period of 20 minutes. After the reaction mixture was stirred at -60 °C for 40 minutes, a solution of Compound **A4** (1.93 g, 4.87 mmol) in dry THF (20 mL) was added slowly. After the completion of addition, the solution was left to stir for 0.5 h at -60 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (100 mL x 3). The organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 10% v/v) to yield Compound **362C**.

[0001268] A solution of Compound **362C** (1.1 g, 2.13 mmol) in a mixture of tetrahydrofuran, water, and glacial acetic acid (25 mL, 1/1/3 v/v/v) was stirred at 35 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove excess solvent. The residue was poured into ethyl acetate (50 mL) and water (20 mL). The mixture was adjusted to pH 7-8 with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound. The crude product was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **362D**.

[0001269] To a solution of Compound **362D** (690 mg, 1.71 mmol) in dry THF (20 mL) maintained at -78 °C was added diisobutylaluminum hydride (1.0 M in toluene, 6.85 mL) dropwise under nitrogen atmosphere over a period of 15 minutes. After the reaction mixture was stirred at -70 °C for 1 h, saturated solution of ammonium chloride solution (10 mL) was added to the mixture slowly. The reaction mixture was extracted with ethyl acetate (50 mL x 3), washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude target compound. The crude product was further purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 50% to 87% v/v) to furnish Compound **362E**.

[0001270] To a solution of Compound **362E** (600 mg, 1.48 mmol) dissolved in dry THF (15 mL) was added triethylamine (0.62 mL, 4.44 mmol). The mixture was cooled to -40 °C, and then methanesulfonyl chloride (0.17 mL, 2.22 mmol) was added dropwise. After the

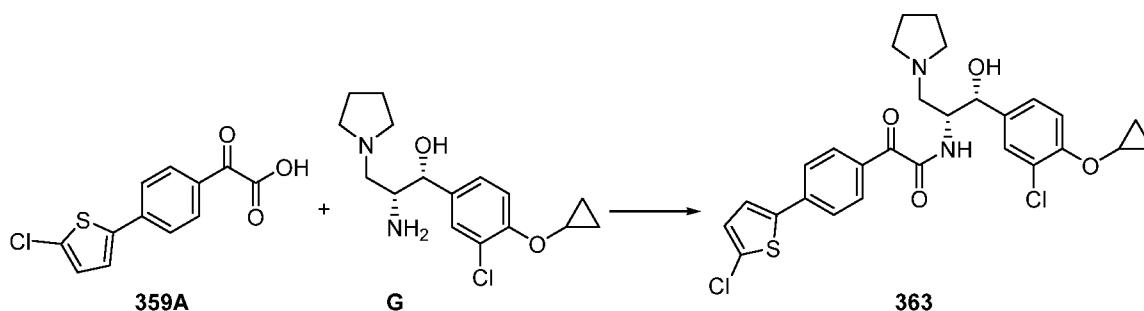
addition was complete, the reaction mixture was stirred at -40 °C for 2 h, diluted with water (30 mL), and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **362F**.

[0001271] To a solution of Compound **362F** (320 mg, 0.66 mmol) in THF (10 mL) was added pyrrolidine (0.55 mL, 6.6 mmol). The reaction mixture was allowed to heat to 50 °C for 16 h. The mixture was diluted with water (10 mL), extracted with ethyl acetate (50 mL x 3), washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 8% v/v) to give Compound **362G**.

[0001272] Compound **362G** (215 mg, 0.47 mmol) was dissolved in methanol (20 mL), and 20% Pd(OH)₂ (45 mg) was added. The mixture was stirred under hydrogen at room temperature overnight. After filtration, the filtrate was evaporated to give the Compound **362H**.

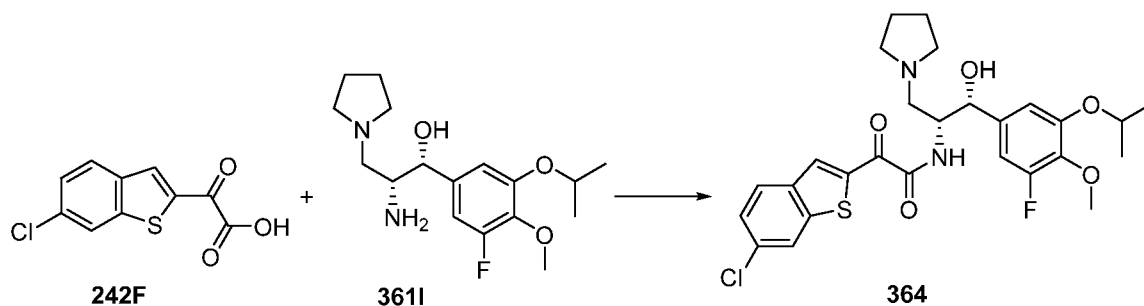
[0001273] To a solution of Compound **362H** (93 mg, 0.29 mmol) in dichloromethane (10 mL) was added Compound **133D** (70 mg, 0.29 mmol) and HATU (164 mg, 0.43 mmol). The mixture was stirred under nitrogen at room temperature overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **362**. LC-MS (ESI) m/z: 551 [M+H]⁺; ¹H-NMR (OMSO-*d*₆, 400 MHz): δ (ppm) 1.23 (s, 3H), 1.28 (s, 3H), 1.88-2.02 (m, 4H), 3.10-3.17 (m, 2H), 3.44-3.54 (m, 4H), 3.98 (s, 2H), 4.50 (s, 1H), 4.77 (s, 1H), 6.01 (d, *J* = 2.8 Hz, 1H), 6.72 (s, 1H), 6.81 (d, *J* = 10.8 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 2H), 7.80-7.92 (m, 6H), 8.73 (d, *J* = 9.2 Hz, 1H), 9.31 (s, 1H).

Example 363



[0001275] To a solution of Intermediate **G** (112 mg, 0.36 mmol) in dichloromethane (10 mL) was added Compound **359A** (80 mg, 0.30 mmol) and HATU (171 mg, 0.45 mmol). The mixture was stirred under nitrogen at room temperature overnight. The resulting mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with prep-HPLC to furnish Compound **363**. LC-MS (ESI) m/z : 559 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.82-0.84 (m, 2H), 1.87-1.91 (m, 2H), 2.02-2.04 (m, 2H), 3.11-3.20 (m, 2H), 3.47-3.55 (m, 4H), 3.92-3.96 (m, 1H), 4.53-4.57 (m, 1H), 4.88 (s, 1H), 6.06 (d, $J = 3.2$ Hz, 1H), 7.27 (d, $J = 4.0$ Hz, 1H), 7.34 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 1.6$ Hz, 1H), 7.62 (d, $J = 4.0$ Hz, 1H), 7.70-7.76 (m, 4H), 8.78 (d, $J = 9.6$ Hz, 1H), 9.48 (s, 1H).

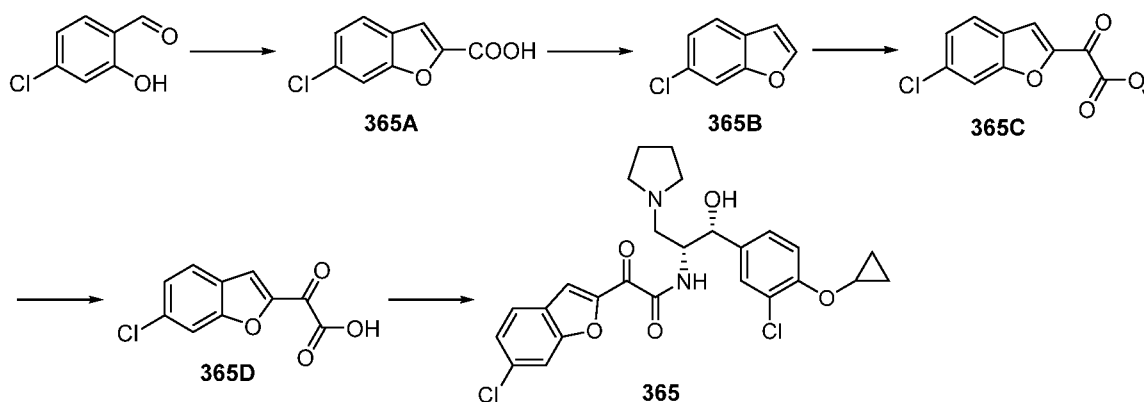
Example 364



[0001276] A mixture of Compound **3611** (100 mg, 0.306 mmol), Compound **242F** (74 mg, 0.306 mmol), and HATU (174 mg, 0.459 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (50 mL), washed with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to give Compound **364**. LC-MS (ESI) m/z : 549 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.17 (d, $J = 6.0$ Hz, 3H), 1.25 (d, $J = 6.0$ Hz, 3H), 1.81-1.88 (m, 2H), 1.98-2.05 (m, 2H), 3.09-3.20 (m, 2H), 3.40-3.57 (m, 4H), 3.71 (s, 3H), 4.44-4.56 (m, 2H), 4.78-4.80 (m, 1H), 6.10 (d, $J = 2.0$ Hz, 1H), 6.80-6.86 (m, 2H),

7.54 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.4$ Hz, 1H), 8.13 (d, $J = 8.8$ Hz, 1H), 8.29 (d, $J = 2.0$ Hz, 1H), 8.55 (s, 1H), 8.60 (d, $J = 9.6$ Hz, 1H), 9.19 (brs, 1H).

Example 365



[0001277] A mixture of 4-chloro-2-hydroxybenzaldehyde (1.56 g, 0.01 mol), diethyl 2-bromomalonate (2.38 g, 0.01 mol), and K_2CO_3 (1.38 g, 0.01 mol) in 2-butanone (80 mL) was refluxed overnight. After completion of the reaction, the resulting mixture was cooled down to room temperature, poured into water, acidified to pH 2 with dilute aqueous sulfuric acid solution (2 *N*), and extracted with ether (40 mL x 3). After removal of the organic solvent, the residue was dissolved in alcoholic potash (prepared from 20 mL of alcohol and 2 g of solid potassium hydroxide) and refluxed for 2 h. The solvent was concentrated and the residue was dissolved in water (20 mL). The aqueous layer was acidified to pH 2 with dilute aqueous sulfuric acid solution (2 *N*) and solid was precipitated. The formed solid were collected with filtration, washed with water (20 mL), and dried to afford Compound **365A**.

[0001278] A solution of Compound **365A** (1.98 g, 10 mmol) and copper powder (0.4 g) were refluxed in quinoline (20 mL) for 2 h. After cooling down to room temperature, the mixture was diluted with ether (80 mL) and washed with diluted aqueous HCl solution (2 *N*, 40 mL x 3). The organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and carefully concentrated at 0 °C to give Compound **365B**.

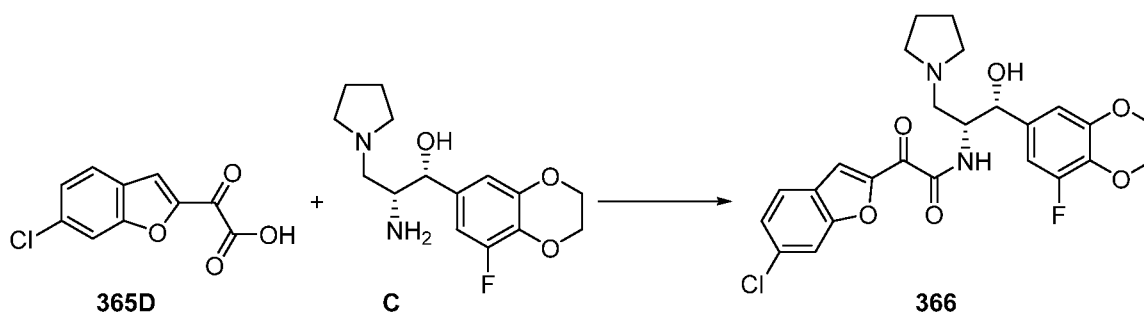
[0001279] To a solution of Compound **365B** (1.53 g, 10 mmol) in THF (30 mL) was added dropwise *n*-BuLi solution (2.5 *M* in hexane, 4 mL, 10 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 0.5 h and the above solution was added to a solution of diethyl oxalate (3 g, 20 mmol) in THF (20 mL) under nitrogen at -78 °C. The mixture was slowly warmed to room temperature and stirred at room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride solution (40 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue

was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish Compound **365C**.

[0001280] To a solution of Compound **365C** (2.4 g, 10 mmol) in THF/H₂O (40 mL/10 mL) was added LiOH·H₂O (840 mg, 20 mmol). The mixture was stirred at room temperature for about 2 h until completion by thin layer chromatography analysis. The reaction mixture was acidified to pH 2 with diluted aqueous HCl solution (1.0 N, 40 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield Compound **365D**.

[0001281] To a mixture of Compound **365D** (112 mg, 0.5 mmol) and Intermediate **G** (155 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with ethyl acetate (50 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC to furnish Compound **365**. LC-MS (ESI) m/z: 517 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.63-0.79 (m, 4H), 1.88-1.99 (m, 4H), 3.13-3.21 (m, 2H), 3.38-3.56 (m, 4H), 3.88-3.89 (m, 1H), 4.43-4.45 (m, 1H), 4.78-4.79 (m, 1H), 6.04 (s, 1H), 7.27-7.39 (m, 3H), 7.47-7.49 (m, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 8.20 (s, 1H), 8.62 (d, *J* = 10.0 Hz, 1H), 9.07 (brs, 1H).

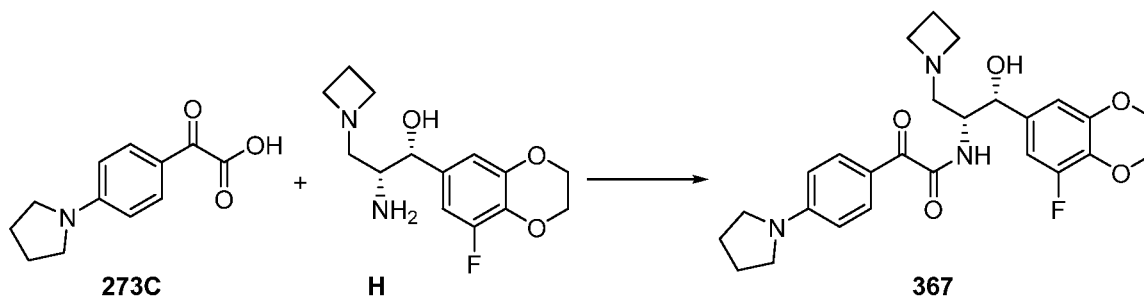
Example 366



[0001282] To a mixture of Compound **365D** (114 mg, 0.5 mmol) and Intermediate **C** (143 mg, 0.5 mmol) in DMF (5 mL) was added HATU (380 mg, 1 mmol). The reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with ethyl acetate (30 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with prep-HPLC to furnish Compound **366**. LC-MS (ESI) m/z: 503 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.84-2.01 (m, 4H), 3.11-3.13 (m, 2H), 3.31-3.54 (m, 4H), 4.23-4.27 (m, 4H), 4.40-4.43 (m, 1H), 4.71 (s, 1H), 6.04 (br s, 1H), 6.72 (s, 1H), 6.77-6.81 (m, 1H), 7.47 (d, *J* = 8.4 Hz,

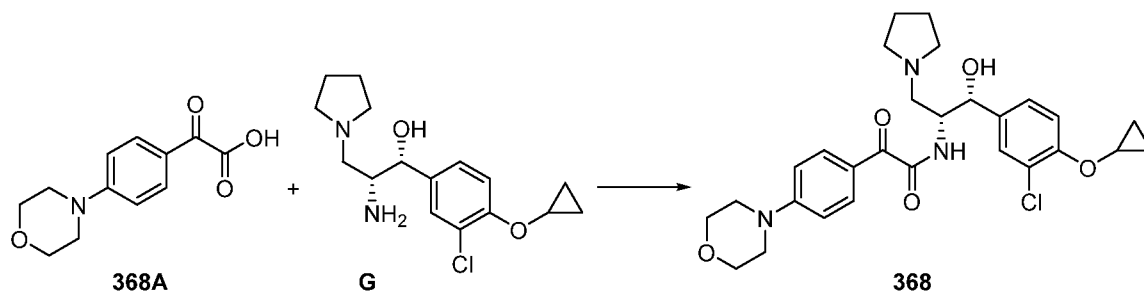
1H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.02 (s, 1H), 8.26 (s, 1H), 8.60 (d, $J = 9.6$ Hz, 1H), 9.04 (br s, 1H).

