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(54) **Title:** USES OF SATL-INDUCIBLE KINASE (SIK) INHIBITORS FOR TREATING OSTEOPOROSIS

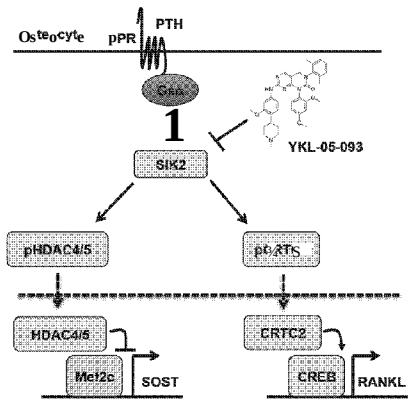
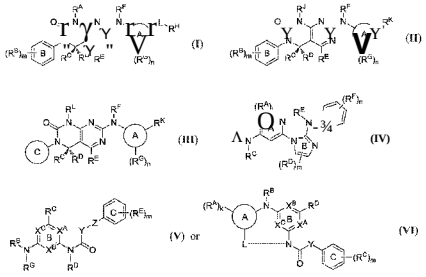


Figure 9



(57) Abstract: The present disclosure provides methods of treating and/or preventing osteoporosis using salt-inducible kinase (SIK) inhibitors. Also provided are methods of using SIK inhibitors for increasing the function of osteocytes, increasing the number of osteoblasts, increasing the activity of osteoblasts, inhibiting the resorption of a bone, decreasing the number of osteoclasts, inhibiting the activity of osteoclasts, increasing the mass of a bone, down-regulating the expression of the gene SOST, and/or inhibiting the activity of sclerostin. The SIK inhibitors may be combined with Src inhibitors or CSF I R inhibitors. Exemplary SIK inhibitors include the compounds of the formula: (I), (II), (III), (rV), (V) or (VI).

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USES OF SALT-INDUCIBLE KINASE (SIK) INHIBITORS FOR TREATING OSTEOPOROSIS

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/396,089, filed September 16, 2016, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Osteoporosis is a serious problem in our aging population, with fragility fractures costing $25 billion annually (1). Novel treatments are needed to boost bone mass. Osteocytes, cells buried within bone, orchestrate bone remodeling by secreting endocrine and paracrine factors (2). Central amongst these are RANKL (encoded by the TNFSFl 1 gene), the major osteocyte-derived osteoclastogenic cytokine (3, 4) and an FDA-approved osteoporosis drug target (5), and sclerostin (encoded by the SOST gene), an osteocyte-derived WNT pathway inhibitor that blocks bone formation by osteoblasts (6) and current osteoporosis drug target (7).

[0003] When given once daily, parathyroid hormone (PTH), is the only approved osteoporosis treatment agent that stimulates new bone formation. The proximal signaling events downstream of Gsa-coupled PTH receptor signaling in bone cells are well-characterized (8), but how cAMP generation in osteocytes is linked to gene expression changes remains unknown. SOST and RANKL are well-established target genes important for the physiological effects of PTH on osteocytes. Among the mechanisms through which PTH stimulates new bone formation, down-regulation of SOST expression in osteocytes plays an important role (9-1 1). PTH also stimulates bone catabolism, in large part through stimulation of osteoclastogenesis via inducing RANKL (12-15), which may limit its therapeutic efficacy (16). Therefore, there is a need for the treatment of osteoporosis.

GOVERNMENT SUPPORT

[0004] This invention was made with government support under grant numbers AR067285, DKOl 1794, and AR066261 awarded by the National Institutes of Health. The government has certain rights in the invention.

SUMMARY OF THE INVENTION

[0005] The present invention is based on the discovery that inhibitors of salt-inducible kinases (SIK) are useful in the treatment and/or prevention of osteoporosis. SIK inhibitors may be able to treat osteoporosis, prevent osteoporosis, increase the function of osteocytes, increase the number of osteoblasts, increase the activity of osteoblasts, inhibit the resorption of a bone, decrease the number of osteoclasts, inhibit the activity of osteoclasts, increase the mass of a bone, down-regulate the expression of the gene SOST, and/or inhibit the activity of sclerostin, in a subject in need thereof. In certain embodiments, the SIK is salt-inducible kinase 1 (SIK1). In certain embodiments, the SIK is salt-inducible kinase 2 (SIK2). In certain embodiments, the SIK is salt-inducible kinase 3 (SIK3).

[0006] Without being bound by any theory, SIK inhibitors may be able to down-regulate the expression of the gene SOST. Down-regulation of the expression of SOST in osteocytes may increase bone formation, *e.g.,* by osteoblasts. The SIK inhibitors may also be able to inhibit the resorption of a bone, *e.g.,* by osteoclasts. The SIK inhibitors may inhibit *(e.g.,* directly inhibit) osteoclasts. The SIK inhibitors may also inhibit proto-oncogene tyrosine-protein kinase Src (Src) and/or colony stimulating factor 1 receptor (CSFIR; macrophage colony stimulating factor (M-CSF) receptor). Src and/or CSFI R may be associated with osteoclast function. The SIK inhibitors may be beneficial as being anabolic agents that also block the resorption of a bone.

[0007] In one aspect, the present disclosure provides methods of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a SIK inhibitor.

[0008] In another aspect, the present disclosure provides methods of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of a SIK inhibitor.

[0009] In another aspect, the present disclosure provides methods of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0010] In another aspect, the present disclosure provides methods of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0011] In another aspect, the present disclosure provides methods of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0012] In another aspect, the present disclosure provides methods of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0013] In another aspect, the present disclosure provides methods of decreasing the number of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0014] In another aspect, the present disclosure provides methods of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0015] In another aspect, the present disclosure provides methods of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

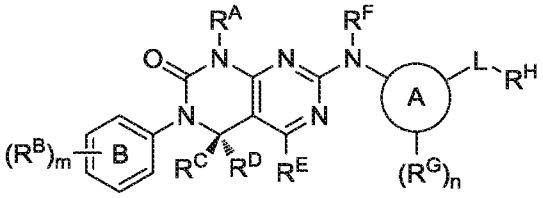
[0016] In another aspect, the present disclosure provides methods of down-regulating the expression of the gene SOST in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0017] In another aspect, the present disclosure provides methods of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0018] In another aspect, the present disclosure provides methods of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[0019] The SIK inhibitors useful in the invention include, but are not limited to, bicyclic urea compounds of any one of Formulae **(I), (II),** and **(III),** imidazolyl compounds of Formula **(IV),** urea and carbamate compounds of Formula **(V),** macrocyclic compounds of Formula **(VI),** and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

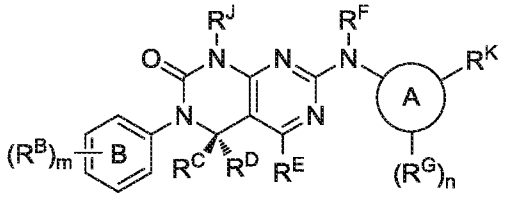
[0020] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula **(I):**



(I),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring A, Ring B, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, L, m, and n are as described herein for Formula **(I).**

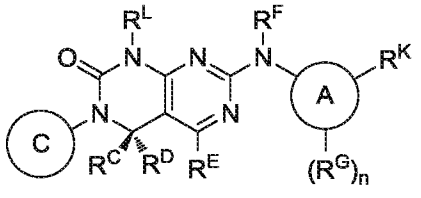
[0021] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula (**II**)**:**



(II),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring A, Ring B, R^J, R^B, R^c, R^D, R^E, R^F, R^G, R^K, m, and n are as described herein for Formula **(II).**

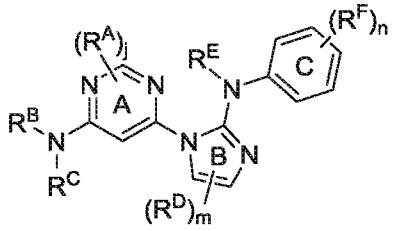
[0022] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula (**III**)**:**



(III),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring A, Ring C, R^L, R^c, R^D, R^E, R^F, R^G, R^K, m, and n are as described herein for Formula **(III).**