Example 367



[0001283] A mixture of Compound **273C** (66 mg, 0.3 mmol), HATU (200 mg, 0.5 mmol), and Intermediate **H** (85 mg, 0.3 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. The mixture was diluted with ethyl acetate (30 mL), washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to yield a crude compound. The crude product was purified with prep-HPLC to furnish Compound **367**. LC-MS (ESI) m/z : 484 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.97-2.00 (m, 4H), 2.24-2.27 (m, 1H), 2.38-2.43 (m, 1H), 3.31-3.35 (m, 6H), 4.07-4.16 (m, 4H), 4.28-4.33 (m, 5H), 4.72 (s, 1H), 6.00 (s, 1H), 6.52-6.54 (m, 2H), 6.72-6.80 (m, 2H), 7.64-7.66 (m, 2H), 8.43 (d, $J = 10$ Hz, 1H), 9.84 (s, 1H).

Example 368

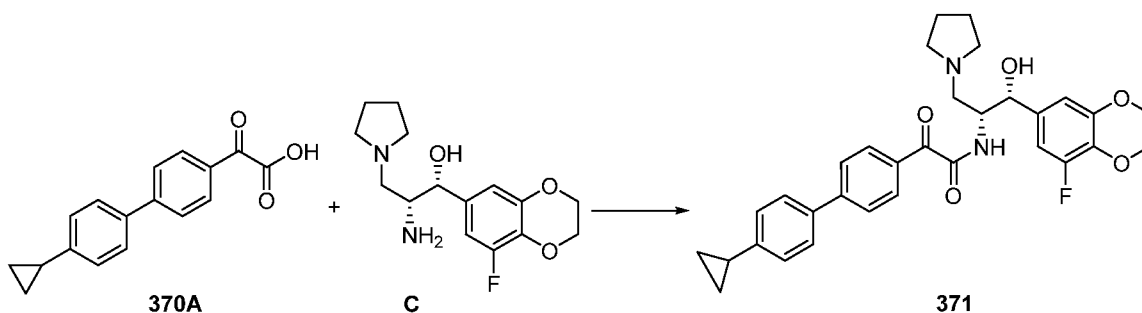


[0001284] A mixture of Intermediate **G** (177 mg, 0.57 mmol), Compound **368A** (117 mg, 0.52 mmol), and HATU (350 mg, 0.92 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **368**. LC-MS (ESI) m/z : 528.2 $[M+H]^+$; 1H -NMR (CD $_3$ OD, 400 MHz): δ (ppm) 0.72-0.86 (m, 4H), 2.03-2.23 (m, 4H), 3.21-3.31 (m, 2H), 3.40-3.43 (m, 4H), 3.55-3.58 (m, 1H), 3.68-3.74 (m, 2H), 3.79-3.89 (m, 6H), 4.70-4.73 (m, 1H), 4.98 (d, $J = 2.8$ Hz, 1H), 6.84 (d, $J = 9.2$ Hz, 2H), 7.38 (s, 2H), 7.44-7.47 (m, 3H).

acetate (100 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with dichloromethane (100 mL x 3). The combined dichloromethane layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **370A**.

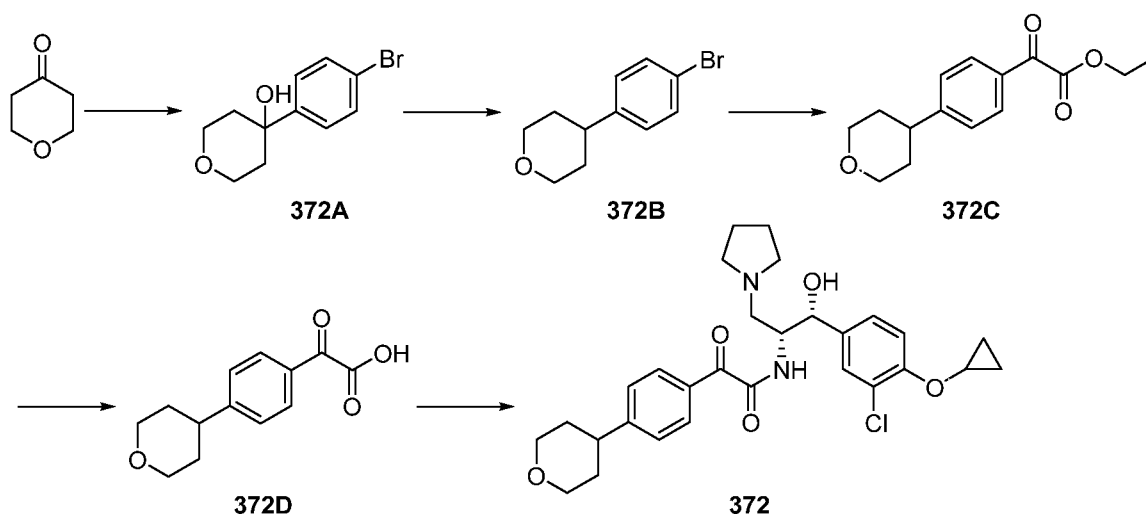
[0001287] A mixture of Compound **370A** (65 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), and Intermediate **G** (74 mg, 0.24 mmol) in DMF (5 mL) was stirred at 25 °C overnight. The mixture was directly purified with prep-HPLC to furnish Compound **370**. LC-MS (ESI) m/z: 559 [M+H]⁺; ¹H-NMR (OMSO-*d*₆, 400 MHz): δ (ppm) 0.65-0.85 (m, 6H), 0.99-1.03 (m, 2H), 1.90-2.02 (m, 5H), 3.12-3.19 (m, 2H), 3.41-3.55 (m, 4H), 3.91-3.96 (m, 1H), 4.55-4.59 (m, 1H), 4.91 (s, 1H), 6.07 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.71-7.74 (m, 4H), 8.80 (d, *J* = 9.6 Hz, 1H), 9.67 (brs, 1H).

Example 371



[0001288] A mixture of Compound **370A** (65 mg, 0.24 mmol), HATU (137 mg, 0.36 mmol), and Intermediate **C** (71 mg, 0.24 mmol) in DMF (5 mL) was stirred at 25 °C overnight. The mixture was directly purified with prep-HPLC to furnish Compound **371**. LC-MS (ESI) m/z: 545 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.72-0.76 (m, 2H), 0.99-1.03 (m, 2H), 1.88-2.02 (m, 5H), 3.11-3.14 (m, 2H), 3.26-3.55 (m, 4H), 4.23-4.29 (m, 4H), 4.49-4.54 (m, 1H), 4.80 (s, 1H), 6.05 (d, *J* = 4.0 Hz, 1H), 6.77 (s, 1H), 6.83 (dd, *J* = 12.0, 1.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 8.74 (d, *J* = 9.6 Hz, 1H), 9.51 (brs, 1H).

Example 372



[0001289] To a solution of tetrahydro-4H-pyran-4-one (380 mg, 3.8 mmol) and 1-bromo-4-iodobenzene (2.4 g, 8.5 mmol) in dry THF (50 mL) was added dropwise *n*-BuLi (2.5 *M* solution in hexane, 1.52 mL, 3.8 mmol) under nitrogen at -78°C over a period of 15 min. The resulting solution was allowed to warm slowly to room temperature and stirred for 3.5 h. The resulting mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate, 100% v/v) to furnish Compound **372A**.

[0001290] To a solution of Compound **372A** (620 mg, 2.42 mmol) in dry dichloromethane (10 mL) was added triethylsilane (0.43 mL, 2.71 mmol). Trifluoroacetic acid (1.83 mL, 24.2 mmol) was added dropwise. After one hour at -78°C , the mixture was warmed to room temperature and stirred for 3 h. The resulting mixture was quenched with aqueous NaOH solution (1 *N*, 5 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 80% v/v) to afford Compound **372B**.

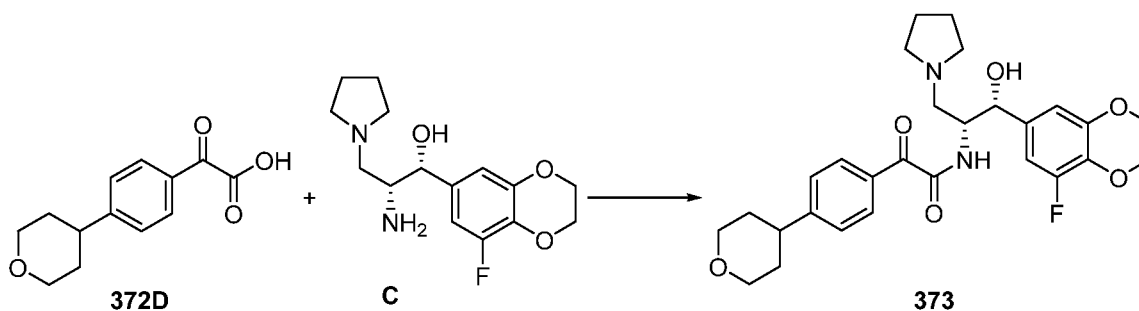
[0001291] To a solution of Compound **372B** (295 mg, 1.23 mmol) in dry THF (20 mL) was added dropwise *n*-BuLi (2.5 *M* solution in hexane, 0.74 mL, 1.84 mmol) under nitrogen at -78°C . After stirring for 30 min, diethyl oxalate (449 mg, 3.07 mmol) was added in one portion. The mixture was stirred at -78°C for about an hour. The resulting mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with

ethyl acetate (50 mL x 3). The organic layer was washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a crude product. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **372C**.

[0001292] To a solution of Compound **372C** (155 mg, 0.59 mmol) in THF (10 mL) was added dropwise a solution of LiOH·H₂O (50 mg, 1.18 mmol) in water (3 mL). The mixture was stirred at room temperature for 3 h. The reaction solution was adjusted to pH 3 with aqueous HCl solution (1 N, 1.5 mL) and separated. The organic layer was dried directly over anhydrous sodium sulfate, filtered, and concentrated to afford Compound **372D**.

[0001293] To a solution of Intermediate **G** (87 mg, 0.28 mmol) in dichloromethane (10 mL) was added Compound **372D** (55 mg, 0.23 mmol) and HATU (134 mg, 0.35 mmol) under nitrogen. The mixture was stirred at room temperature overnight. The resulting mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with dichloromethane (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude product. The crude product was purified with prep-HPLC to furnish Compound **372**.
 LC-MS (ESI) *m/z*: 527 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.68-0.84 (m, 4H), 1.62-1.69 (m, 4H), 1.87-2.03 (m, 4H), 2.83-2.91 (m, 1H), 3.11-3.20 (m, 2H), 3.44-3.54 (m, 6H), 3.95-3.97 (m, 3H), 4.53-4.58 (m, 1H), 4.87 (s, 1H), 6.05 (d, *J* = 4.0 Hz, 1H), 7.34-7.42 (m, 5H), 7.62 (d, *J* = 8.4 Hz, 2H), 8.76 (d, *J* = 9.6 Hz, 1H), 9.51 (s, 1H).

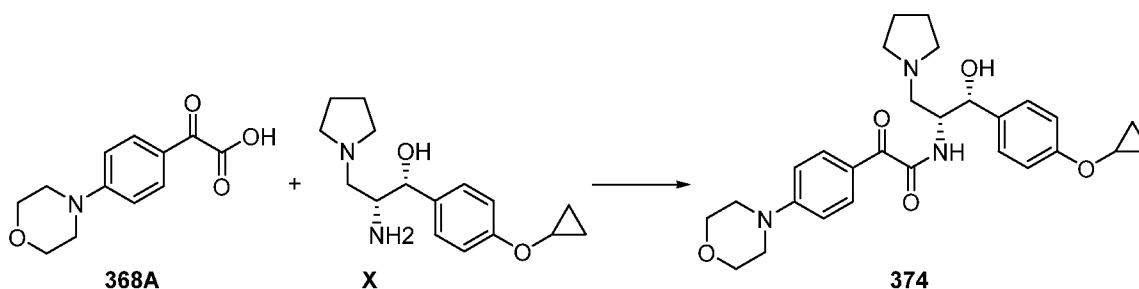
Example 373



[0001294] To a solution of Intermediate **C** (83 mg, 0.28 mmol) in dichloromethane (10 mL) was added Compound **372D** (55 mg, 0.23 mmol) and HATU (134 mg, 0.35 mmol) under nitrogen. The mixture was stirred at room temperature overnight. The resulting mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with dichloromethane (50 mL x 3). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude product. The crude product was purified with prep-HPLC to furnish Compound **373**.

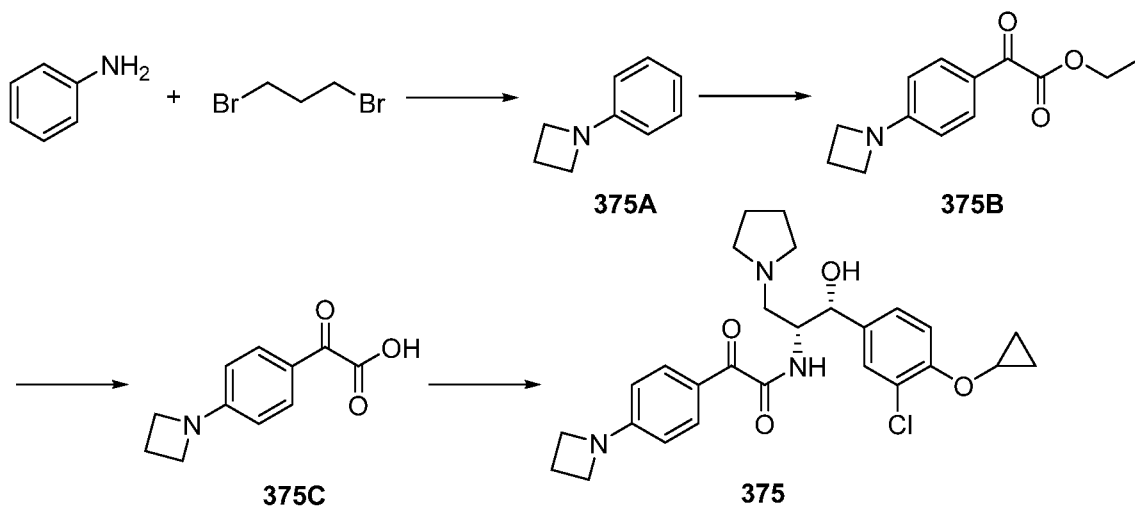
LC-MS (ESI) m/z : 513 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.66-1.71 (m, 4H), 1.87-2.02 (m, 4H), 2.85-2.91 (m, 1H), 3.10-3.16 (m, 2H), 3.48-3.54 (m, 6H), 3.95-3.98 (m, 2H), 4.26-4.29 (m, 4H), 4.47-4.52 (m, 1H), 4.77 (s, 1H), 6.03 (d, $J = 2.4$ Hz, 1H), 6.75 (s, 1H), 6.81 (dd, $J = 11.2, 1.6$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H), 8.70 (d, $J = 9.6$ Hz, 1H), 9.42 (s, 1H).