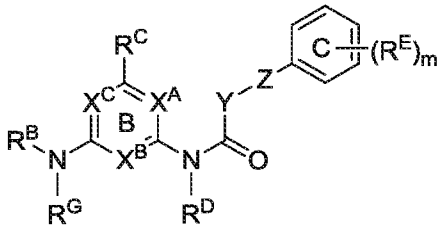
[0023] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula (**IV**):



(**IV**),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^A, R^B, R^C, R^D, R^E, R^F, j, m, and n are as described herein for Formula **(IV).**

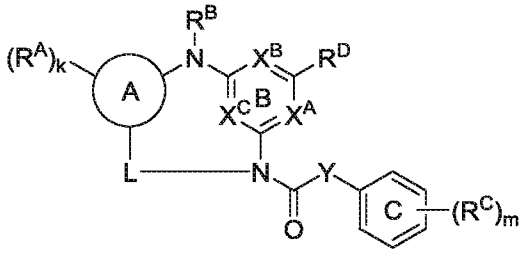
[0024] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula (**V**):



(**V**),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein X^A, X^B, X^C, Y, Z, R^B, R^C, R^D, R^E, R^G, and m are as described herein for Formula **(V).**

[0025] In certain embodiments, the SIK inhibitor for use in the invention described herein is a compound of Formula (**VI**):



(**VI**),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring A, X^A, X^B, X^C, L, Y, R^A, R^B, R^C, R^D, k, and m are as described herein for Formula **(VI).**

[0026] In another aspect, the present disclosure provides pharmaceutical compositions comprising:

a SIK inhibitor;

a Src inhibitor; and

optionally a pharmaceutically acceptable excipient.

[0027] In another aspect, the present disclosure provides pharmaceutical compositions comprising:

a SIK inhibitor;

a CSF1R inhibitor; and

optionally a pharmaceutically acceptable excipient.

[0028] In another aspect, the present disclosure provides uses of the SIK inhibitors in a method described herein.

[0029] In another aspect, the present disclosure provides uses of the pharmaceutical compositions in a method described herein.

[0030] The present disclosure refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

DEFINITIONS

[0031] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0032] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and

the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et ah, Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et ah, Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw--Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0033] In a formula, — is absent or a single bond, and = or ≡ is a single or double bond. In a formula, ∿ is a single bond where the stereochemistry of the moieties immediately attached thereto is not specified. Such a ∿ bond may be —• or ·····.

f0034] The term "heteroatom" refers to an atom that is not hydrogen or carbon. In certain embodiments, the heteroatom is nitrogen. In certain embodiments, the heteroatom is oxygen. In certain embodiments, the heteroatom is sulfur.

[0035| When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, **Ci,** C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0036| The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0037j The term "alkyl" refers to a radical of a straight--chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups

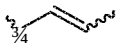
include methyl (C_1), ethyl (C_2), propyl (C_3) *(e.g.,* n–propyl, isopropyl), butyl (C_4) (e.g., n–butyl, tert–butyl, sec–butyl, iso–butyl), pentyl (CV) *(e.g.,* n–pentyl, 3–pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C_6) *(e.g.,* n–hexyl). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (Cg), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents *(e.g.,* halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{i-10} alkyl (such as unsubstituted Ci-6 alkyl, *e.g.,* –CH_3 (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.,* unsubstituted «-propyl *(n-Pr),* unsubstituted isopropyl (/-Pr)), unsubstituted butyl (Bu, *e.g.,* unsubstituted n-butyl *(n-Bu),* unsubstituted *tert*-butyl *(tert-Bu* or r-Bu), unsubstituted sec-butyl (*sec*-Bu), unsubstituted isobutyl (/-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl (such as substituted C_{1-6} alkyl, *e.g.,* –CF_3, Bn).

[0038] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("Ci_{-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. In some embodiments, all of the haloalkyl hydrogen atoms are replaced with chloro to provide a "perch loroalkyl" group. Examples of haloalkyl groups include –CF_3, -CF_2CF_3, -$CF_2CF_2CF_3$, -CCl_3, -$CFCl_2$, -CF_2Cl, and the like.

[0039] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom *(e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within *(i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroCi$_{-10}$ alkyl"). In some embodiments, a

heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroQ$_{1-9}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroCi$_{1-8}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroCi$_{1-7}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroQ$_{1-6}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroCi$_{1-5}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and lor 2 heteroatoms within the parent chain ("heteroCi$_{1-4}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroCi$_{1-3}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroCi$_{1-2}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroCi alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC$_{2-6}$ alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroCi$_{1-10}$ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroCi$_{1-10}$ alkyl.

[0040] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds *(e.g.,* 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C$_{2-9}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C$_{2-8}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C$_{2-7}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C$_{2-6}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C$_{2-5}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C$_{2-4}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C$_{2-3}$ alkenyl"). In some embodiments, an alkenyl

group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (Cs), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (Cg), octatrienyl (Cg), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-10} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is unspecified *(e.g.,* –CH=CHCH$_3$ or ) may be an (*E*)- or (Z)-double bond.

[0041] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom *(e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within *(i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and lor 2 heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3}

alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0042] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds *(e.g.,* 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted **C2-10** alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0043] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom *(e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within *(i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10}

alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and lor 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has *2* to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

1044 The term "'carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl

(C_5), cyclopenteny] (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (Cg), cyclooctenyl (Cg), bicyclo[2.2. 1Jheptanyl (C_7), bicyclo[2.2.2]octanyl (Cg), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_y), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydra -1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic *(e.g.,* containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C-C double bonds in the carbocyclic ring system, as valency permits.

[0045] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C4 -6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("Cs-< cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups

include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (Cg). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0046] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic *(e.g.,* a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3-14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl is substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[0047] In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0048] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation.

indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0049] The term "aryl" refers to a radical of a monocyclic or polycyclic *(e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system *(e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C^aryl"; *e.g.,* naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0050] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0051] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic *(e.g.,* bicyclic, tricyclic) 4n+2 aromatic ring system *(e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point

of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom *(e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom *(e.g., 2-*indolyl) or the ring that does not contain a heteroatom *(e.g.,* 5–indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[0052] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and

sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5--14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0053] Exemplary 5–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5–membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazoiyl. Exemplary 5–membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6--membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, ptendinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl and phenazinyl.

[0054] "Heteroaralkyl" is a subset of "alky!" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0055] The term "unsaturated bond" refers to a double or triple bond.

[0056] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0057] The term "saturated" refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[0058] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.,* alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0059] A group is optionally substituted unless expressly provided otherwise. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted *(e.g.,* "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0060] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-N0_2$, $-N_3$, $-S0_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$,