Example 374



[0001295] A mixture of Intermediate **X** (77 mg, 0.34 mmol), Compound **368A** (55 mg, 0.24 mmol), and HATU (175 mg, 0.46 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **374**. LC-MS (ESI) m/z : 494.2 $[M+H]^+$; 1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.68-0.69 (m, 2H), 0.77-0.81 (m, 2H), 2.05-2.22 (m, 5H), 3.20-3.30 (m, 2H), 3.40-3.42 (m, 4H), 3.53-3.60 (m, 1H), 3.66-3.72 (m, 2H), 3.76-3.85 (m, 7H), 4.66-4.69 (m, 1H), 4.97 (d, $J = 2.8$ Hz, 1H), 6.88 (d, $J = 9.2$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.60 (d, $J = 9.2$ Hz, 2H).

Example 375



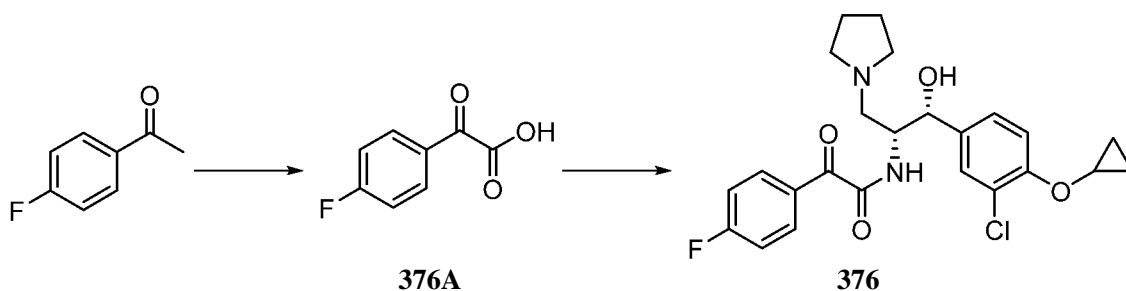
[0001296] To a solution of aniline (9.3 g, 100 mmol) in DMF (350 mL) was added cesium carbonate (100 g, 306 mmol) and 1, 3-dibromopropane (27 g, 135 mmol). The mixture was stirred for 24 h while keeping inner temperature between 60 °C and 65 °C. After the reaction mixture was cooled to ambient temperature, the dark solution was diluted with water (400 mL) and extracted with ethyl acetate (300 mL x 3). The combined organic phases were washed with brine (150 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product as a brown oil. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **375A**.

[0001297] To a solution of compound **375A** (900 mg, 6.8 mmol) and aluminum trichloride (5.0 g, 37.9 mmol) in dichloromethane (30 mL) was added dropwise ethyl 2-chloro-2-oxoacetate (1.06 g, 8.0 mmol) at 0 °C. The mixture was stirred for 4 hours while keeping the temperature at 0 °C. The mixture was poured into ice water and extracted with ethyl acetate (50 mL x 3). The resulting product was concentrated under reduced pressure, and the resultant residue was purified with silica gel column chromatography (ethyl acetate in petroleum ether, 30% v/v) to give Compound **375B**.

[0001298] To a solution of Compound **375B** (333 mg, 1.00 mmol) in MeOH (10 mL) was added LiOH·H₂O (90 mg, 2.14 mmol) and water (2 mL). The reaction mixture was stirred at 15 °C for 4 h. The reaction mixture was neutralized with HCl (1 N). The resulting mixture was evaporated. The residue was dissolved in water (5 mL). The mixture was extracted with ethyl acetate (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and evaporated to give Compound **375C**.

[0001299] A mixture of Intermediate **G** (203 mg, 0.65 mmol), Compound **375C** (110 mg, 0.53 mmol), and HATU (350 mg, 0.92 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (150 mL), washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with prep-HPLC to give Compound **375**. LC-MS (ESI) m/z: 498.2 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.69-0.87 (m, 4H), 1.90-2.26 (m, 4H), 3.01-3.27 (m, 2H), 3.43-3.68 (m, 4H), 3.70-3.95 (m, 2H), 4.19-4.42 (m, 2H), 4.77 (s, 1H), 4.98-5.17 (m, 2H), 5.53-5.92 (m, 1H), 6.96-7.31 (m, 5H), 7.36-7.57 (m, 3H).

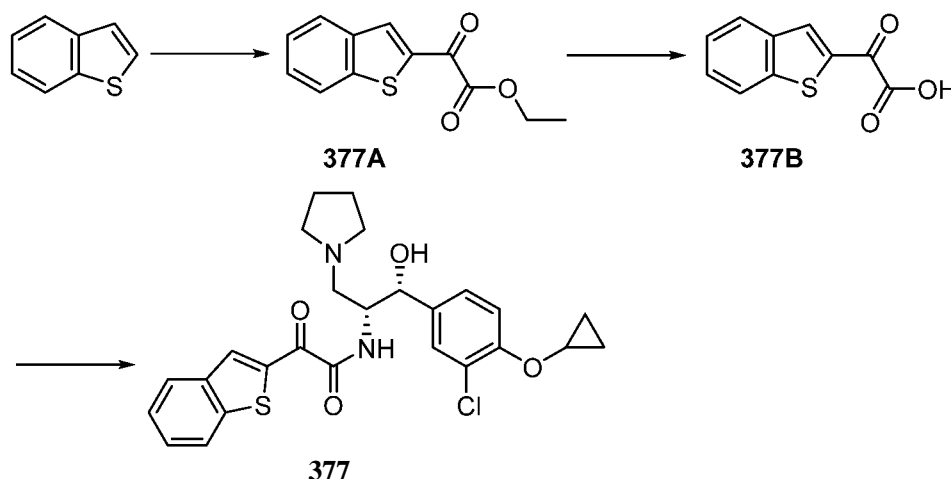
Example 376



[0001300] A mixture of 1-(4-fluorophenyl)ethan-1-one (5.00 g, 36.20 mmol) and SeO_2 (6.06 g, 54.30 mmol) in pyridine (20 mL) was stirred at 70 °C for 16 h. After filtration to remove the resultant solid, the filtrate was evaporated to give a residue. The crude product was dissolved in aqueous sodium hydroxide solution (1 M, 20 mL) and water (50 mL) and extracted with diethyl ether (160 mL) to remove by-product. The aqueous solution was adjusted to pH 1 with concentrated hydrochloric acid (4 mL) and extracted with dichloromethane (100 mL x 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated to afford Compound **376A**.

[0001301] A mixture of Compound **376A** (54 mg, 0.32 mmol), Intermediate **G** (100 mg, 0.32 mmol), and HATU (183 mg, 0.48 mmol) in dichloromethane (3 mL) was stirred at 20 °C for 16 h. The mixture was diluted with ethyl acetate (100 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and evaporated to give a residue. The crude product was purified with prep-HPLC to afford Compound **376**. LC-MS (ESI) m/z : 461 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 0.66-0.83 (m, 4H), 1.86-2.02 (m, 4H), 3.12-3.18 (m, 2H), 3.46-3.53 (m, 4H), 3.89-3.95 (m, 1H), 4.48-4.55 (m, 1H), 4.85 (s, 1H), 6.08 (s, 1H), 7.30-7.42 (m, 5H), 7.89 (t, $J = 8.8$ Hz, 2H), 8.74 (d, $J = 9.6$ Hz, 1H), 9.57 (s, 1H).

Example 377

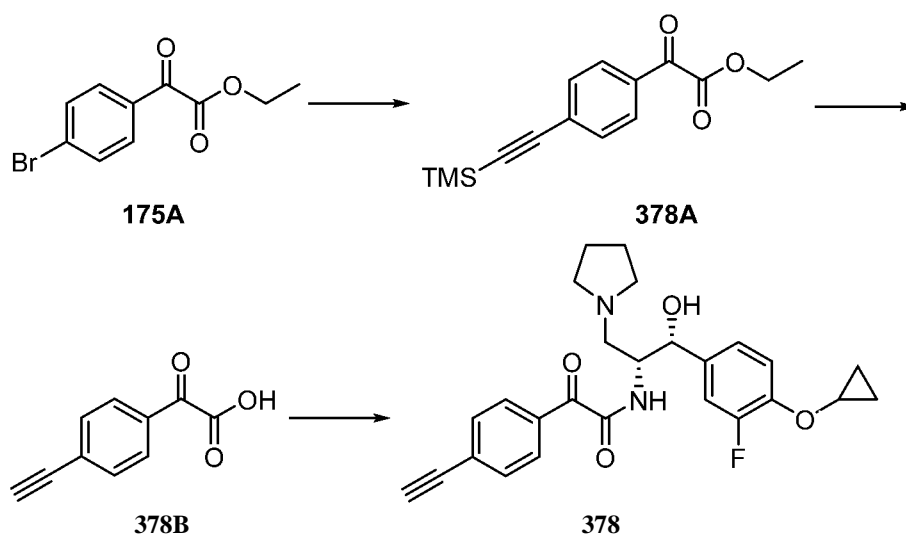


[0001302] To a solution of benzo[b]thiophene (1 g, 7.5 mmol) in THF (25 mL) was added dropwise n-BuLi (3.6 mL, 8.9 mmol) under nitrogen at -78 °C. The resulting mixture was stirred at -78 °C for 15 min. To the resulting mixture was added diethyl oxalate (3.3 g, 8.9 mmol) quickly. The mixture was stirred for 1 h at -78 °C, quenched with sat. ammonium chloride solution, treated with water (50 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **377A**.

[0001303] To a solution of Compound **377A** (1.5 g, 6.4 mmol) in THF (50 mL) was added dropwise LiOH·H₂O (538 mg, 12.8 mmol) in water (4 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 1 h. The mixture was adjusted to pH 1 with diluted HCl. The resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was concentrated, treated with petroleum ether (50 mL), and stirred for 30 min. The yellow solid was formed and filtered to furnish Compound **377B**.

[0001304] A mixture of Compound **377B** (100 mg, 0.48 mmol), Intermediate **G** (150 mg, 0.48 mmol), and HATU (277 mg, 0.73 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The mixture was treated with water (10 mL), extracted with dichloromethane (20 mL x 2), washed with water (20 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with prep-HPLC to furnish Compound **377**. LC-MS (ESI) m/z: 499 [M+H]⁺; ¹H-NMR (acetone-*d*₆, 400 MHz): δ (ppm) 0.60-0.81 (m, 4H), 2.23 (s, 2H), 2.93 (s, 3H), 3.50 (s, 2H), 3.81-3.85 (m, 2H), 4.00-4.06 (m, 3H), 4.86 (t, *J* = 7.2 Hz, 1H), 5.15 (d, *J* = 2.8 Hz, 1H), 7.33-7.41 (m, 2H), 7.47-7.53 (m, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 8.04-8.09 (m, 2H), 8.14-8.19 (m, 1H), 8.64 (s, 1H), 9.52 (s, 1H).

Example 378

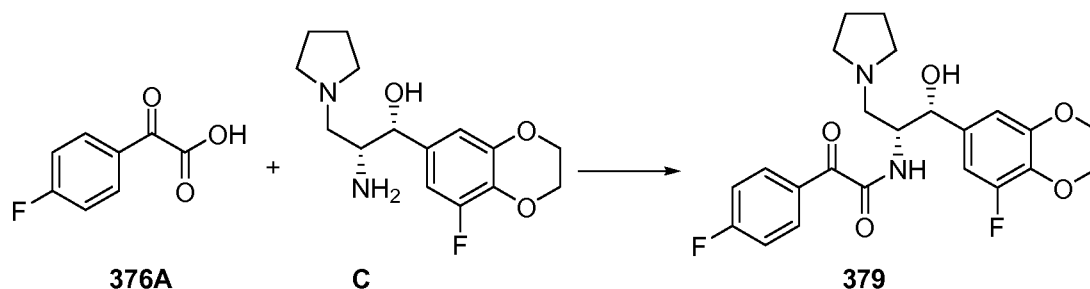


[0001305] To a solution of compound **175A** (2.57 g, 10.0 mmol), CuI (190 mg, 1.0 mmol), and Pd(PPh₃)₂Cl₂ (210 mg, 0.3 mmol) in triethylamine (80 mL) was added dropwise ethynyltrimethylsilane (1.17 g, 12.0 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 90 °C for 30 minutes. Solids were collected with filtration and washed with acetate ethyl (80 mL x 2). The filtrate was concentrated under reduced pressure to give a residue, which was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to yield compound **378A**.

[0001306] To a solution of Compound **378A** (500 mg, 1.8 mmol) in THF (5 mL) was added LiOH·H₂O (113 mg, 2.7 mmol) in water (2.0 mL). The resulting mixture was stirred at room temperature for 2 h, evaporated, treated with water (5 mL), and adjusted to pH 2 with diluted HCl. The mixture was extracted with ethyl acetate (10 mL x 3), washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to afford the Compound **378B**.