-N(OR^{cc})R^{bb}, -SH, —SR^{aa}, —SSR^{cc}, —C(=Q)R^{aa}, —C0$_2$H, —CHO, —C(OR^{cc})$_2$, —CO$_2$R^{aa}, -OC(=0)R^{aa}, —OC()$_2$R^{aa}, -C(=0)N(R^{bb})$_2$, —OC(=0)N(R^{bb})$_2$, —NR^{bb}C(=0)R^{aa}, —NR^{bb}C0$_2$R^{aa}, —NR^{bb}C(=0)N(R^{bb})$_2$, —C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -OC(=NR^{bb})R^{aa}, -OC(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})$_2$, -OC(=NR^{bb})N(R^{bb})$_2$, -NR^{bb}C(=NR^{bb})N(R^{bb})$_2$, -C(=0)NR^{bb}S0$_2$R^{aa}, -NR^{bb}S0$_2$R^{aa}, -S0$_2$N(R^{bb})$_2$, -S0$_2$R^{aa}, -SO$_2$OR^{aa}, —OSO$_2$R^{aa}, -S(-0)R^{aa}, —OS(=0)R^{aa}, -Si(R^{a})$_3$, -OSi(R^{aa})$_3$ -C(=S)N(R^{bb})$_2$, -C(=0)SR^{aa}, -C(=S)SR^{aa}, -SC(=S)SR^{aa}, -SC(=0)SR^{aa}, —OC(=0)SR^{aa}, —SC(=0)OR^{aa}, —SC(=0)R^{aa}, —P(=0)(R^{aa})$_2$, —P(<))(OR^{cc})$_2$, —OP(=0)(R^{aa})$_2$, —OP(=0)(OR^{cc})$_2$, —P(=0)(N(R^{bb})$_2$)$_2$, —OP(=0)(N(R^{bb})$_2$)$_2$, -NR^{bb}P(=0)(R^{aa})$_2$,-NR^{bb}P(=0)(OR^{cc})$_2$, -NR^{bb}P(=0)(N(R^{bb})$_2$)$_2$, -P(R^{cc})$_2$, -P(OR^{cc})$_2$, -P(R^{cc})$_3$$^+X^-$, -P(OR^{cc})$_3$$^+X^-$, -P(R^{cc})$_4$, -P(OR^{cc})$_4$, -OP(R^{cc})$_2$, -OP(R^{cc})$_3$$^+X^-$, -OP(OR^{cc})$_2$, -OP(OR^{cc})$_3$$^+X^-$, -OP(R^{cc})$_4$, -OP(OR^{cc})$_4$, -B(R^{aa})$_2$, -B(OR^{cc})$_2$, -BR^{aa}(OR^{cc}), C$_{1-10}$ alkyl, C$_{1-10}$ perhaloalkyl, C$_{2-10}$ alkenyl, C$_{2-10}$ alkynyl, heteroC$_{1-10}$ alkyl, heteroC$_{2-10}$ alkenyl, heteroC$_{2-10}$ alkynyl, C$_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, C$_{6-14}$ aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X$^-$ is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =0, =S, =NN(R^{bb})$_2$, =NNR^{bb}C(=0)R^{aa}, =NNR^{bb}C(=0)OR^{aa}, =NNR^{bb}S(=0)$_2$R^{aa}, =NR^{bb}, or =NOR^{cc};

each instance of R^{aa} is, independently, selected from C$_{1-10}$ alkyl, C$_{1-10}$ perhaloalkyl, C$_{2-10}$ alkenyl, C$_{2-10}$ alkynyl, heteroC$_{1-10}$ alkyl, heteroC$_{2-10}$alkenyl, heteroC$_{2-10}$alkynyl, C$_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, C$_{6-14}$ aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, —OH, —OR^{aa}, -N(R^{cc})$_2$, -CN, -C(=0)R^{aa}, -C(=0)N(R^{cc})$_2$, -CO$_2$R^{aa}, -S0$_2$R^{aa}, -C(=NR^{cc})OR^{aa}, -C(-NR^{cc})N(R^{cc})$_2$, -S0$_2$N(R^{cc})$_2$, —S0$_2$R^{cc}, —S0$_2$OR^{cc}, —SOR^{aa}, -C(=S)N(R^{cc})$_2$, -C(=0)SR^{cc}, -C(=S)SR^{cc}, -P(=0)(R^{aa})$_2$, -P(=0)(OR^{cc})$_2$, -P(=0)(N(R^{cc})$_2$)$_2$, C$_{1-10}$ alkyl, C$_{1-10}$ perhaloalkyl, C$_{2-10}$ alkenyl, C$_{2-10}$ alkynyl, heteroC$_{1-10}$alkyl, heteroC$_{2-10}$alkenyl, heteroC$_{2-10}$alkynyl, C$_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, C$_{6-14}$

aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC$_{1-10}$ alkyl, heteroC$_{2-10}$ alkenyl, heteroC$_{2-10}$ alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, -CN, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC$_{1-6}$alkyl, heteroC$_{2-6}$alkenyl, heteroC$_{2-6}$alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC$_{1-6}$ alkyl, heteroC$_{2-6}$alkenyl, heteroC$_{2-6}$ alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC$_{1-6}$alkyl, heteroC$_{2-6}$alkenyl, heteroC$_{2-6}$alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, -CN, -NO$_2$, -N$_3$, -SO$_2$H, -SO$_3$H, -OH, -OC$_{1-6}$ alkyl, -ON(C$_{1-6}$ alkyl)$_2$, -N(C$_{1-6}$ alkyl)$_2$, -N(C$_{1-6}$ alkyl)$_3^+X^-$, -NH(C$_{1-6}$ alkyl)$_2^+X^-$, -NH$_2$(C$_{1-6}$ alkyl)$^+X^-$, -NH$_3^+X^-$, -N(OC$_{1-6}$ alkyl)(C$_{1-6}$ alkyl), -N(OH)(C$_{1-6}$ alkyl), -NH(OH), -SH, -SC$_{1-6}$ alkyl, -SS(C$_{1-6}$ alkyl), -C(=O)(C$_{1-6}$ alkyl), -CO$_2$H, -CO$_2$(C$_{1-6}$ alkyl), -OC(=O)(C$_{1-6}$ alkyl), -OCO$_2$(C$_{1-6}$ alkyl), -C(=O)NH$_2$, -C(=O)N(C$_{1-6}$ alkyl)$_2$, -OC(=O)NH(C$_{1-6}$ alkyl), -NHC(=O)(C$_{1-6}$ alkyl), -N(C$_{1-6}$ alkyl)C(=O)(C$_{1-6}$ alkyl), -NHCO$_2$(C$_{1-6}$ alkyl), -NHC(=O)N(C$_{1-6}$ alkyl)$_2$, -NHC(=O)NH(C$_{1-6}$ alkyl), -NHC(=O)NH$_2$, -C(=NH)O(C$_{1-6}$ alkyl), -OC(=NH)(C$_{1-6}$ alkyl), -OC(=NH)OC$_{1-6}$ alkyl, -C(=NH)N(C$_{1-6}$ alkyl)$_2$, -C(=NH)NH(C$_{1-6}$ alkyl), -C(=NH)NH$_2$, -OC(=NH)N(C$_{1-6}$ alkyl)$_2$, -OC(NH)NH(C$_{1-6}$ alkyl), -OC(NH)NH$_2$, -NHC(NH)N(C$_{1-6}$ alkyl)$_2$, -NHC(=NH)NH$_2$, -NHSO$_2$(C$_{1-6}$ alkyl), -SO$_2$N(C$_{1-6}$ alkyl)$_2$, -SO$_2$NH(C$_{1-6}$ alkyl), -SO$_2$NH$_2$, -SO$_2$C$_{1-6}$ alkyl, -SO$_2$OC$_{1-6}$ alkyl, -OSO$_2$C$_{1-6}$ alkyl, -SOC$_{1-6}$ alkyl, -Si(C$_{1-6}$ alkyl)$_3$, -OSi(C$_{1-6}$ alkyl)$_3$ -C(=S)N(C$_{1-6}$ alkyl)$_2$, C(=S)NH(C$_{1-6}$ alkyl), C(=S)NH$_2$, -C(=O)S(C$_{1-6}$ alkyl), -C(=S)SC$_{1-6}$ alkyl, -SC(=S)SC$_{1-6}$ alkyl, -P(=O)(OC$_{1-6}$ alkyl)$_2$, -P(=O)(C$_{1-6}$ alkyl)$_2$, -OP(=O)(C$_{1-6}$ alkyl)$_2$, -OP(=O)(OC$_{1-6}$ alkyl)$_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC$_{1-6}$alkyl, heteroC$_{2-6}$alkenyl, heteroC$_{2-6}$alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0061] In certain embodiments, the molecular weight of a substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, and/or

chlorine atoms. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond donors. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond acceptors.

[0062] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCBiiMe_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0063] The term "halo" or "halogen" refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0064] The term "hydroxyl" or "hydroxy" refers to the group -OH. The term "substituted hydroxyl" or "substituted hydroxyl," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-QC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb}))_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0065] The term "thiol" or "thio" refers to the group -SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than

hydrogen, and includes groups selected from –SR[aa], -S=SR[cc], –SC(=S)SR[aa], -SC(=O)SR[aa], –SC(=O)OR[aa], and –SC(=O)R[aa], wherein R[aa] and R[cc] are as defined herein.

[0066] The term "amino" refers to the group -NH2. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0067] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from -NH(R[bb]), -NHC(=O)R[aa], -NHCO2R[aa], -NHC(=O)N(R[bb])2, -NHC(=NR[bb])N(R[bb])2, -NHSO2R[aa], –NHP(=O)(OR[cc])2, and –NHP(=O)(N(R[bb])2)2, wherein R[aa], R[bb] and R[cc] are as defined herein, and wherein R[bb] of the group -NH(R[bb]) is not hydrogen.

[0068] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from -N(R[bb])2, -NR[bb]C(=O)R[aa], -NR[bb]CO2R[aa], -NR[bb]C(=O)N(R[bb])2, -NR[bb]C(=NR[bb])N(R[bb])2, -NR[bb]SO2R[aa], -NR[bb]P(=O)(OR[cc])2, and –NR[bb]P(=O)(N(R[bb])2)2, wherein R[aa], R[bb], and R[cc] are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0069] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from -N(R[bb])3 and -N(R[bb])3+X-, wherein R[bb] and X- are as defined herein.

[0070] The term "sulfonyl" refers to a group selected from –SO2N(R[bb])2, –SO2R[aa], and -SO2OR[aa], wherein R[aa] and R[bb] are as defined herein.

[0071] The term "sulfinyl" refers to the group –S(=O)R[aa], wherein R[aa] is as defined herein.

[0072] The term "carbonyl" refers a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones (-C(=O)R[aa]), carboxylic acids (-CO2H), aldehydes (–CHO), esters (-CO2R[aa], –C(=O)SR[aa], –C(=S)SR[aa]), amides (–C(=O)N(R[bb])2, -C(=O)NR[bb]SO2R[aa], -C(=S)N(R[bb])2), and imines (-C(=NR[bb])R[aa], -C(=NR[bb])OR[aa]), -C(=NR[bb])N(R[bb])2), wherein R[aa] and R[bb] are as defined herein.

[0073] The term "silyl" refers to the group -Si(R^{aa})$_3$, wherein R^{aa} is as defined herein.

[0074] The term "oxo" refers to the group =0, and the term "thiooxo" refers to the group =S.

[0075] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})$_2$, -CN, -C(=0)R^{aa}, -C(=0)N(R^{cc})$_2$, -C0$_2R^{m}$, -S0$_2R^{aa}$, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})$_2$, -S0$_2$N(R^{cc})$_2$, -SQ$_2R^{cc}$, -S0$_2$QR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})$_2$, -C(=0)SR^{cc}, -C(=S)SR^{cc}, -P(=0)(OR^{cc})$_2$, -P(=0)(R^{aa})$_2$, -P(=0)(N(R^{cc})$_2$)$_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroCi-ioalkyl, heteroC$_{2-10}$alkenyl, heteroC$_{2-10}$alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0076] In certain embodiments, the substituent present on the nitrogen atom is an nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, -OH, -OR^{aa}, -N(R^{cc})$_2$, -C(=0)R^{aa}, -C(=0)N(R^{cc})$_2$, -CO$_2R^{aa}$, -S0$_2R^{aa}$, -C(=NR^{cc})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})$_2$, -S0$_2$N(R^{cc})$_2$, -S0$_2R^{cc}$, -S0$_2$QR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})$_2$, -C(=0)SR^{cc}, -C(=S)SR^{cc}, Ci$_{-10}$ alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, heteroCi$_{-10}$ alkyl, heteroC$_{2-10}$alkenyl, heteroC$_{2-10}$alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0077] For example, nitrogen protecting groups such as amide groups (*e.g.*, -C(=0)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide,

picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenyl alanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, *(N*'-dithiobenzyloxyacylamino)acetamide, *3-(p*-hydroxyphenyl jpropanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*—acetylmethionine derivative, *o*–nitrobenzam ide and *o*–(benzoyloxymethyl)benzamide.

[0078] Nitrogen protecting groups such as carbamate groups *(e.g.,* –C(=0)OR [sup]a2[/sup]) include, but are not limited to, methyl carbamate, ethyl carbamate, 9–fluorenyl methyl carbamate (Fmoc), 9-(2-sul fo)fluoren ylmeth y1carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydroth ioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–{1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1-methyl- 1-(4-biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate *(t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2-*(N,N* -dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC or Boc), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), ally! carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), /*>*–methoxybenzyl carbamate (Moz), *p* –nitobenzyl carbamate, /*>*–bromobenzyl carbamate, *p* -chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenyimethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2-(l,3-dithianyl)] methyl carbamate (Dmoc), 4-meth yIthiopheny1carbamate (Mtpc), 2,4–dimethylthiopheny1carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro-/*>*-acyloxybenzyl carbamate, *p* –(dihydroxyboryl)benzy 1carbamate, 5–benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), m-nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–

dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p'*-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0079] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0080] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-p-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-

allylamine, *N*–[2–{trimethylsilyl)ethoxy]niethylamine (SEM), *N*-3-acetoxypropylamine, *N*–(1–isopropyl–4–nitra –2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, Λ'-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*- 5--dibenzosubery!amine, *N*–triphenylmethylamine (Tr), *N*--[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenyl amine (PhF), *N*–2,7--dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*- 2-picolylamino *N'*-oxide, *N*-l,l-dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, Λ-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*–{*N'*./V–<limethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*-p-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*–(5–chlora –2–hydroxyphenyl)phenylmethyleneamine, *N*–-cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo– 1-cyclohexenyl)amine, *N*–borane derivative, *N*–-diphenylborinic acid derivative, *N*–[phenyKpentaacylchromium– or tungsten)acyl] amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[0081] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SIl^{aa}$, $-C(=O)R^{aa}$, $-C0_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})2$, $-S(=O)R^{aa}$, $-S0_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

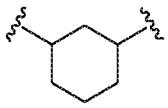
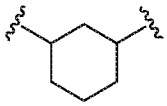
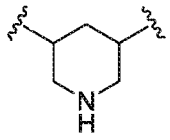
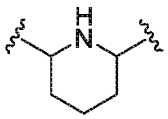
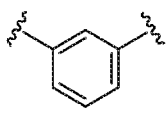
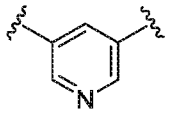
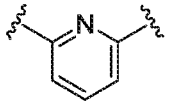
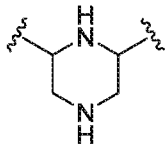
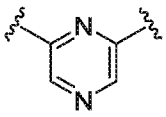
[0082] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), i-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-

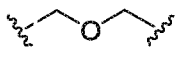
methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, a-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl

carbonate (TMSEC), 2–{phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*-butyl carbonate (BOC or Boc), p-nitrophenyl carbonate, benzyl carbonate, /»–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*-nitrobenzyl carbonate, />-nitrobenzyl carbonate, S-benzyl thiocarbonate, 4-ethoxy-l-napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–{dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–{methylthiomethoxy)ethyl, 4–{methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6-dichloro–4–methylphenoxyacetate, 2,6–dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, a–naphthoate, nitrate, alkyl N,N,N',*N*'–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0083] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, - R^{aa}, –$N(R^{bb})_2$, -C(=0)SR^{aa}, –$C(=O)R^{aa}$, -C0 $_2R^{aa}$, -C(=0)$N(R^{bb})_2$, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -C(=NR^{bb})$N(R^{bb})_2$, -S(=0)R^{aa}, –SO_2R^{aa}, - $Si(R^{aa})_3$, -$P(R^{cc})_2$, –$P(R^{cc})_3^+X^-$, –$P(OR^{cc})_2$, -$P(OR^{cc})_3^+X^-$, -P(=0)$(R^{aa})_2$, -P(=0)$(OR^{cc})_2$, and -P(=0)$(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis,* T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0084] A "hydrocarbon chain" refers to a substituted or unsubstituted divalent alkyl, alkenyl, or alkynyl group. A hydrocarbon chain includes (1) one or more chains of carbon atoms immediately between the two radicals of the hydrocarbon chain; (2) optionally one or more hydrogen atoms on the chain(s) of carbon atoms; and (3) optionally one or more substituents ("non-chain substituents," which are not hydrogen) on the chain(s) of carbon atoms. A chain of carbon atoms consists of consecutively connected carbon atoms ("chain atoms") and does not include hydrogen atoms or heteroatoms. However, a non-chain substituent of a hydrocarbon chain may include any atoms, including hydrogen atoms, carbon atoms, and heteroatoms. For example, hydrocarbon chain - $C^AH(C^BH_2C^CH_3)$– includes one chain atom C^A, one