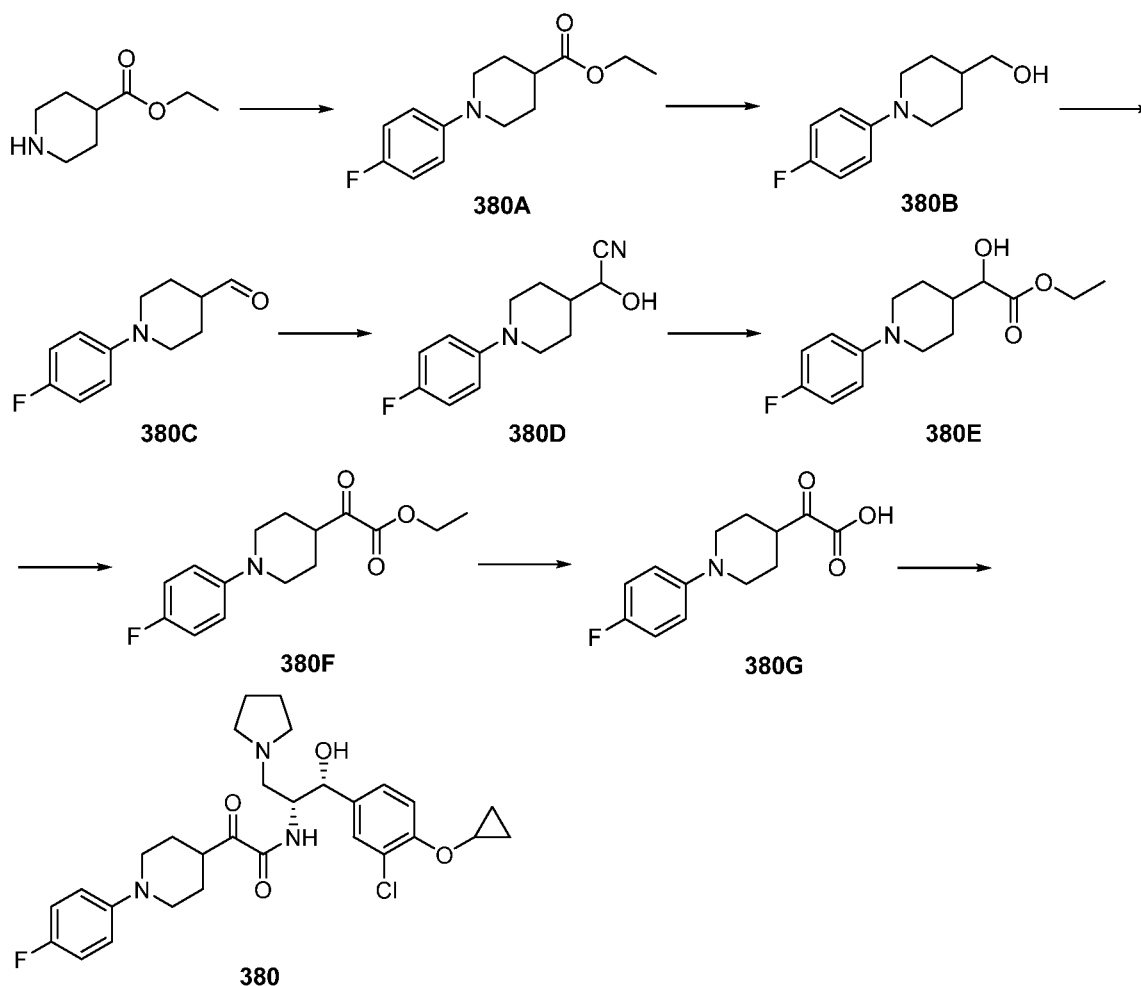
[0001307] To a solution of Compound **378B** (34 mg, 0.2 mmol) in DMF (3 mL) was added Intermediate **S** (59 mg, 0.2 mmol) and HATU (114 mg, 0.3 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was purified with prep-HPLC to give Compound **378**. LC-MS (ESI) m/z: 451 [M+H]⁺; ¹H-NMR (acetone-*d*₆, 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.79-0.81 (m, 2H), 2.04-2.09 (m, 4H), 3.60-3.63 (m, 3H), 3.88-3.93 (m, 5H), 4.00 (s, 1H), 4.81-4.83 (m, 1H), 5.15 (d, *J* = 2.8 Hz, 1H), 7.23-7.25 (m, 2H), 7.33-7.35 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 8.15-8.18 (m, 1H), 9.31 (brs, 1H).

Example 379



[0001308] A mixture of Compound **376A** (54 mg, 0.32 mmol), Intermediate **C** (95 mg, 0.32 mmol), and HATU (183 mg, 0.48 mmol) in dichloromethane (3 mL) was stirred at 20 °C for 16 h. The mixture was diluted with ethyl acetate (100 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and evaporated to give a residue. The crude product was purified with prep-HPLC to afford Compound **379**. LC-MS (ESI) m/z : 447 $[M+H]^+$; 1H -NMR ($OMSO-d_6$, 400 MHz): δ (ppm) 1.83-2.04 (m, 4H), 3.07-3.19 (m, 2H), 3.41-3.47 (m, 4H), 4.27 (s, 4H), 4.42-4.50 (m, 1H), 4.75 (s, 1H), 6.04 (s, 1H), 6.74 (s, 1H), 6.80 (d, $J = 10.4$ Hz, 1H), 7.36 (t, $J = 8.8$ Hz, 2H), 7.93-7.98 (m, 2H), 8.70 (d, $J = 9.6$ Hz, 1H), 9.40 (s, 1H).

Example 380



[0001309] A mixture of ethyl piperidine-4-carboxylate (10 g, 64 mmol), 1-fluoro-4-iodobenzene (14 g, 64 mmol), K_2CO_3 (17.6 g, 127 mmol), and L-proline (1.46 g, 12.7 mmol) in DMSO (50 mL) was stirred under nitrogen at 85 °C for 12 h. The resulting mixture was added $NH_3 \cdot H_2O$ (50 mL), extracted with ethyl acetate (100 mL x 2), washed with water (100 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **380A**.

[0001310] To a solution of $AlLiH_4$ (1.2 g, 31 mmol) in THF (100 mL) was added Compound **380A** (7.9 g, 31 mmol) in THF (50 mL) dropwise under nitrogen at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h, quenched with $Na_2SO_4 \cdot 10H_2O$. The mixture was treated with silica gel and filtered. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **380B**.

[0001311] To a cooled $-78\text{ }^{\circ}\text{C}$ solution of oxalyl chloride (9.1 g, 72 mmol) in dichloromethane (150 mL) was added dropwise DMSO (7.5 g, 96 mmol), maintaining the internal temperature below $-40\text{ }^{\circ}\text{C}$. After 30 min, Compound **380B** (5 g, 24 mmol) in dichloromethane (10 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 min, triethylamine (12 g, 120 mmol) was added dropwise, and the mixture was warmed to room temperature stirred for 2 h. The mixture was treated with water (100 mL), extracted with dichloromethane (50 mL x 2), washed with water (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to furnish Compound **380C**.

[0001312] Compound **380C** (3.3 g, 16 mol) was added to a solution of $\text{Na}_2\text{S}_2\text{O}_5$ (3 g, 16 mol) in water (100 mL). The mixture was stirred for 2 h at room temperature. After the addition of NaCN (1.6 g, 32 mmol) the resulting mixture was stirred for 15 h, diluted with ethyl acetate (50 mL), extracted with ethyl acetate (100 mL x 2), washed with sat. sodium bicarbonate (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to afford the crude Compound **380D**.

[0001313] To a solution of Compound **380D** (3.7 g, 15.8 mmol) in ethanol (80 mL) cooled to $0\text{ }^{\circ}\text{C}$ was bubbled a gentle stream of HCl gas (dried over con. H_2SO_4) for 5 h. The mixture was treated with water slowly at $0\text{ }^{\circ}\text{C}$, stirred at room temperature for 2 h, adjusted to pH 8 with NaOH (1 M), extracted with dichloromethane (50 mL x 2), washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **380E**.

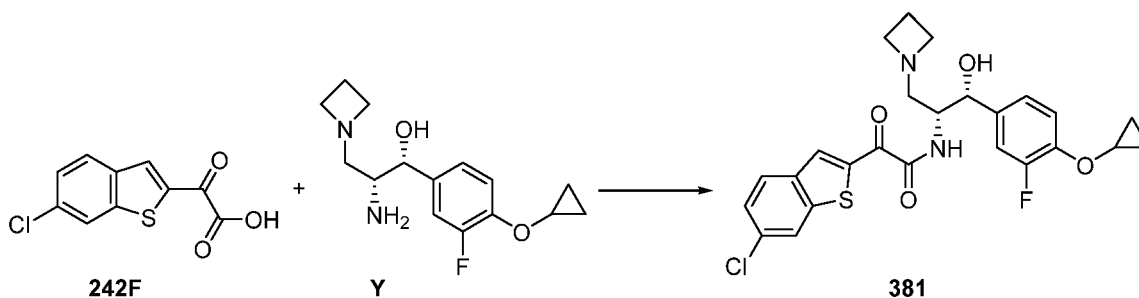
[0001314] To a cooled $-78\text{ }^{\circ}\text{C}$ solution of oxalyl chloride (3.66 g, 28.8 mmol) in dichloromethane (50 mL) was added dropwise DMSO (3 g, 38.4 mmol), maintaining the internal temperature below $-40\text{ }^{\circ}\text{C}$. After 30 min, Compound **380E** (2.7 g, 9.6 mmol) in dichloromethane (10 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 min, triethylamine (4.85 g, 48 mmol) was added dropwise, and the mixture was warmed to room temperature stirred for 2 h. The mixture was treated with water (100 mL), extracted with dichloromethane (50 mL x 2), washed with water (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to furnish Compound **380F**.

[0001315] To a solution of Compound **380F** (878 mg, 3.14 mmol) in THF (20 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (264 mg, 6.29 mmol) in water (2 mL) at $-30\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 2 h, evaporated, treated with water, adjusted to pH 2 with diluted HCl,

and lyophilized. The solid was purified with reverse phase chromatography using eluent (acetonitrile in water, from 1% to 100% v/v) to furnish Compound **380G**.

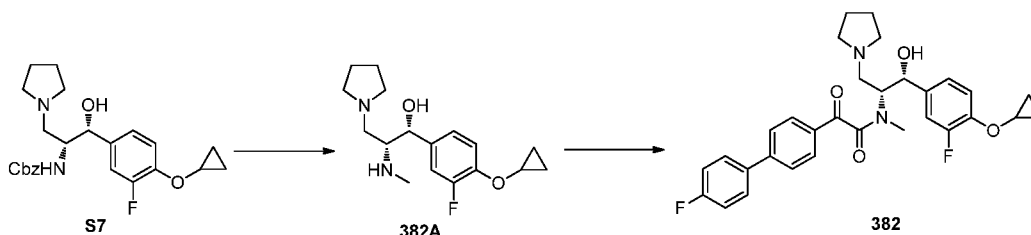
[0001316] A mixture of Compound **380G** (300 mg, 1.19 mmol), Intermediate **G** (370 mg, 1.19 mmol), and HATU (681 mg, 0.73 mmol) in DMF (15 mL) was stirred at room temperature for 12 h. The mixture was treated with water (10 mL), extracted with dichloromethane (20 mL x 2), washed with water (20 mL x 3) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with reverse phase chromatography eluting with (acetonitrile in water, from 1% to 100% v/v) to furnish Compound **380**. LC-MS (ESI) m/z : 544 $[M+H]^+$; 1H -NMR (acetone- d_6 , 400 MHz): δ (ppm) 0.69-0.84 (m, 4H), 1.68 (s, 1H), 1.92-2.13 (m, 9H), 3.15-3.37 (m, 4H), 3.62-3.69 (m, 3H), 3.82-3.89 (m, 4H), 4.65-4.68 (m, 1H), 5.09 (s, 1H), 7.14-7.19 (m, 1H), 7.34-7.40 (m, 5H), 7.79-7.81 (m, 1H), 8.21 (s, 1H), 11.31 (s, 1H).

Example 381



[0001317] A mixture of Intermediate **Y** (70 mg, 0.25 mmol), HATU (143 mg, 0.37 mmol), and Compound **242F** (60 mg, 0.25 mmol) in DMF (5 mL) was stirred at 25 °C overnight. The mixture was directly purified with prep-HPLC to furnish Compound **381**. LC-MS (ESI) m/z : 503 $[M+H]^+$; 1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.61-0.79 (m, 4H), 2.24-2.42 (m, 2H), 3.33-3.49 (m, 2H), 3.82-3.91 (m, 1H), 4.02-4.33 (m, 5H), 4.77 (d, $J = 4.0$ Hz, 1H), 6.03 (brs, 1H), 7.13-7.20 (m, 2H), 7.36 (t, $J = 8.4$ Hz, 1H), 7.56 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.30 (d, $J = 2.0$ Hz, 1H), 8.52 (s, 1H), 8.56 (d, $J = 10.0$ Hz, 1H), 9.44 (brs, 1H).

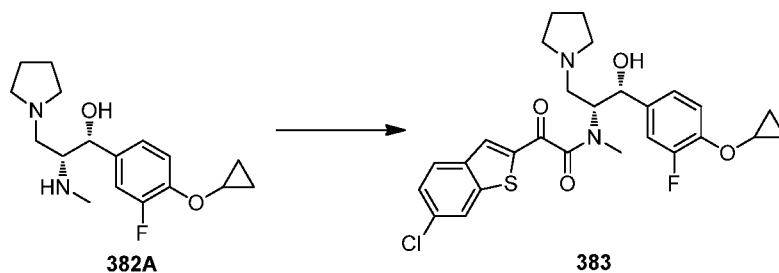
Example 382



[0001318] To a solution of AlLiH_4 (76 mg, 2 mmol) in THF (15 mL) was added Intermediate **S7** (430 mg, 1 mmol) in THF (5 mL) dropwise under nitrogen atmosphere. The resulting mixture was stirred at 60 °C for 3 h and quenched with aqueous Na_2SO_4 solution. The filtrate was concentrated to afford a crude product, which was purified by prep-HPLC to give Compound **382A** (240 mg, yield 78%). LC-MS (ESI) m/z : 309 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.75-0.85 (m, 4H), 1.76-1.79 (m, 4H), 2.34 (s, 3H), 2.43-2.59 (m, 6H), 2.87-2.91 (m, 1H), 3.77-3.82 (m, 1H), 4.63-4.69 (m, 1H), 7.02-7.12(m, 2H), 7.22-7.26 (m, 1H).

[0001319] A mixture of Compound **382A** (92 mg, 0.33 mmol), Compound **133D** (73 mg, 0.30 mmol), and HATU (137 mg, 0.36 mmol) in DMF (4 mL) was stirred at 25 °C for 4 h. Then it was purified by prep-HPLC to give Compound **382** (70 mg, yield 36%) as a white solid. LC-MS (ESI) m/z : 535 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$, 400 MHz): δ (ppm) 0.61-0.90 (m, 4H), 2.06-2.25 (m, 4H), 3.08-3.27 (m, 3H), 3.45 (s, 2H), 3.71-4.46 (m, 5H), 5.08-5.38 (m, 1H), 5.57-5.72 (m, 1H), 6.88-7.85 (m, 11H), 9.20-9.95 (m, 1H).

Example 383



[0001320] A mixture of Compound **382A** (140 mg, 0.45 mmol), Compound **242F** (98 mg, 0.40 mmol), and HATU (182 mg, 0.48 mmol) in DMF (3 mL) was stirred at 25 °C for 15 h. It was purified by prep-HPLC to give Compound **383** (88 mg, yield 34%) as a white solid. LC-MS (ESI) m/z : 531 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz): δ (ppm) 0.30-0.84 (m, 4H), 1.88-2.04 (m, 4H), 2.99-3.29 (m, 6H), 3.55-3.69 (m, 2H), 3.81-4.08 (m, 2H), 4.31-4.78 (m, 1H), 4.95-5.15 (m, 1H), 6.04-6.19 (m, 1H), 6.90-7.71 (s, 5H), 7.86-8.12 (m, 1H), 8.26-8.32 (m, 1H), 9.38-9.53 (m, 1H).

BIOLOGICAL EXAMPLES

[0001321] The following describes ways in which the compounds described herein were tested to measure in vitro activity in enzymatic and cell-based assays. A person of ordinary skill in the art would know that variations in the assay conditions could be used to determine the activity of the compounds.

Assay 1: GCS Enzymatic Assay

[0001322] This assay was modified based on the study by Larsen et al. (*J.Lipid Res.* **2011**, 53, 282). Madin-Darby canine kidney (MDCK) cell lysate was prepared using M-PER Mammalian Protein Extraction Reagent (Thermal Scientific) in the presence of a protease inhibitor cocktail (Roche). Protein concentration was determined using BCA assay kit (Pierce). Sixty micrograms of MDCK cell lysate was incubated with various concentrations of a compound described herein from 0.001 μM -10 μM , respectively, in 100 mM Tris buffer (pH 7.5) containing 10 mM MgCl_2 , 1 mM dithiothreitol, 1 mM EGTA, 2 mM NAD, 100 μM UDP-glucose, 10 μM C6-NBD-Ceramide (Matreya LLC, Pleasant Gap, PA), 35 μM dioleoylphosphatidylcholine and 5 μM sulfatide (Sigma) in a final reaction volume of 100 μL at 37 °C for 1 hour. 0.1% DMSO was used as mock treatment or control. The reaction was terminated by adding 100 μL acetonitrile solution and subjected to LC/MS analysis.