hydrogen atom on C^A, and non-chain substituent $-(C^BH_2C^CH_3)$. The term "C_x hydrocarbon chain," wherein x is a positive integer, refers to a hydrocarbon chain that includes x number of chain atom(s) between the two radicals of the hydrocarbon chain. If there is more than one possible value of x, the smallest possible value of x is used for the definition of the hydrocarbon chain. For example, -CH(C$_2$¾)- is a Ci hydrocarbon chain, and  is a C_3 hydrocarbon chain. When a range of values is used, the meaning of the range is as described herein. For example, a C_{3-10} hydrocarbon chain refers to a hydrocarbon chain where the number of chain atoms of the shortest chain of carbon atoms immediately between the two radicals of the hydrocarbon chain is 3, 4, 5, 6, 7, 8, 9, or 10. A hydrocarbon chain may be saturated *(e.g.,* -(CH$_2$)$_4$-). A hydrocarbon chain may also be unsaturated and include one or more C=C and/or C≡C bonds anywhere in the hydrocarbon chain. For instance, –CH=CH–(CH$_2$)$_2$- , **-CH$_2$-C≡C-CH$_2$- ,** and - C≡C-CH=CH- are all examples of a unsubstituted and unsaturated hydrocarbon chain. In certain embodiments, the hydrocarbon chain is unsubstituted *(e.g.,* - C≡C- or -(CH$_2$)$_4$-). In certain embodiments, the hydrocarbon chain is substituted *(e.g.,* -CH(C$_2$¾)- and –CF$_2$–). Any two substituents on the hydrocarbon chain may be joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring. For instance,  ,  ,  ,  ,  , and  are all examples of a hydrocarbon chain. In contrast, in certain embodiments,  and  are not within the scope of the hydrocarbon chains described herein. When a chain atom of a C_x hydrocarbon chain is replaced with a heteroatom, the resulting group is referred to as a C_x hydrocarbon chain wherein a chain atom is replaced with a heteroatom, as opposed to a C_{x-1} hydrocarbon chain. For example,

 is a C_3 hydrocarbon chain wherein one chain atom is replaced with an oxygen atom.

[0085] The term "leaving group" is given its ordinary meaning in the art of synthetic organic chemistry and refers to an atom or a group capable of being displaced by a nucleophile. Examples of suitable leaving groups include, but are not limited to, halogen (such as F, CI, Br, or I (iodine)), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy *(e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N,O*-dimethylhydroxylamino, pixyl, and haloformates. In some cases, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, -QTs), methanesulfonate (mesylate, *-QMs),p*-bromobenzenesulfonyloxy (brosylate, –OBs), or trifluoromethanesulfonate (triflate, -OTf). In some cases, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some cases, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide *(e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties. In certain embodiments, the leaving group is an activated substituted hydroxyl group *(e.g.*, -OC(=0)SR ^{aa}, -OC(=0)R ^{aa}, -OC0 $_2$R^{aa}, -OC(=0)N(R ^{bb})$_2$, -OC(=NR^{bb})R^{aa}, –OC(=NR^{bb})OR^{aa}, –OC(=NR^{bb})N(R^{bb})$_2$, –OS(=O)R^{aa}, –OSO$_2$R^{aa}, –OP(R^{cc})$_2$, –OP(R^{cc})$_3$, –OP(=0)$_2$R^{aa}, –0P(=O)(R ^{aa})$_2$, –OP(=0)(OR ^{cc})$_2$, -OP(=0) $_2$N(R^{bb})$_2$, or -OP(=0)(NR ^{bb})$_2$, wherein R^{a}, R^{bb}, and R^{cc} are as defined herein).

[0086] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences,* 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid

addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}$ alkyl$)_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0087] The term "solvate" refers to forms of the compound, or salt thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0088] The term "hydrate" refers to a compound that is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore,

a hydrate of a compound may be represented, for example, by the general formula R·x H_2O, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, ***e.g.,*** monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, ***e.g.,*** hemihydrates (R-0.5 H_2O)), and polyhydrates (x is a number greater than 1, ***e.g.,*** dihydrates (R-2 H_2O) and hexahydrates (R-6 H_2O)).

[0089] The term "tautomers" or "tautomeric" refers to two or more interconvertiblecompounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency ***(e.g.***, a single bond to a double bond, a triple bond to a single bond, or ***vice versa).*** The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations ***(i.e.,*** the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0090] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[0091] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory ***(i.e.,*** as (+) or **(-)-isomers** respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0092] The term "polymorphs" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate.

Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0093] The term "prodrugs" refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo.* Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs,* pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C_1-Cgalkyl, C_2-Cg alkenyl, C_2-C_8 alkynyl, aryl, C_7-C_{12} substituted aryl, and C7-C 12 arylalkyl esters of the compounds described herein may be preferred.

[0094] The "molecular weight" of a monovalent moiety –R is calculated by subtracting 1 from the molecular weight of the compound R-H. The "molecular weight" of a divalent moiety –L– is calculated by subtracting 2 from the molecular weight of the compound H-L-H.

[0095] The terms "composition" and "formulation" are used interchangeably.

[0096] A "subject" to which administration is contemplated refers to a human (i.e., male or female of any age group, *e.g.,* pediatric subject *(e.g.,* infant, child, or adolescent) or adult subject *(e.g.,* young adult, middle-aged adult, or senior adult)) or non–human animal. In certain embodiments, the non–human animal is a mammal *(e.g.,* primate *(e.g.,* cynomolgus monkey or rhesus monkey), commercially relevant mammal *(e.g.,* cattle, pig, horse, sheep, goat, cat, or dog), or bird *(e.g.,* commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a

transgenic animal or genetically engineered animal. A "patient" refers to a human subject in need of treatment of a disease described herein.

[0097] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[0098] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms *(e.g.,* in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay and/or prevent recurrence.

[0099] The term "prevent" refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population.

[00100] The terms "condition," "disease," and "disorder" are used interchangeably.

[00101] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactically effective treatment. In certain embodiments, an effective amount is the amount of a compound or pharmaceutical composition described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound or pharmaceutical composition described herein in multiple doses.

[00102] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition

or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent.

[00103] A "prophylactically effective amount" of a compound described herein is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[00104] A "kinase" is a type of enzyme that transfers phosphate groups from high energy donor molecules, such as ATP, to specific substrates, referred to as phosphorylation. Kinases are part of the larger family of phosphotransferases. One of the largest groups of kinases are protein kinases, which act on and modify the activity of specific proteins. Kinases are used extensively to transmit signals and control complex processes in cells. Various other kinases act on small molecules such as lipids, carbohydrates, amino acids, and nucleotides, either for signaling or to prime them for metabolic pathways. Kinases are often named after their substrates. More than 500 different protein kinases have been identified in humans. These exemplary human protein kinases include, but are not limited to, salt-inducible kinase (S1K, *e.g.*, salt-inducible kinase 1 (SIKl), salt-inducible kinase 2 (SIK2), salt-inducible kinase 3 (SIK3)).

[00105] The term "salt-inducible kinase" or "SIK" refers to a subfamily of serine/threonine protein kinases including SIKl, SIK2, and SIK3 that belong to an AMP-activated protein kinase family.

[00106] The terms "SIK inhibitor" and "inhibitor of SIK" are used interchangeably.

[00107] The term "inhibition", "inhibiting", "inhibit," or "inhibitor" refer to the ability of a compound to reduce, slow, halt, and/or prevent activity of a particular

biological process ***(e.g.,*** kinase activity) in a cell relative to vehicle (veh, Veh, or VEH).

[00108] When a compound, pharmaceutical composition, method, or use is referred to as "selectively" or "specifically" modulating ***(e.g.,*** increasing or inhibiting) the activity of a first protein kinase, the compound, pharmaceutical composition, method, or use modulates the activity of the first protein kinase to a greater extent ***(e.g.,*** not less than about 2-fold, not less than about 5-fold, not less than about 10-fold, not less than about 30-fold, not less than about 100-fold, not less than about 1,000-fold, or not less than about 10,000-fold) than the activity of at least a second protein kinase that is different from the first protein kinase.

BRIEF DESCRIPTION OF THE DRAWINGS

[00109] **Figures** 1A to 1D**: HDAC4 and HDAC5 control osteocyte** biology ***in vivo.*** (Figure 1A) Endogenous MEF2C was immunoprecipitated from Ocy454 cells, followed by immunoblotting for the indicated proteins. Data shown in this figure is representative of n=3 independent experiments. (Figure IB) Osteocyte density in cortical bone 3 mm below the growth plate. 4-5 mice per genotype were analyzed, * indicates $p<0.01$ versus WT by Student's unpaired 2 tailed t-test. (Figure 1C) Representative H+E section demonstrating increased osteocyte density and disorganized cortical bone in double-knockout (DKO) (HDAC4†7f;HDAC5-/-;DMP1-Cre) mice. (Figure ID) Sections were stained with Sirius Red and analyzed under polarized light to view collagen fiber organization. Disorganized collagen fibers are only seen in DKO sections. Error bars indicate s.e.m for all figures.

[001 10] **Figures 2A to 2H: Class Ila HDACs are required for PTH-induced SOST suppression *in vitro.*** (Figure 2A) Ocy454 cells were transfected with GFP-HDAC5 and then treated with PTH (50 nM) for the indicated times. Cytosolic (c) and nuclear (n) lysates were prepared and immunoblotted as indicated. (Figure 2B) Ocy454 cells were treated with PTH (50 nM) for 30 minutes. Whole cell lysates were prepared and immunoblotted as indicated. Similar results were observed in 4 independent experiments. (Figure 2C) Ocy454 cells with (WT, clone 17) and without (Null, clone 8) Gsa were treated with PTH (50 nM for 30 minutes) and analyzed as in Figure 2A. (Figure 2D) Ocy454 cells with (WT) and without (Null) Gsa were treated with either PTH (50 nM) or forskolin (5 ng/mL) for 30 minutes and analyzed as in Figure 2B. (Figure 2E) Ocy454 cells were exposed to the indicated combinations of

HDAC4-targeting sgRNAs (with Cas9) and HDAC5 shRNA-expressing lentiviruses, and whole cell lysates were analyzed by immunoblotting as indicated. (Figure 2F) WT, HDAC5 shRNA, HDAC4 KO, and DKO Ocy454 cells were treated with PTH (1 nM) for 4 hours, and SOST (left) and RANKL (right) mRNA transcript abundance was measured by RT-qPCR. For all cell culture experiments therein, values represent mean of n=3 biologic replicates. * indicates $p<0.05$ comparing the effects of PTH to vehicle for each cell line. (Figures 2G to 2H) MEF2C chromatin immunoprecipitation was performed, and enrichment for the +45 kB enhancer determined (relative to control IgG ChIP). * indicates $p<0.G5$ comparing fold enrichment of PTH versus vehicle by Student's unpaired 2 tailed t-test.

[00111] Figures 3A to 3D: Class IIa HDACs are required for **PTH-induced SOST suppression *in vivo.*** (Figures 3A and 3B) 6 week old mice of the indicated genotype were treated with vehicle or PTH (1-34, 300 μg/kg) and sacrificed 90 minutes later. Bone RNA was obtained and RANKL and SOST transcript abundance was determined by RT-qPCR. * indicates $p<0.05$ comparing vehicle and PTH for each genotype. N=6-8 mice per group were analyzed. (Figure 3C) Representative photomicrographs of sclerostin immunohistochemistry from WT and DKO mice treated with vehicle or PTH. (Figure 3D) Quantification of immunohistochemistry results. Cortical osteocytes in a fixed region of bone 3 mm below the tibial growth plate were counted and scored as either sclerostin-positive or negative. N=6-8 mice per group were analyzed. * indicates $p<0.01$ comparing vehicle and PTH for each genotype by Student's unpaired 2 tailed t-test. In the Figures, "VEH" or "veh" denotes vehicle.

1001 12] Figures 4A to 4M: **SIK2 is an HDAC4/5 N-terminal kinases whose activity is regulated by PTH signaling.** (Figure 4A) Ocy454 cells were infected with the indicated combination of shRNA-expressing lentiviruses, and whole cell lysates were analyzed by immunoblotting as indicated. (Figure 4B) Ocy454 cells were treated with vehicle or PTH (50 nM) for 30 minutes, and whole cell lysates were analyzed by immunoblotting using phospho-specific antibodies. In the bottom panels, SIK3 immunoprecipitation was performed first, followed by immunoblotting as indicated. pPKA is an antibody that recognizes a degenerate consensus PKA substrate motif. (Figure 4C) Ocy454 cells were treated with PTH (50 nM) for the indicated times. Whole cell lysates were generated followed by immunoblotting as indicated. (Figure 4D) Ocy454 cells infected with either control (shLacZ), shSIK2-, or shSIK3-

expressing lentiviruses were treated with PTH (1 nM) for 4 hours. RNA was isolated and Cited 1 RNA transcript abundance was measured by RT-qPCR. * indicates $p<0.05$ comparing vehicle and PTH for each cell line. In Figure 4D, for each cell line, the left bar refers to vehicle, and the right bar refers to PTH. (Figure 4E) Control and shSIK2 cells were treated with PTH (50 nM for 30 minutes) and then analyzed as in Figure 4B. (Figures 4F to 4G) Control, shSIK2, and shSIK3 cells were treated as in Figure 4D, and SOST and RANKL transcript abundance measured by RT-qPCR. * indicates $p<0.05$ comparing vehicle and PTH. In Figures 4F to 4G, for each cell line, the left bar refers to vehicle, and the right bar refers to PTH. (Figure 4H) Left, control and shSIK2 cells were treated with vehicle, PTH (25 nM), or forskolin (FSK, 5 ug/mL) for 30 minutes followed by cAMP radioimmunoassay. Middle/right, cells were treated with PTH (2.5 nM) or forskolin (500 ng/mL) for 4 hours, gene expression was analyzed by RT-qPCR. * indicates $p<0.05$ comparing vehicle and treatment. (Figure 41) RNA from femurae of 5 week old WT (SIK2 f/f) or SIK2^{Ocy-KO} (SIK2 f/f;DMPl-Cre) mice (n=3/group) was isolated and SIK2 and PTH receptor (PPR) transcripts were measured by RT-qPCR. * indicates $p<0.001$ comparing WT and SIK2 cKO mice. (Figures 4J to 4K) Mice as in Figure 41 were treated with a single dose of PTH (1 mg/kg) and sacrificed 2 hours later. Bone RNA was isolated from bilateral femurae and expression of Citedl, SOST, and RANKL was determined by RT-qPCR. * indicates $p<0.05$ comparing vehicle and PTH within a given genotype. (Figure 4L) Ocy454 cells were infected with shRNA-expressing lentiviruses targeting CRTC1, CRTC2, or CRTC3. Cells were then treated with PTH (1 nM for 4 hours) and RANKL transcript abundance was measured by RT-qPCR. In Figure 4L, for each cell line, the left bar refers to vehicle, and the right bar refers to PTH. (Figure 4M) Ocy454 cells were treated with vehicle or PTH (20 nM for 60 minutes) followed by chromatin immunoprecipitation for CRTC2. Recovered DNA was quantified by qPCR using primer pairs detecting the indicated regions of the RANKL enhancer (based on enhancers described by (44)) and data are expressed as fold enrichment versus control IgG CMP. * indicates $p<0.05$ comparing vehicle and PTH. The -23kB and -75 kB enhancers correspond to the previously-described "D2" and "D5" enhancers. In Figure 4D, the left bars correspond to vehicle, and the right bars correspond to PTH.