[0001323] The quantitative analysis of NBD-Ceramide and glucosylceramide was performed on a Shimadzu ultra-fast liquid chromatography (Shimadzu, Japan) coupled with API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Concord, Ontario, Canada). Sample separation was conducted on a Waters Xbridge™ BEH130 CI8, 100 mmx4.6 mm i.d, 3.5 μm (Milford, MA, USA). The mobile phase consisted of water and acetonitrile supplemented with 0.1% formic acid (v/v). The flow rate was 1.0 mL/min. The initial mobile phase was 20% acetonitrile and was ramped in a linear fashion to 50% acetonitrile in 0.4 min. From 0.4 to 1.5 min, the gradient was ramped to 98% acetonitrile, and then was held at 100% until 8.0 min. Acetonitrile was reset to 20% in 1.5 min, and maintained until 10.0 min. The total run time was 10.0 min. The MS/MS detection was performed in ESI positive mode. The mass transition of NBD-Ceramide was m/z 576.36→558.40 under the collision energy of 15 V, and the mass transition of glucosylceramide was m/z 738.35→558.40 under 21V collision energy. The cell lysate was diluted with equal volume of acetonitrile. Aliquots of 50 μL diluted samples were added to 1.5 mL tubes, and 100 μL of acetonitrile containing internal standard (100 ng/mL tolbutamide) were added for protein precipitation. The mixture were vortexed and then

centrifuged at 13000 rpm for 10 min. 70 μ L of supernatant were mixed with 140 μ L of H₂O and the final solution were injected for LC/MS/MS analysis and IC₅₀'s and/or percent inhibitions calculated.

Assay 2: K562 Cell-based Assay

[0001324] This assay was modified based on the study by Gupta et al. (*J.Lipid Res.* **2010**, *51*, 866). K562 cells were seeded into 12-well plates at 3×10^5 cells/well/mL in RPMI-1640 medium with 5% FBS and incubated at 37 °C for 24 h. One μ L of a compound described herein at desired concentration (10 mM, 1 mM, 0.1 mM, 0.01 mM, 0.001 mM and 0.0001 mM in DMSO) or DMSO was added into corresponding well and mixed. Cells were incubated at 37 °C for 4h. Then 100 μ L of RPMI-1640 medium containing 110 μ M of NBD-Ceramide, 11% BSA, 5% FBS, and corresponding concentration of a compound described herein was added into each well and mixed. Cells were incubated for additional 0.5 h at 37 °C, followed by washing the cells with ice-cold PBS (pH 7.4) twice with centrifugation and resuspended with 50 μ L cold PBS+1% Triton X-100. The cell lysate was sonicated for 15 min before adding equal volume of methanol for LCMS analysis. A small aliquot of cell lysate was used to determine protein concentration by BCA assay kit.

[0001325] The HPLC equipment and methods used in **Assay 1** were used in this assay as well and IC₅₀'s were calculated.

Assay 3: NCI/ADR-Res Cell-based Assay

[0001326] NCI/ADR-RES cells were seeded into 12-well plates (4×10^5 cells/well) in RPMI-1640 medium with 10% FBS and incubated at 37 °C for 24 h. Before treatment with a compound described herein, cell culture media were removed and replaced with 1 mL per well RPMI-1640 medium containing 5% FBS and a compound as described herein at desired concentrations (10 μ M, 1 μ M, 0.1 μ M, 0.01 μ M, 0.001 μ M, and 0.0001 μ M), respectively, or 0.1% DMSO only. Cells were cultured for 4 hours at 37 °C followed by replacing the media with RPMI-1640 containing 1% BSA and 10 μ M of C6-NBD-Ceramide in the present of a compound described herein, and incubated for additional 0.5 hour at 37 °C. Cells were then washed twice with ice-cold PBS (pH 7.4), scraped with 50 μ L cold PBS+1% Triton X-100. The cell lysate was sonicated for 15 min before adding equal volume of methanol for LCMS analysis. A small aliquot of cell lysate was used to determine protein concentration by BCA assay kit.

[0001327] The HPLC equipment and methods used in **Assay 1** were used in this assay as well and IC₅₀'s and % inhibition were calculated.

[0001328] Using the above assays, the following compounds were tested. In the tables below, "nt" means that the compound was not tested in the assay. Either IC₅₀ or % inhibition data are included in the tables. The % inhibition data is identified by an asterix ("*"). For IC₅₀ data, "A" means the compound had an IC₅₀ of greater than zero but less than or equal to about 50 nM and "B" means the compound had an IC₅₀ is greater than about 50 but less than or equal to about 5000 nM. For % inhibition data, "A*" means the compound had a % inhibition of a percent inhibition of greater than or equal to about 50% and "B*" means the compound had a % inhibition of greater than or equal to about 3% but less than about 50%.

[0001329] **Table 1.** The data provided is the IC₅₀ (nM) generated from Assay 1, except as otherwise noted by *, which is % inhibition, also generated from Assay 1.

Cmpd No.	Name	Data
1	2-(2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
2	2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B
3	2-(5-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
4	2-(5-chlorobenzo[b]thiophen-2-yl)-2,2-difluoro-N-((2R)-1-(3-fluoro-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
5A	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((2R)-1-(3-fluoro-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B
5	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1S,2R)-1-(3-fluoro-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A
5B	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1R,2R)-1-(3-fluoro-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
6	2-(5-chlorobenzo[d]thiazol-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
7	2-(5,6-dichloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
8	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1R,2R)-1-(2-fluoro-5-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
8J	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1S,2R)-1-(2-fluoro-5-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
10	2-(5-chloro-1-methyl-1H-benzo[d]imidazol-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
11	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
12B	2-(2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1S,2R)-1-(7-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B
13	2-(7,8-dihydro-6H-cyclopenta[g]quinoxalin-7-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-	B

	yl)propan-2-yl)-2,2-difluoroacetamide	
14	2-(5-chloro-1-methyl-1H-indol-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
15	2-(5,7-dichlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
16	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(3-(pyridin-2-yl)phenyl)butanamide	A
17	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-3-(naphthalen-2-yl)propanamide	B
18	2-(5,6-dichlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
19	2-(4,5-dichlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
20	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-3-(3-(pyridin-2-yl)phenyl)propanamide	B*
21	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-fluoro-2,3-dihydro-1H-inden-2-yl)acetamide	A
22	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
22K	N-((1S,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	B*
23	2-(benzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
24	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-fluorobenzofuran-2-yl)acetamide	A
25	(E)-4-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluorobut-3-enamide	B*
26	N-((1R,2R)-3-(3-amino-8-azabicyclo[3.2.1]octan-8-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B*
28	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-fluorobenzo[b]thiophen-2-yl)acetamide	A
30	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-	A

	(trifluoromethyl)benzofuran-2-yl)acetamide	
31	2-(5-bromobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
32C	N-((1S,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B*
32D	N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
33A	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-(7-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
33	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-(7-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
34G	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(quinolin-6-yl)propan-2-yl)acetamide	B*
34	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(quinolin-6-yl)propan-2-yl)acetamide	A*
36C	2-(5-chlorobenzofuran-2-yl)-N-((1S,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(3,3-dimethylpyrrolidin-1-yl)-1-hydroxypropan-2-yl)-2,2-difluoroacetamide	B*
37G	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(4-(trifluoromethoxy)phenyl)propan-2-yl)acetamide	B*
37	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(4-(trifluoromethoxy)phenyl)propan-2-yl)acetamide	B*
38	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-((S)-3-fluoropyrrolidin-1-yl)-1-hydroxypropan-2-yl)-2,2-difluoroacetamide	B*
39	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-((R)-2-methylpyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
40	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-((S)-2-methylpyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
41	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-3-(3,3-difluoropyrrolidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoroacetamide	B*
44H	N-((1S,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B*
44	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A

46	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-((R)-3-fluoropyrrolidin-1-yl)-1-hydroxypropan-2-yl)-2,2-difluoroacetamide	B
47	N-((1R,2R)-1-(3-chloro-4-((tetrahydrofuran-3-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
48	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(2-azaspiro[3.3]heptan-2-yl)propan-2-yl)-2,2-difluoroacetamide	B*
49	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-1-(1-methyl-1H-indazol-5-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B
50	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(pyridin-2-yl)-2,3-dihydro-1H-inden-2-yl)acetamide	A
51	N-((1R,2R)-3-(2-azabicyclo[2.2.1]heptan-2-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
52	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
53	N-((1R,2R)-3-(7-azabicyclo[2.2.1]heptan-7-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
54	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-1-(1-methyl-1H-indazol-6-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
54G	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-hydroxy-1-(1-methyl-1H-indazol-6-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
56	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-1-(6-methoxypyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A
57B	N-[2-(2H,3H-benzo[e],4-dioxan-6-yl)(1R)-2-hydroxy-1-(pyrrolidinylmethyl)ethyl]-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
57	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-deutero-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
57C	2-(5-chlorobenzofuran-2-yl)-N-((1S,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-deutero-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
59	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(3-(difluoromethyl)-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B
591	2-(5-chlorobenzofuran-2-yl)-N-((1S,2R)-1-(3-(difluoromethyl)-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
60	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-	A

	yl)propan-2-yl)-2,2-dideutero-acetamide	
61	N-((1R,2R)-1-(7-bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B*
62	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(3,3-dimethylazetidid-1-yl)-1-hydroxypropan-2-yl)-2,2-difluoroacetamide	B*
63	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
64	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A
65	N-((1R,2R)-1-(8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
66	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(3-methylazetidid-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
67	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
68G	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(5-chlorobenzofuran-2-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
68	2-(5-chlorobenzofuran-2-yl)-N-((1S,2R)-1-(5-chlorobenzofuran-2-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B*
69	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	A
69A	N-((1S,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	B
70	2-(2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
71	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
72	(E)-2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	A
73	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(5-(pyridin-2-yl)-2,3-dihydro-1H-inden-2-yl)acetamide	A
74	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A

Table 2. The data provided is the IC₅₀ (nM) generated from Assay 1, except as otherwise noted by *, which is % inhibition, also generated from Assay 1.

Cmpd No.	Name	Data
77	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4,5,6,7-tetrahydro-2H-isoindol-1-yl)acetamide	B*
78	N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-oxoacetamide	A
79	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-oxoacetamide	A
80	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B
82	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A
83	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
84	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A
85	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)acetamide	A
86	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A
87	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)butanamide	A
88	2,2-difluoro-4-(6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)butanamide	A*
89	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-oxoacetamide	A
90	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-oxobutanamide	A
91	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)acetamide	B*
92	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-	A

	chloro-2,3-dihydro-1H-inden-2-yl)-2,2-difluoroacetamide	
93	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A
94	N-((1R,2R)-1-(3-chloro-4-isopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
95	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
96	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(3-methylazetidin-1-yl)propan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A*
97	2,2-difluoro-4-(6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)butanamide	A*
98	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-(hydroxyimino)acetamide	A
99	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(6-cyclopropoxy-pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
100	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(3-methylazetidin-1-yl)propan-2-yl)-2-oxoacetamide	B*
101	N-((1R,2R)-1-(6-cyclopropoxy-pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A
102	(E)-2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(3-methylazetidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	A
103	2-(5-chlorobenzofuran-2-yl)-2,2-difluoro-N-((1S,2R)-1-hydroxy-1-(2-isopropoxy-pyridin-4-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	B*
104	(E)-2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	A
105	N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
106	(E)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	A
107	2,2-difluoro-N-((1R,2R)-1-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)-4-(naphthalen-2-yl)butanamide	A
108	2,2-difluoro-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)-4-(naphthalen-2-yl)butanamide	B

109	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(naphthalen-2-yl)butanamide	A
110	N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
111	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-oxobutanamide	A
112	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	A
113	N-((1S,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	B*
114	2,2-difluoro-4-(6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-hydroxy-1-(2-isopropoxy-pyridin-4-yl)-3-(pyrrolidin-1-yl)propan-2-yl)butanamide	A*
115	(E)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	A
116	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
117	N-((1S,2R)-1-(2,2-dimethylchroman-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	B*
118	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	B
119	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,2-dimethylchroman-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A*
120	N-((1R,2R)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A*
121	N-((1R,2R)-1-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	B*
122	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-oxoacetamide	A*
123	N-((1R,2R)-1-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A*
124	N-((1S,2R)-1-(3-chloro-4-morpholinophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	B*
125	N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
126	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-	A

	difluoroacetamide	
127	N-((1R,2R)-1-(3-chloro-4-morpholinophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B
128	N-((1R,2R)-1-(4-(2-(azetidin-1-yl)ethoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
129	N-((1R,2R)-1-(3-chloro-4-(oxetan-3-yloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
130	N-((1R,2R)-1-(3-chloro-4-(oxetan-3-yloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	A
131	N-((1R,2R)-1-(4-(2-(azetidin-1-yl)ethoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A*
132	2-(6-chloronaphthalen-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
133	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
134	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	A*
135	2-(6-chloronaphthalen-2-yl)-2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A
136	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-(hydroxyimino)acetamide	A
137	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	B*
138	(E)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyimino)acetamide	A
139	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chloronaphthalen-2-yl)-2,2-difluoroacetamide	A*
140	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
141	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(hydroxyimino)-4-(naphthalen-2-yl)butanamide	A
142	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)-4-(naphthalen-2-	A

	yl)butanamide	
143	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(naphthalen-2-yl)-2-oxobutanamide	A
144	N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
145	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-4-(naphthalen-2-yl)-2-oxobutanamide	A*
146	N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chloronaphthalen-2-yl)-2,2-difluoroacetamide	A
147	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(naphthalen-2-yl)-2-oxobutanamide	A*
148	(E)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)-4-(naphthalen-2-yl)butanamide	A
149	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
150	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
151	2-(6-chloronaphthalen-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
152	N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
153	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyimino)acetamide	A
154	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-oxobutanamide	B*
155	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyimino)acetamide	A
156	2-(7-chloronaphthalen-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
157	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
158	(E)-2-(6-chloronaphthalen-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	A

159	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
160	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
161	N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
162	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A*
163	N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
164	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(hydroxyimino)-4-(naphthalen-2-yl)butanamide	A*
165	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(5,6,7,8-tetrahydronaphthalen-2-yl)butanamide	A
166	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(5,6,7,8-tetrahydronaphthalen-2-yl)butanamide	A
167	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)butanamide	A
168	N-((1S,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	B*
169	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-(hydroxyimino)acetamide	A*
170	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-4-(naphthalen-2-yl)-2-oxobutanamide	B*
171	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
172	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chloronaphthalen-2-yl)-2-oxoacetamide	A
173	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chloronaphthalen-2-yl)-2-(hydroxyimino)acetamide	A
174	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)thiophen-2-yl)-2-oxoacetamide	A
175	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)-2-oxoacetamide	A

176	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)-2-oxoacetamide	A
177	(E)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-r-biphenyl]-4-yl)-2-(hydroxyimino)acetamide	A
178	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(5-fluoropyridin-2-yl)phenyl)acetamide	A *
179	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(5-fluoropyridin-2-yl)phenyl)acetamide	A *
180	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(4-fluorophenyl)thiophen-2-yl)acetamide	A *
181	(Z)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)thiophen-2-yl)-2-(hydroxyimino)acetamide	A
182	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(pyridin-2-yl)phenyl)acetamide	A
183	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)acetamide	A
184	(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)-2-(hydroxyimino)acetamide	A
185	2-(5-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	B *
186	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(pyridin-2-yl)phenyl)acetamide	A *
187	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(pyridin-2-yl)phenyl)acetamide	A
188	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(6-chloronaphthalen-2-yl)-2-oxoacetamide	A *
189	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)-2-oxoacetamide	A *
190	(E)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-fluoropyridin-2-yl)phenyl)-2-(hydroxyimino)acetamide	A *
191	(E)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(6-chloronaphthalen-2-yl)-2-(hydroxyimino)acetamide	A

192	2-(5-chloro-2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A *
193	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)butanamide	A *
194	N-((1R,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
195	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyridin-2-yl)phenyl)acetamide	A *
196	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(imidazo[1,2-a]pyridin-2-yl)acetamide	B *
197	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-(4-fluorophenoxy)phenyl)-2-oxoacetamide	A
198	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)butanamide	A *
199	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(imidazo[1,2-a]pyridin-2-yl)acetamide	B *
200	N-((2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(piperidin-1-yl)phenyl)acetamide	A
201	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(3-(4-fluorophenoxy)phenyl)acetamide	A *
202	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)acetamide	A
203	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-(4-fluorophenoxy)phenyl)-2-oxoacetamide	A
204	N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
205	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
206	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(3-(4-fluorophenoxy)phenyl)acetamide	A *
207	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A

208	N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
209	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(naphthalen-2-yl)-2-oxoacetamide	A
210	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-(4-fluorophenoxy)phenyl)acetamide	A
211	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(2-(4-fluorophenyl)thiazol-4-yl)acetamide	B*
212	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)acetamide	A
213	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(2-(4-fluorophenyl)thiazol-4-yl)acetamide	B*
214	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyridin-2-yl)phenyl)acetamide	A
215	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)thiazol-5-yl)-2-oxoacetamide	B*
216	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-methyl-1H-indazol-5-yl)-2-oxoacetamide	A
217	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-methyl-1H-indazol-5-yl)-2-oxoacetamide	A
218	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(4-fluorophenyl)thiophen-2-yl)acetamide	B*
219	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)thiophen-2-yl)-2-oxoacetamide	A*
220	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
221	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)thiazol-4-yl)acetamide	A*
222	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(2-(4-fluorophenyl)thiazol-5-yl)acetamide	B*
223	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
224	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-methyl-1H-indazol-5-yl)-2-	A*

	oxoacetamide	
225	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-chlorobenzo[b]thiophen-5-yl)-2-oxoacetamide	B*
226	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)thiazol-4-yl)-2-oxoacetamide	B*
227	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-oxo-2-(4-(piperidin-1-yl)phenyl)acetamide	A
228	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyridin-2-yl)phenyl)acetamide	A
229	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)thiazol-4-yl)-2-oxoacetamide	B*
230	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)thiophen-2-yl)-2-oxoacetamide	A
231	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(piperidin-1-yl)phenyl)acetamide	A
232	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(1-methyl-1H-indazol-6-yl)phenyl)acetamide	A
233	2-(benzo[b]thiophen-5-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
234	N-((1R,2R)-1-(8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
235	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(1-methyl-1H-indazol-6-yl)phenyl)acetamide	A
236	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-6-yl)phenyl)acetamide	A
237	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4-(2-methyl-2H-indazol-6-yl)phenyl)acetamide	A
238	N-((2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(3-(piperidin-1-yl)phenyl)acetamide	B*
239	2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)thiophen-2-yl)acetamide	A
240	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-methyl-2H-indazol-	A

	5-yl)phenyl)-2-oxoacetamide	
241	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(4-fluorophenoxy)phenyl)-2-oxoacetamide	A
242	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	A
243	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
244	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-methyl-1H-indazol-6-yl)-2-oxoacetamide	A
245	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-methyl-1H-indazol-6-yl)-2-oxoacetamide	A*
246	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-methyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
247	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(6-(4-fluorophenyl)pyridin-3-yl)acetamide	A*
248	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(3-(4-fluorophenoxy)phenyl)-2-oxoacetamide	A
249	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-(4-fluorophenoxy)phenyl)-2-oxoacetamide	A
250	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-3-yl)-2-oxoacetamide	A
251	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-3-yl)-2-oxoacetamide	A
252	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(4-fluorophenyl)piperazin-1-yl)-2-oxoacetamide	A*
253	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
254	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(4-fluorophenyl)piperazin-1-yl)-2-oxoacetamide	A
255	2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
256	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indazol-6-	A

	yl)phenyl)-2-oxoacetamide	
257	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-isopropyl-2H-indazol-6-yl)phenyl)-2-oxoacetamide	A
258	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
259	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-isopropyl-2H-indazol-5-yl)phenyl)-2-oxoacetamide	A
260	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(4-fluorophenyl)pyridin-2-yl)acetamide	A
261	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-(1-methyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A*
262	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(4-fluorophenyl)piperazin-1-yl)-2-oxoacetamide	B*
263	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-chlorobenzo[b]thiophen-5-yl)phenyl)-2-oxoacetamide	A
264	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-(4-fluorophenyl)pyridin-2-yl)-2-oxoacetamide	A
265	N-((1R,2R)-1-(4-cyclopropoxy-3-(trifluoromethyl)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B*
266	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indol-5-yl)phenyl)-2-oxoacetamide	A
267	2-(4'-chloro-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
268	N-((1R,2R)-1-(5-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
269	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indol-5-yl)phenyl)-2-oxoacetamide	A
270	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
271	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-benzo[d]imidazol-5-yl)phenyl)-2-oxoacetamide	A
272	2-(4'-chloro-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-	A

	yl)propan-2-yl)-2-oxoacetamide	
273	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyrrolidin-1-yl)phenyl)acetamide	A
274	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)acetamide	A
275	2-(4-(1-cyclopropyl-1H-indazol-5-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
276	N-((1R,2R)-1-(8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
277	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
278	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
279	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(4-(1-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
280	2-(4-(benzo[d]isoxazol-6-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
281	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
282	2-(4-(1-cyclopropyl-1H-indazol-6-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
283	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
284	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-cyclopropyl-2H-indazol-6-yl)phenyl)-2-oxoacetamide	A
285	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4-(1-cyclopropyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
286	2-(4'-(4-fluoro-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(8-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propan-2-yl)-2-oxoacetamide	B
287	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-(4-fluorophenyl)pyridin-3-yl)-2-oxoacetamide	A
288	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorobenzyl)-1H-indazol-5-	A

	yl)-2-oxoacetamide	
289	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorobenzyl)-1H-indazol-5-yl)-2-oxoacetamide	A
290	2-(4-(benzo[d]isoxazol-5-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
291	N-((1R,2R)-1-(4-(tert-butoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B
292	2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
293	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
294	2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
295	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-2'-methyl-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B
296	2-(4-(benzo[d]thiazol-5-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
297	2-(4-(benzo[d]thiazol-6-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
298	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-2-methyl-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
299	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-2-methyl-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
300	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
301	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
302	2-(8-bromodibenzo[b,d]furan-2-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
303	N-[(1R,2R)-2-(3-chloro-4-cyclopropoxyphenyl)-2-hydroxy-1-(pyrrolidinylmethyl)ethyl]-2-[4-(4-fluorophenyl)phenyl]acetamide	A
304	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorobenzyl)-2H-indazol-5-yl)-2-oxoacetamide	A

305	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorobenzyl)-2H-indazol-5-yl)-2-oxoacetamide	A
306	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indazol-6-yl)-2-oxoacetamide	A
307	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indazol-6-yl)-2-oxoacetamide	A
308	2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
309	N-((1R,2R)-1-(3-chloro-4-(cyclopentyloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
310	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-isopropyl-3-methyl-2H-indazol-5-yl)phenyl)-2-oxoacetamide	A
311	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-isopropyl-2H-indazol-5-yl)-2-oxoacetamide	A
312	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-isopropyl-2H-indazol-6-yl)-2-oxoacetamide	A
313	N-((1R,2R)-1-(3-chloro-4-cyclobutoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
314	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-3-methyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
315	2-(4'-fluoro-2'-methyl-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
316	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-isopropyl-2H-indazol-6-yl)-2-oxoacetamide	A
317	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-3-methyl-1H-indazol-5-yl)-2-oxoacetamide	A
318	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1,3-dimethyl-1H-indazol-5-yl)phenyl)-2-oxoacetamide	A
319	N-((1R,2R)-1-(benzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
320	N-((1R,2R)-1-(3-chloro-4-(cyclopropylthio)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
321	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indazol-5-yl)-2-	A

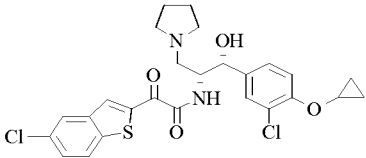
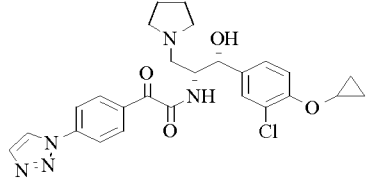
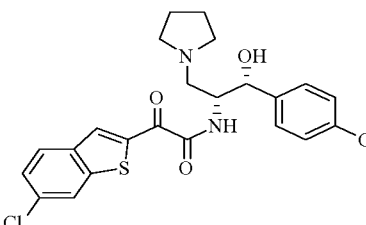
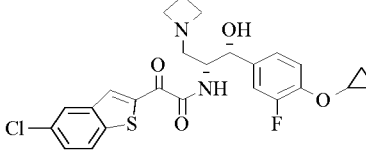
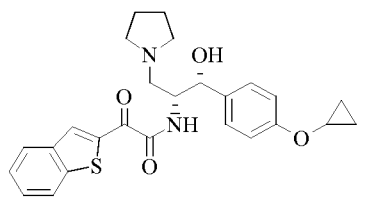
	oxoacetamide	
322	2-(4-(1,3-dimethyl-1H-indazol-5-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
323	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indol-5-yl)-2-oxoacetamide	A
324	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indol-5-yl)-2-oxoacetamide	A
325	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-morpholinophenyl)-2-oxoacetamide	A
326	(S)-N-(1-(3-chloro-4-cyclopropoxyphenyl)-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B
327	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-oxo-2-(4-(pyrrolidin-1-yl)phenyl)acetamide	A
328	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-chloronaphthalen-2-yl)-2,2-difluorobutanamide	A
329	N-((1R,2R)-1-(3-chloro-4-(vinylloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
330	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-pyrazol-4-yl)phenyl)-2-oxoacetamide	A
331	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indol-6-yl)-2-oxoacetamide	A
332	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-isopropyl-1H-indol-6-yl)-2-oxoacetamide	A
333	N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
334	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-3-methyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
335	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-isopropyl-3-methyl-2H-indazol-6-yl)phenyl)-2-oxoacetamide	A
336	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2-isopropyl-3-methyl-2H-indazol-6-yl)phenyl)-2-oxoacetamide	A
337	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-3-methyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
338	N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-	A

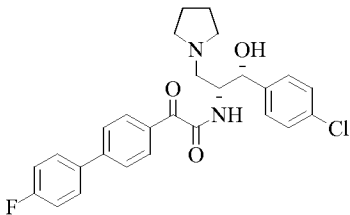
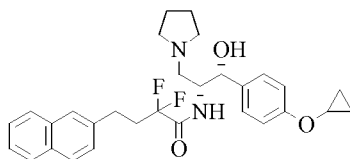
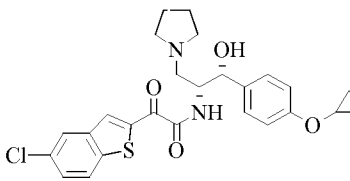
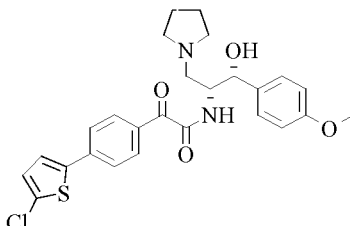
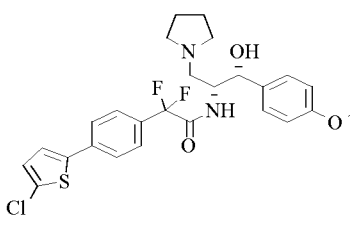
	oxoacetamide	
339	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
340	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1,3-dimethyl-1H-indazol-6-yl)phenyl)-2-oxoacetamide	A
341	2-(4-(1,3-dimethyl-1H-indazol-6-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
342	2-(4-(2,3-dimethyl-2H-indazol-6-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
343	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyrrolidin-1-yl)phenyl)acetamide	A
344	N-((1R,2R)-1-(3-fluoro-4-isopropoxy-5-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,r-biphenyl]-4-yl)-2-oxoacetamide	A
345	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indol-6-yl)phenyl)-2-oxoacetamide	A
346	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-indol-6-yl)phenyl)-2-oxoacetamide	A
347	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(2,3-dimethyl-2H-indazol-6-yl)phenyl)-2-oxoacetamide	A
348	2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(3-fluoro-4-isopropoxy-5-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
349	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-cyclopropyl-1H-pyrazol-3-yl)phenyl)-2-oxoacetamide	A
350	2-(4-(1-cyclopropyl-1H-pyrazol-3-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
351	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-pyrazol-3-yl)phenyl)-2-oxoacetamide	A
352	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(1-isopropyl-1H-pyrazol-3-yl)phenyl)-2-oxoacetamide	A
353	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorophenyl)-1H-indazol-5-yl)-2-oxoacetamide	A
354	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)-2H-indazol-5-	A

	yl)-2-oxoacetamide	
355	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4'-(prop-1-en-2-yl)-[1,1'-biphenyl]-4-yl)acetamide	A
356	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
357	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
358	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
359	2-(4-(5-chlorothiophen-2-yl)phenyl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
360	2-(4-(5-chlorothiophen-2-yl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
361	N-((1R,2R)-1-(3-fluoro-5-isopropoxy-4-methoxyphenyl)-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B
362	N-((1R,2R)-1-(8-fluoro-3,3-dimethyl-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	A
363	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-chlorothiophen-2-yl)phenyl)-2-oxoacetamide	A
364	2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(3-fluoro-5-isopropoxy-4-methoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
365	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chlorobenzofuran-2-yl)-2-oxoacetamide	A
366	2-(6-chlorobenzofuran-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
367	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-oxo-2-(4-(pyrrolidin-1-yl)phenyl)acetamide	nt
368	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-(4-morpholinophenyl)-2-oxoacetamide	A
369	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(4-morpholinophenyl)-2-oxoacetamide	A
370	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-	A

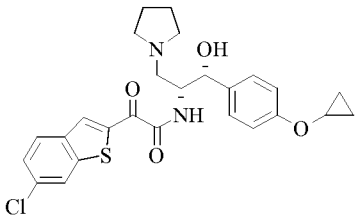
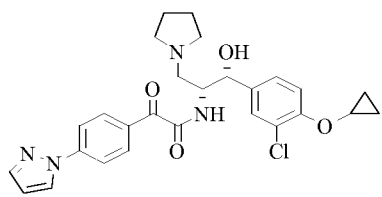
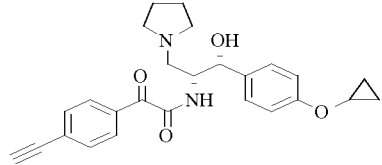
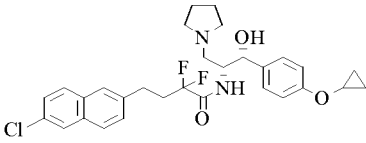
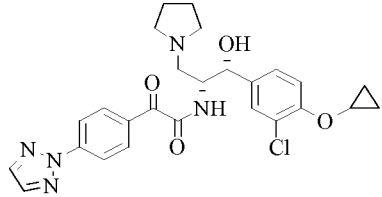
	2-oxoacetamide	
371	2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
372	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(tetrahydro-2H-pyran-4-yl)phenyl)acetamide	A
373	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(tetrahydro-2H-pyran-4-yl)phenyl)acetamide	A
374	N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-morpholinophenyl)-2-oxoacetamide	B
375	2-(4-(azetidin-1-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
376	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-fluorophenyl)-2-oxoacetamide	A
377	2-(benzo[b]thiophen-2-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
378	N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-ethynylphenyl)-2-oxoacetamide	A
379	N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-fluorophenyl)-2-oxoacetamide	A
380	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorophenyl)piperidin-4-yl)-2-oxoacetamide	B
381	N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxypropan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	A
382	N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-N-methyl-2-oxoacetamide	A
383	2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-N-methyl-2-oxoacetamide	A

Table 3. The data provided is the IC₅₀ (nM) generated from Assay 1, except as otherwise noted by *, which is % inhibition, also generated from Assay 1.