(00113| Figures 5A to 5J: Small molecule SIK inhibitors regulate SOST and RANKL expression by osteocytes. (Figure 5A) Structure of YKL-04-114 (top

panel, left), **YKL** -05-093 (top panel, **right),** and **YKL** -05-093 K_d determination curves for SIK2 (bottom panels). For the ¾ determination curves, the y-axis represents the amount of bound kinase measured by qPCR (see methods), and the x-axis represents the corresponding compound concentration in **nM.** (Figure 5B) Ocy454 cells were treated with YKL-Q4- 114 (10 μM**)** for the indicated times, followed by immunoblotting of whole cell lysates as indicated. (Figure 5C) Ocy454 cells were treated with the indicated concentrations of YKL-04-1 14 for 60 minutes, followed by immunoblotting of whole cell lysates as indicated. (Figure 5D) Left: Ocy454 cells were treated with vehicle, PTH (50 **nM),** or YKL-05-093 (10 μM**)** for 60 minutes. Cytosol and nuclear fractions were then generated, followed by immunoblotting as indicated. Right: quantification of nuclear fraction (defined as nuclear/total) of HDAC4 or CRTC2. * indicates p<0.01 comparing treatment vs vehicle. (Figure 5E) Top: Ocy454 cells were treated with the indicated concentrations of YKL-04- 114 for 4 hours, followed by RT-qPCR. Bottom: Cells were treated with YKL-04-1 14 (0.5 μM**)** for the indicated times. * indicates p<0.05 comparing treatment vs vehicle. (Figure 5F) Cells lacking SIK2, SIK3 or both were treated with YKL-05-093 (10 μM for 45 minutes). Quantification of HDAC4 S246 phosphorylation, as assessed by densitometric analysis of immunoblots, is shown. * indicates p<0.01 comparing treatment vs vehicle. # indicates p<0.05 for the same comparison. In Figure 5F, for each cell line, the left bar refers to vehicle, and the right bar refers to YKL-05-093. (Figure 5G) Control and S1K2/3 deficient cells were treated with YKL-05-093 (0.5 μM**)** for 4 hours and SOST transcript abundance was measured by RT-qPCR. (Figure 5H) Control and CRTC2 shRNA cells were treated with PTH (1 **nM)** or YKL-05-093 (0.5 μM**)** for 4 hours and RANKL transcript abundance was measured by RT-qPCR. (Figure 51) Control and Gsa-deficient Ocy454 cells were treated with **PTH** (1 nM), YKL-05-093 (0.5 μM**),** or forskolin (5 μg/mL) and SOST and RANKL transcript abundance was determined by RT-qPCR. ForFigures 511 and 51, * indicates p<0.05 comparing treatment and vehicle. (Figure 5J) Control and Gsa-deficient Ocy454 cells were treated with PTH (50 nM), YKL-05-093 (10 μM**),** or forskolin (5 μg/mL**)** for 30 minutes. Whole cell lysates were generated and immunoblotted as indicated.

[001 14] Figures 6A to 6J: YKL-05-093 effects on gene expression significantly overlap with **PTH.** (Figure 6A) Venn diagram showing overlap between differentially-expressed genes (fold chance >2, FDR<0.05) determined by RNA-Seq from Ocy454 cells treated with vehicle, PTH (1 nM), or YKL-05-093 (0.5

μM) for 4 hours. (Figure 6B) Heat map showing 6 different clusters of differentially expressed genes. Each row corresponds to a single differentially expressed gene. Color coding is with respect to the average log2 (fold change) for each gene comparing treatment to vehicle. Genes were ordered by the strength of the significance of the fold change comparing PTH and vehicle. (Figures 6C to 6H) Ocy454 cells were treated with vehicle, PTH (1 nM), and YKL-05-093 (0.5 μM) for 4 hours, and RT-qPCR was performed for the indicated gene. FAM69C and KLHL30 are regulated by PTH alone, ADAMTS1 and DUSP6 are regulated by YKL-05-093 alone, and WNT4 and CD200 are regulated by both PTH and YKL-05-093. (Figures 6I to 6J) Control and SIK2/3 deficient cells were treated with vehicle or YKL-05-093 (0.5 μM) for 4 hours, and WNT4 and CD200 transcript abundance determined by RT-qPCR. For all panels, * indicates $p<0.05$ comparing vehicle and compound or PTH treatment by Student's unpaired 2 tailed t-test. In Figures 6I to 6J, for each cell line, the left bar refers to vehicle, and the right bar refers to YKL-05-093.

[00115] Figures 7A to 7I: Effects **of YKL-05-093 administration on bone gene expression *in vivo.*** (Figures 7A and 7B) 8 week old C57B/6 mice (n=4/group) were treated with the indicated dose of YKL-05-093 via intraperitoneal injection. 2 hours later, bone RNA was isolated and transcript abundance was measured by RT-qPCR. # indicates $p<0.05$ versus vehicle, and * indicates $p<0.01$ versus vehicle by Student's unpaired 2 tailed t-test. (Figure 7C) Left: sclerostin immunohistochemistry was performed 2 hours after intraperitoneal injection with either vehicle or YKL-05-093 (20 μηηοΐ/kg). Right: quantification of sclerostin-positive cortical osteocytes, n=4 mice per treatment group, * indicated $p<0.01$ versus vehicle. (Figures 7D to 7I) Genes regulated by PTH and YKL-05-093 ***in vitro*** are also regulated by YKL-05-093 *in vivo.* Mice were treated with YKL-05-093 (20 μηιο ΐ¾) and bone RNA collected 2 hours later as in Figure 7A. * indicates $p<0.05$ versus vehicle. In Figures 7A, 7B, and 7D to 7I, "umol" denotes μmol. In Figures 7D to 7I, each of the right bars corresponds to YKL-05-093.

[00116] Figures 8A to 8M: YKL-05-099 (05-099) **increases bone formation and bone mass *in vivo.*** (Figure 8A) Ocy454 cells were treated with the indicated doses of YKL-05-093 (05-093), YKL-05-099, or PTH for 20 minutes. Whole cell extracts were generated, followed by immunoblotting. (Figure 8B) Control or shSIK2/3 Ocy454 cells were treated with YKL-05-093 or YKL-05-099 (1 μM) for 4 hours. RNA was prepared, and gene expression analyzed by RT-qPCR. Both YKL-

05-093 and YKL-05-099 regulate SOST and RANKL expression in control, but not SIK2/3-deficient cells. (Figure 8C) 8 week old male mice (n=5/group) were treated with a single LP. dose of YKL-05-099 (20 μηθΙ/**kg**) or vehicle. 2 hours later, animals were sacrificed, RNA was prepared from femurs, and gene expression analyzed by RT-qPCR. SOST down-regulation was observed in response to YKL-05-099, but the p value for this difference was 0.105. * indicates p<0.01 . (Figure 8D) 8 week old male mice were treated with vehicle (n=8) or YKL-05-099 (n=7, 10 μπιοϊ/**kg**, LP.) once daily 5 days per week for 2 weeks. Animals were sacrificed 2 hours after the final dose, and RNA from femurs analyzed for the indicated genes. BGLAP encodes osteocalcin. * indicated p<0.01 versus vehicle, # indicates p<0.05 versus vehicle. (Figures 8E to 8K), static and dynamic histomorphometry were performed on the tibia from the same mice as in Figure 8D. Each data point represents an individual mouse, p values for each difference are shown on the graph. (Figure 8L) Representative photomicrograph showing increased osteoblasts on cancellous bone surfaces from YKL-05-099-treated mice. (Figure 8M) Dual calcein/demeclocycline images demonstrating increased mineralizing surface in YKL-05-099-treated mice. In Figure 8M, the left panel corresponds to vehicle, and the right panel corresponds to YKL-05-099.

[00117] **Figure 9:** Model showing PTH **signaling via inhibition of** SIK2 **in osteocytes.** In the absence of PTH signaling, SIK2 tonically phosphorylates its substrates HDAC4/5 and CRTC2, leading to their cytoplasmic retention. PTH signaling leads to PKA-mediated phosphorylation of SIK2 which inhibits its cellular activity. This in turn reduces phosphorylation of HDAC4/5 and CRTC2, leading to their nuclear translocation. In the nucleus, HDAC4/5 block MEF2C-driven SOST expression, while CRTC2 enhances CREB-mediated RANKL gene transcription.