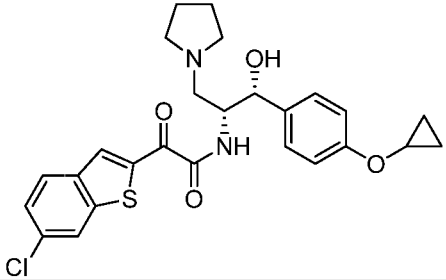
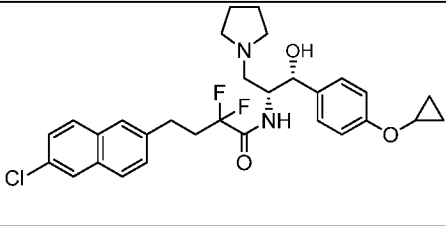
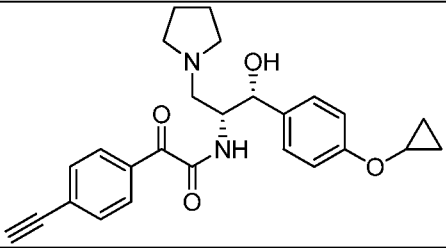
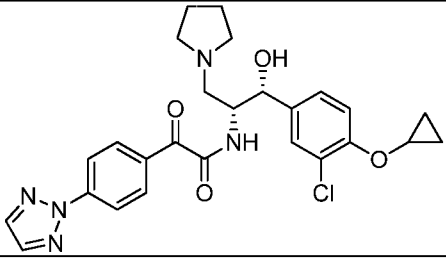
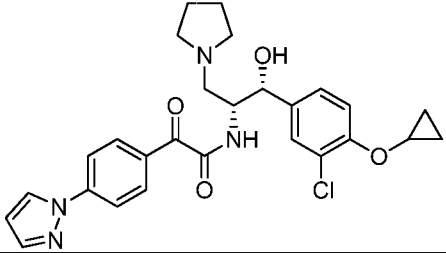
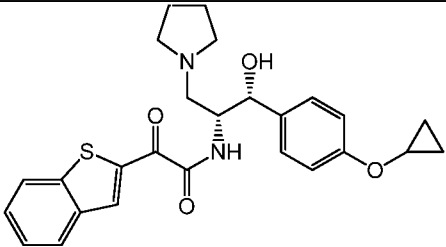
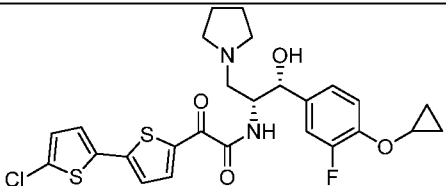
Ex	Structure	Name	Data
384		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	A
385		2-(4-(1H-1,2,3-triazol-1-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
386		2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
387		N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	A
388		2-(benzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A

389		N-((1R,2R)-1-(4-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	B
390		N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-4-(naphthalen-2-yl)butanamide	A
391		2-(5-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
392		2-(4-(5-chlorothiophen-2-yl)phenyl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
393		2-(4-(5-chlorothiophen-2-yl)phenyl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A

394		N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide	A
395		N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-cyclopropylphenyl)-2-oxoacetamide	A
396		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(5-chlorothiophen-2-yl)phenyl)-2,2-difluoroacetamide	A
397		2-(4-(5-chlorothiophen-2-yl)phenyl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	A
398		2-(4-(5-chlorothiophen-2-yl)phenyl)-2,2-difluoro-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	A

399		2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
400		2-(4-(1H-pyrazol-1-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A
401		N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-ethynylphenyl)-2-oxoacetamide	B
402		4-(6-chloronaphthalen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluorobutanamide	B
403		2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	A

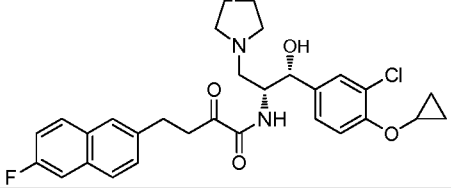
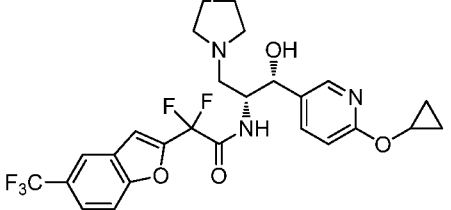
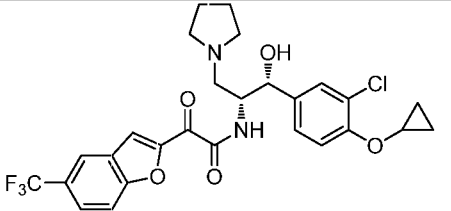
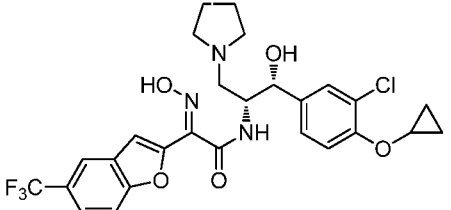
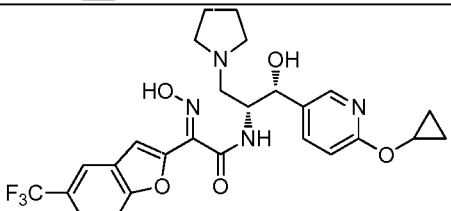
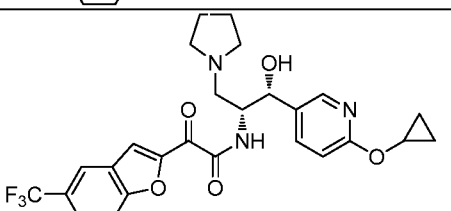
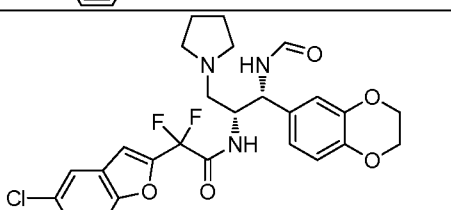
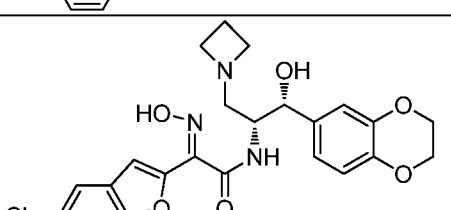
404		N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-N-methyl-2-oxoacetamide	A
405		2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-(difluoromethoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	B
406		(E)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	A*
407		N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
408		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(isoxazolidin-2-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
409		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(isoxazolidin-2-yl)propan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	nt

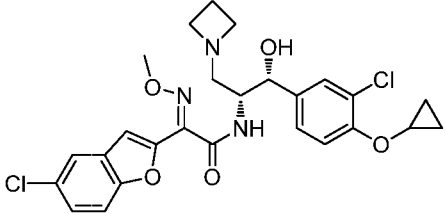
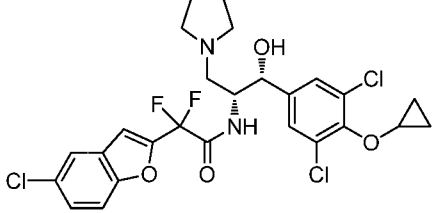
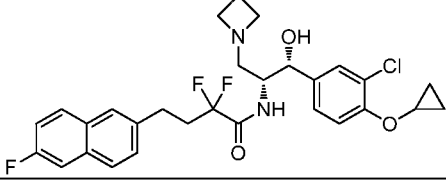
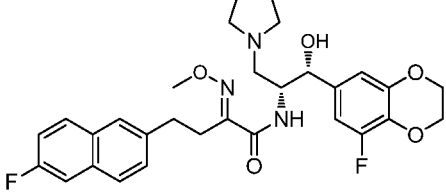
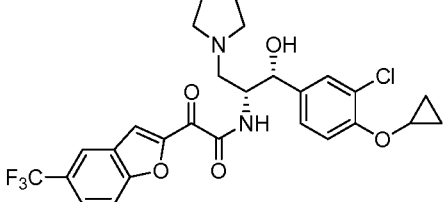
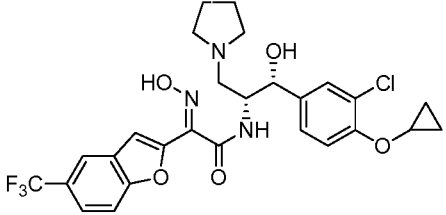
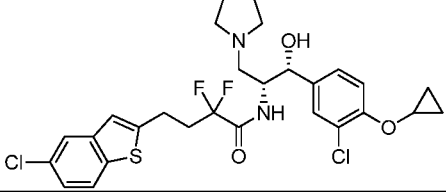
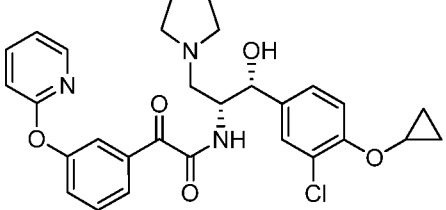
410		2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
411		4-(6-chloronaphthalen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluorobutanamide	nt
412		N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-ethynylphenyl)-2-oxoacetamide	nt
413		2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
414		2-(4-(1H-pyrazol-1-yl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
415		2-(benzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
416		2-(5'-chloro-[2,2'-bithiophen]-5-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt

417		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2',4'-difluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
418		2-(3-chloropyrrolo[1,2-b]pyridazin-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
419		2-(7-chloroimidazo[1,2-a]pyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
420		N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(6-(trifluoromethyl)furo[3,2-c]pyridin-2-yl)acetamide	nt
421		2-(6-chlorofuro[3,2-b]pyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
422		N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(2-(trifluoromethyl)furo[2,3-d]pyrimidin-6-yl)acetamide	nt
423		2-(5-chlorothieno[3,2-b]furan-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt

424		2-(5-chlorothieno[2,3- <i>d</i>]oxazol-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
425		2-(2-chlorofuro[2,3- <i>d</i>]thiazol-5-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
426		3-(3-chlorobenzyl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluorobut-3-enamide	nt
427		2-(5-chlorobenzofuran-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxy-3-(2,2,5,5-tetradeuteropyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
428		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-((4-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)methoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	nt
429		2-(5-chloro-2,3-dihydro-1 <i>H</i> -inden-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-((4-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)methoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
430		2-(5-chlorobenzofuran-2-yl)-2,2-difluoro- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-hydroxy-1-(4-((4-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)methoxy)phenyl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	nt
431		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(4-chloro-3-((4-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)methoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2,2-difluoroacetamide	nt

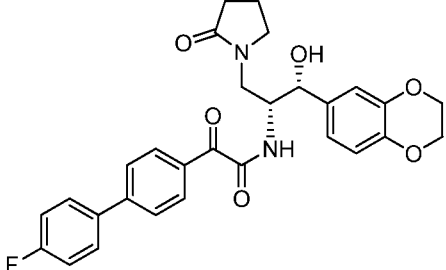
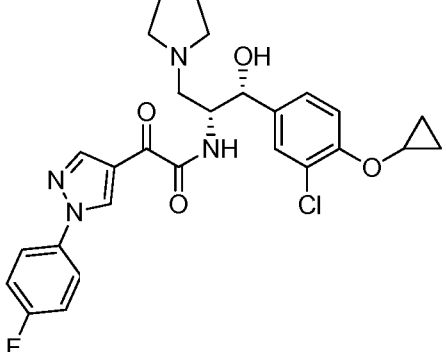
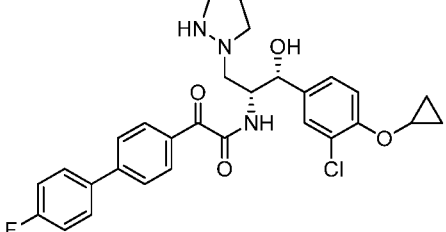
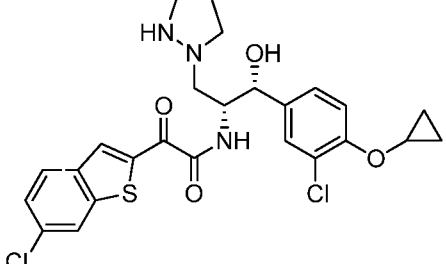
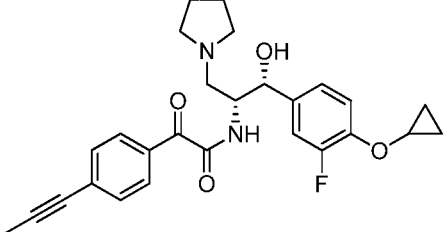
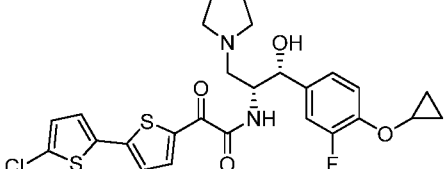
432		2-(5-chlorobenzofuran-2-yl)-2,2-difluoro- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-hydroxy-1-(2-isopropoxy)pyridin-4-yl)-3-(pyrrolidin-1-yl)propan-2-ylacetamide	nt
433		2-(5-chlorobenzofuran-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
434		(<i>E</i>)-2-(5-chlorobenzofuran-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	nt
435		2-(5-chloro-2,3-dihydro-1 <i>H</i> -inden-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
436		(<i>E</i>)-2-(5-chloro-2,3-dihydro-1 <i>H</i> -inden-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)acetamide	nt
437		2-(5-chlorobenzofuran-2-yl)-2,2-difluoro- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-hydroxy-1-(6-(4-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)methoxy)pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)acetamide	nt
438		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-oxobutanamide	nt
439		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxy)pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(hydroxyimino)butanamide	nt

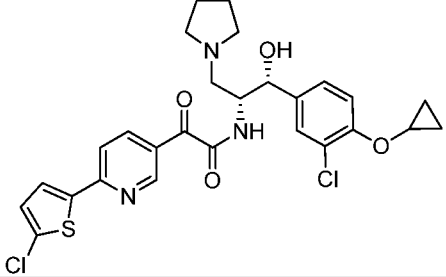
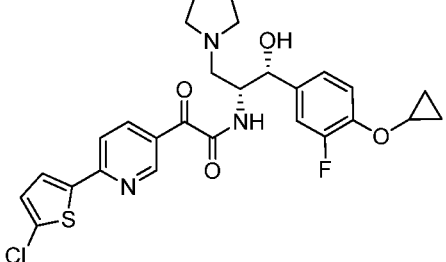
440		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-oxobutanamide	nt
442		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
443		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
444		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
445		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
446		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
447		2-(5-chlorobenzofuran-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-formamido-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
448		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-(hydroxyimino)acetamide	nt

449		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(5-chlorobenzofuran-2-yl)-2-(methoxyimino)acetamide	nt
450		2-(5-chlorobenzofuran-2-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3,5-dichloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoroacetamide	nt
451		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2,2-difluoro-4-(6-fluoronaphthalen-2-yl)butanamide	nt
452		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(8-fluoro-2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(6-fluoronaphthalen-2-yl)-2-(methoxyimino)butanamide	nt
453		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
454		(<i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(hydroxyimino)-2-(5-(trifluoromethyl)benzofuran-2-yl)acetamide	nt
455		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-4-(5-chlorobenzo[<i>b</i>]thiophen-2-yl)-2,2-difluorobutanamide	nt
456		<i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(3-(pyridin-2-yloxy)phenyl)acetamide	nt

457		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-((1-methyl-1H-indazol-6-yl)oxy)phenyl)-2-oxoacetamide	nt
458		N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(3-((1-methyl-1H-indazol-6-yl)oxy)phenyl)-2-oxoacetamide	nt
459		N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorophenyl)-1H-imidazol-4-yl)-2-oxoacetamide	nt
460		2-(1-(6-chloronaphthalen-2-yl)-1H-pyrazol-3-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
461		2-(1-(6-chloronaphthalen-2-yl)-1H-pyrazol-4-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
462		N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)-2-oxoacetamide	nt
463		2-(4-(6-chloronaphthalen-2-yl)-1-methyl-1H-imidazol-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
464		N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4-(4-fluorophenyl)-1-methyl-1H-imidazol-2-yl)-2-oxoacetamide	nt

465		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenoxy)pyridin-4-yl)-2-oxoacetamide	nt
466		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2,2-difluoro-2-(2-(4-fluorophenoxy)pyridin-4-yl)acetamide	nt
467		N-((1R,2R,3S)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)butan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
468		N-((1R,2R)-1-(3-chloro-4-(difluoromethoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	nt
469		2-(6-chlorobenzo[b]thiophen-2-yl)-N-((1R,2R)-1-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt
470		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(2-oxopyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt

471		N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(2-oxopyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
472		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)-2-oxoacetamide	nt
473		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide	nt
474		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chlorobenzo[b]thiophen-2-yl)-2-oxoacetamide	nt
475		N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(prop-1-yn-1-yl)phenyl)acetamide	nt
476		2-(5'-chloro-[2,2'-bithiophen]-5-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt

477		N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-(5-chlorothiophen-2-yl)pyridin-3-yl)-2-oxoacetamide	nt
478		2-(6-(5-chlorothiophen-2-yl)pyridin-3-yl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide	nt

Sandhoff Disease Mouse Model

[0001330] The murine model of Sandhoff disease is a knock out (KO) of the HEXB gene, which codes for beta-hexosaminidase in mice, as it does in humans. This KO mouse displays a phenotype closely resembling that seen in humans, although at a more advanced age, compared to humans. At ~3 months of age, the animals develop tremor and increased limb tone, which is worse in the hind legs. These manifestations become progressively more severe until 4-5 months of age, when the animals become moribund and rapidly lose weight. The motor phenotype has been quantified by activity monitor, bar-crossing, and inverted screen tests (Jayakumar M et al *Blood* **2001**, 97, 327-329; Cachon-Gonzalez et al *PNAS* **2006**, 103(27), 1037-10378). Histologically, the mouse neurons appear to be distended by lysosomal storage material, and signs of neuroinflammation are present. Biochemically, levels of beta-hexosaminidase are absent, and accumulations of gangliosides GM2, GA2, as well as sialic acid, can be demonstrated (Cachon-Gonzalez et al 2006; Arthur et al *Neurochem Res* **2013**, DOI 10.1007/s11064-013-0992-5).

[0001331] To evaluate the potential efficacy of different BioMarin substrate reduction compounds in Sandhoff disease, homozygous male mice are mated with heterozygous females. All pups (approximately 50% KO and 50% het) in a litter are treated by daily IP or SC injection with the same test (or control) article for 14 days, beginning at 3 days old. The chosen route of administration is determined based on pharmacokinetic/pharmacodynamic properties of the compound to be tested. At the end of the dosing period, pups are deeply anesthetized using isoflurane through nose cones (4% for induction and 1.5% for maintenance), blood is collected by cardiac puncture method, then the mice are euthanized. Brains and livers are collected and snap frozen. These tissues are used for analysis of experimental endpoints (GM2 and sialic acid in brain, GA2 and sialic acid in liver). An additional tissue sample (tail tip or toe) is collected and snap frozen, then sent for genotyping.

[0001332] 1(f) tested compounds are found which have a marked effect on the experimental endpoints, an additional experiment is performed looking at effects on activity, inverted screen, and bar crossing tests, as well as average survival time, compared to vehicle-treated mice.

Polycystic Kidney Disease Mouse Model

[0001333] To jck mice is administered a compound of the invention ad libitum in food (standard chow) from 26-64 days of age. Control jck mice are fed a control diet from 26-64 days of age. At 63 days of age, the animals are transferred to metabolic cages for 24 hour

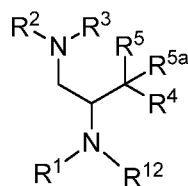
urine collection. At 64 days of age, animals are sacrificed, weighed, and blood is collected by heart puncture for serum isolation. Kidneys are isolated, bisected, and weighed and half of each kidney is fixed in 4% paraformaldehyde in PBS overnight for paraffin embedding and hematoxylin and eosin staining. Kidney weight to body weight ratio is used to determine activity of the compound. Cyst volume is measured by quantitating the percentage of cystic area in histological sections of kidneys from the treated and control animals and multiplied by the kidney/body weight ratio. Kidney function is assessed by measuring blood urea nitrogen (BUN) levels in serum samples derived from animals at sacrifice. BUN levels are elevated in untreated controls while the treated animals demonstrated a significant reduction of BUN levels.

[0001334] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following description. It should be understood, however, that the description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present description will become apparent from this detailed description.

[0001335] All publications including patents, patent applications and published patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



Formula I;

wherein

R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$ or $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$;

X^1 is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^7 groups;

R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 R^8 ;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1, 2, 3, or 4 R^9 groups;

R^5 is $-OH$, and R^{5a} is hydrogen;

R^6 and R^{6a} are halo; R^6 and R^{6a} are deuterium; or R^6 and R^{6a} together with the carbon to which they are attached form $C(=NOH)$ or $C(O)$;

each R^7 , when present, is independently nitro, cyano, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, haloalkoxy, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenoxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a} ;

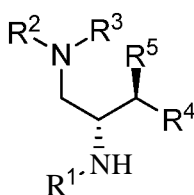
each R^{7a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R^8 , when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl; or two R^8 together with the carbon to which they are attached form $C(O)$;

each R^9 , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy,

heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a} ; each R^{9a} , when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino; and R^{12} is hydrogen or C_{1-5} alkyl; optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

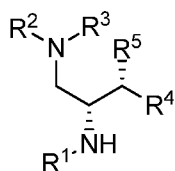
2. The compound of claim 1, wherein the compound of Formula I is according to Formula 1(b):



Formula 1(b)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound of Formula I is according to Formula 1(c):



Formula 1(c)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3, wherein R^2 and R^3 together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R^8 ; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein R^2 and R^3 together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring, optionally substituted with 1 or 2 R^8 ; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
6. The compound of any one of claims 1-5, wherein R^4 is aryl which is optionally substituted with 1, 2, or 3 R^9 groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
7. The compound of claim 6, wherein each R^9 , when present, is independently halo, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyloxy, or heterocycloalkylalkyloxy; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
8. The compound of claim 6, wherein R^4 is phenyl substituted with a halo and a cycloalkyloxy group; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
9. The compound of any one of claims 1-5, wherein R^4 is heteroaryl which is optionally substituted with 1, 2, or 3 R^9 groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
10. The compound of claim 9, wherein R^4 is 2,3-dihydrobenzo[ϵ][1,4]dioxin-6-yl optionally substituted with a halo; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
11. The compound of any one of claims 1-10, wherein R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-10, wherein R^1 is $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
13. The compound of claim 12, wherein X^1 is C_{1-3} alkylene; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
14. The compound of any one of claims 1-13, wherein R^{1a} is aryl optionally substituted with 1, 2, or 3 R^7 groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
15. The compound of claim 14, wherein R^{1a} is phenyl optionally substituted with 1 R^7 group, wherein each R^7 , when present, is independently phenyl, heterocycloalkyl, or heteroaryl; where the phenyl and the heteroaryl are independently optionally substituted with 1 or 2 R^{7a} ; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
16. The compound of any one of claims 1-13, wherein R^{1a} is heteroaryl optionally substituted with 1, 2, or 3 R^7 groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
17. The compound of claim 16, wherein R^{1a} is heteroaryl optionally substituted with 1 or 2 R^7 groups, wherein each R^7 , when present, is independently halo, alkyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, or heteroaryl; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1 R^{7a} ; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
18. The compound of any one of claims 1-17, wherein R^6 and R^{6a} together with the carbon to which they are attached form $C(O)$ or $C(=NOH)$; optionally as a tautomer, a single

stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

19. The compound of claim 18, wherein R^6 and R^{6a} together with the carbon to which they are attached form $C(O)$; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

20. The compound of any one of claims 1-17, wherein R^6 and R^{6a} are halo; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

21. The compound of claim 20, wherein R^6 and R^{6a} are fluoro; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 wherein:

R^1 is $-C(O)C(R^6)(R^{6a})R^{1a}$ or $-C(O)C(R^6)(R^{6a})-X^1-R^{1a}$;

X^1 is alkylene, alkenylene, or cycloalkylene;

R^{1a} is alkyl, heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^7 groups;

R^2 and R^3 together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R^8 ;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^9 groups;

R^5 is $-OH$, and R^{5a} is hydrogen;

R^6 and R^{6a} are halo; or R^6 and R^{6a} together with the carbon to which they are attached form $C(=NOH)$ or $C(O)$;

each R^7 , when present, is independently nitro, cyano, halo, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenoxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a} ;

each R^{7a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently amino, alkylamino, dialkylamino, alkyl, halo, or cycloalkyl; or two R⁸ together with the carbon to which they are attached form C(O);
 each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a};
 each R^{9a}, when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy-carbonyl, amino, alkylamino, and dialkylamino; and
 R¹² is hydrogen or CH₃;
 optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 wherein:

R¹ is -C(0)C(R⁶)(R^{6a})R^{1a} or -C(0)C(R⁶)(R^{6a})-X¹-R^{1a};

X¹ is alkylene;

R^{1a} is heterocycloalkyl, aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁷ groups;

R² and R³ together with the nitrogen to which they are attached form a 4-5 membered monocyclic heterocycloalkyl ring or a 7-8 membered bicyclic heterocycloalkyl; each of which is optionally substituted with 1 or 2 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is -OH, and R^{5a} is hydrogen;

R⁶ and R^{6a} are halo; or R⁶ and R^{6a} together with the carbon to which they are attached form or C(O);

each R⁷, when present, is independently nitro, cyano, halo, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, phenylalkyl, phenyloxy, heteroaryl, heteroarylalkyl, or heteroaryloxy; where the phenyl and the heteroaryl, either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{7a};

each R^{7a}, when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl;

each R⁸, when present, is independently amino, alkylamino, dialkylamino, alkyl, or halo;

each R⁹, when present, is independently amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, hydroxy, alkoxy, alkenyloxy, hydroxyalkyloxy, haloalkoxy, cycloalkylthio,

cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the heterocycloalkyl and the phenyl, either alone or as part of another group, are independently optionally substituted with 1 or 2 R^{9a}; each R^{9a}, when present, is independently selected from alkyl and halo; and R¹² is hydrogen or CH₃; optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

24. A compound selected from Tables 1, 2 or 3; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

25. A compound selected from the group consisting of:

N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(6-chloronaphthalen-2-yl)-2-oxoacetamide;

N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxo-2-(4-(pyridin-2-yl)phenyl)acetamide;

N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-(2-(4-fluorophenyl)thiazol-5-yl)-2-oxoacetamide;

N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-oxoacetamide; and

2-(4'-chloro-[1,1'-biphenyl]-4-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-2-oxoacetamide.

26. A pharmaceutical composition comprising i) a compound of any one of claims 1-25 optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and ii) a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

27. A method of treating a disease or disorder comprising administering a compound according to any one of claims 1-25 or the pharmaceutical composition of claim 26.

28. The method of claim 27, wherein the disease or disorder is a glycolipid storage disease; a disease associated with glycolipid accumulation; a disease that causes renal hypertrophy or hyperplasia; a disease that causes hyperglycemia or hyperinsulemia; a cancer in which glycolipid synthesis is abnormal; an infectious disease caused by organisms which use cell surface glycolipids as receptors or in which synthesis of glucosylceramide is essential or important; atherosclerosis; polycystic kidney disease; renal hypertrophy; diabetes mellitus; breast cancer; renal adenocarcinoma; brain cancer; neuroblastoma; lung cancer; intestinal cancer; pancreatic cancer; prostate cancer; a neuronal disorder; a neuronal injury; an inflammatory disease or disorder; or obesity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/056555

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	C07D405/14	C07D319/18	C07D405/12	C07D407/12	C07D417/12
	C07D307/79	C07D409/12	C07D213/64	C07D295/12	C07D309/10
	C07D311/12	C07D413/12	C07D265/30	C07D205/04	C07D333/16

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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data, CHEM ABS Data, BEI LSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 2009/045503 AI (GENZYME CORP [US] ; NATOLI THOMAS A [US] ; IBRAGHINOV-BESKROVNAYA OXANA) 9 April 2009 (2009-04-09) page 61; example 1E12; compound 31 page 116, line 22 page 117; claim 1 -----	1-28
X	wo 2008/150486 A2 (GENZYME CORP [US] ; SI EDEL CRAIG [US] ; BASTOS CECILIA M [US] ; HARRIS DA) 11 December 2008 (2008-12-11) page 5, line 9 page 166; compound 31 page 294; claim 1 page 344; claim 84 ----- -/- .	1-28

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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 21 November 2014	Date of mailing of the international search report 01/12/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Jeanjean , Fabien
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 2013/095089 AI (LARSEN SCOTT [US] ET AL) 18 April 2013 (2013-04-18) page 27; claim 1 -----	1-28
E	WO 2014/150043 AI (CONCERT PHARMACEUTICALS INC [US]) 25 September 2014 (2014-09-25) page 27; claim 15; table 1; compound 102 -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/056555
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