[001 18] Figures 10A **to 10E.** (Figure 10A) Cortical and (Figure 10B) trabecular **micro-CT** results from 8 week old mice of the indicated compound heterozygous genotype. The high bone mass observed in SOST+/- mice is not observed in SOST/HDAC5 compound heterozygotes. (Figure 1OC) Representative sagittal images from mice analyzed inFigures 10A and 10B. (Figure 10D) Male WT **(n**=5), HDAC4 ^{OcyKO} **(n**=6), LIDAC5-/- **(n**=5), and DKO **(n=6)** mice were treated with anti-sclerostin antibody (50 **mg/kg)** twice weekly from 2 to 8 weeks of age. Distal femur BV/TV was determined by micro-CT. 2 way ANOVA analysis revealed a significant interaction between genotype and Scl-Ab treatment, therefore post-hoc t

tests were performed to determine effects of Scl Ab treatment within each genotype. Individual p values for each comparison are noted on the graph. (Figure 10E) Dual calcein/demeciocycline images showing reduced endocortical bone formation in DKO mice.

[00119] **Figures** 11A to 11I. (Figure 11A) Ocy454 cells were treated with the indicated concentrations (in molar) of PTH for 30 minutes, followed by immunoblotting as indicated. (Figure 11B) Immunoblots from individual single cell clones isolated after exposure to Gsa sgRNA/Cas9 targeting the indicated GNAS exon. Clones 11 and 17 show intact Gsa expression, while the other clones show no detectable Gsa protein. Clone 8, not shown here, also was isolated after exposure to the sgRNA sequence targeting GNAS exon 1. (Figure 11C) WT and Gsa KO cells were treated with the indicated concentrations of PTH and cAMP levels were measured by RIA 20 minutes later. No detectable PTH-induced increases in cAMP were observed in cells lacking Gsa. (Figure 11D) As in Figure 1lC, except cells were treated with other agents known to stimulate cAMP production. (Figure 1IE) WT and Gsa null cells were treated with the indicated concentrations of PTH and analyzed by immunoblotting as in Figure 11A. (Figure 11F) Cells lacking Gsα were infected with control or MEF2C shRNA lentiviruses, followed by immunoblotting as indicated. (Figure 11G) Cells from Figure 11F were allowed to differentiate for the indicated times at 37°C, and sclerostin ELISAs were then performed from the conditioned medium. While Gsa KO cells showed increased sclerostin secretion, MEF2C shRNA abrogates this effect. (Figure 11H) Cells lacking Gsa were infected with lentiviruses to over-express HDAC5 S/A (S259/498A) and analyzed by immunoblotting. (Figure 1II) Cells from Figure 11H were analyzed as in Figure 11G. HDAC5 S/A overexpression dramatically reduces sclerostin secretion by Gsa deficient cells.

100120] **Figures** 12A **to** 12F. (Figure **12A)** Immunoblot showing Ocy454 cells uninfected with lentivirus, infected with control lentivirus (LV-GFP), or infected with lentivirus overexpressing FLAG-tagged Cas9. (Figure 12B) Sclerostin ELISA demonstrating no effect of Cas9 expression on Ocy454 cell sclerostin secretion in the absence of sgRNA co-expression. (Figure 12C) Ocy454 cells were transfected with PX458 plasmid which co-expresses a sgRNA of interest, Cas9, and eGFP. 48 hours later, eGFP positive cells were sorted by flow cytometry into 96 well plates at a density of 1 cell per well. Clones were identified, expanded, and analyzed by immunoblotting. (Figure 12D) Representative immunoblot of single cell clones

isolated after exposure to an sgRNA targeting HDAC4. Starred clones show no detectable HDAC4 protein. (Figure 12E) Genomic DNA was isolated from individual HDAC4 deficient clones followed by allele-specific sequencing. As shown in the example here, cells without HDAC4 protein show bi-allelic HDAC4 insertion/deletions resulting in frameshift mutations. N17 refers to the 17th nucleotide within the 20mer sgRNA sequence, where insertions/deletions are most likely to occur. The sequences, from top to bottom and left to right, correspond to SEQ ID NOs: 1-4. (Figure 12F) Ocy454 cells were treated with PTH (1 nM) for the indicated times, and MEF2C transcript abundance was measured by RT-qPCR. # indicates $p<0.05$, and * indicates $p<0.01$ vs vehicle.

[00121] **Figures 13A to 13J.** (Figure 13A) 8 week old female mice of the indicated genotypes were treated with vehicle or hPTH (1-34, 100 mcg/kg) once daily, 5 days per week, for 4 weeks. Micro-CT analysis of bone volume fraction of the primary spongiosa is shown. 2 way ANOVA revealed a significant ($p<0.01$) interaction between genotype and drug treatment. Therefore, posthoc t tests were performed comparing effects of vehicle and PTH within each genotype. * indicates $p<0.01$. (Figure 13B) Ocy454 cells were treated with vehicle, PTH (50 nM), okadaic acid (OA, 300 nM), staurosporine (sts, 1 μM), or PTH plus okadaic acid. When okadaic acid was used, cells were pre-treated with this agent for 20 minutes. 30 minutes later, whole cell lysates were obtained followed by immunoblotting as indicated. Okadaic acid does not block the ability of PTH to induce HDAC4/5 dephosphorylation. (Figure 13C) Ocy454 cells were treated with okadaic acid (300 nM), PTH (1 nM), and both. 4 hours later, RNA was isolated and SOST transcript abundance was analyzed by RT-qPCR. (Figure 13D) Ocy454 cells were infected with control (shLacZ) or PP2A catalytic subunit (c.s.) shRNA-expressing lentiviruses. Cells were then treated with the indicated concentrations of PTH for 30 minutes followed by immunoblotting as indicated. (Figure 13E) Cells from Figure 13D were treated with the indicated concentrations of PTH and SOST transcript abundance was measured by RT-qPCR 4 hours later. (Figure 13F) Control, shSIK2, and shSISO Ocy454 cells were subjected to subcellular fractionation followed by immunoblotting for the indicated proteins. (Figure 13G) Control (shLacZ) and shSIK2 cells were treated with the indicated concentrations of PTH or isoproterenol (iso), and cAMP levels were determined by RIA. While shSIK2 cells show reduced cAMP levels at all doses compared to control cells, significant upregulation (versus vehicle) in these

cells is noted at doses above 4 nM. (Figure 13FI) Ocy454 cells were infected with shRNAs targeting CRTC1, CRTC2, and CRTC3. Knockdown efficiency and specificity for each gene was then measured by **RT-qPCR.** (Figure **13**I) **CRTC2** shRNAs effectively reduce CRTC2 protein levels. "1-**1**", "2-1", "2-2", "3-1", and "3-2" denote the gene **CRTC** targeted for sh**RNA**-mediated knockdown. (Figure 13J) CRTC2 knockdown cells show normal PTH-induced cAMP generation as measured by radioimmunoassay.

[00122] Figures 14A to 14B. (Figure 14**A**) Dendrogram showing effects of **YKL-05-093** on different classes of kinases. The location of SIK kinases is denoted with an asterix. **SIK** refers to SIK1, and **QSK** refers to **SIK3** in these assays. See *Table 3* for more details. Kinase group names follow standard nomenclature: AGC (containing PKA, **PKG, PKC** families), CAMK (calcium/calmodulin-dependent protein kinases), CK1 (casein kinase 1), CMGC (containing CDK, MARK, GSK3, CLK families), STE (homologs of yeast sterile 7, sterile 11, and sterile 20 kinases), TK (tyrosine kinase), and TKL (tyrosine kinase-like). Image generated using TRE*Espot*™ Software Tool and reprinted with permission from **KINOME***scan*®, a division of DiscoveRx Corporation, © DISCOVERX CORPORATION 2010. (Figure 14B) Ocy454 cells were treated with PTH, forskolin, or **YKL**-05-093 (05-093), and **cAMP** levels were measured by **RIA** 20 minutes later. **YKL** -05-093 does not induce cAMP generation.

[00123] Figures ISA **to 15E.** (Figures 15A and 15B) Simulation results demonstrating that the overlap between the group of genes co-regulated in the same direction by **PTH** and **YKL** -05-093 **(YKL)** is not due to random chance. (Figures 15C and 15D) Gene ontology analysis of genes up- or down-regulated by both PTH and **YKL**-05-093. (Figure 15E) Control and shSIK2/3 cells were treated with vehicle or **YKL**-05-093 (0.5 μM) for 4 hours, and the indicated genes were measured by **RT**-qPCR. In Figure 15E, for each gene, the four bars from left to right refer to shLZ+VEH, shLZ+05093, **shS2/3+VEH,** and shS2/3+05093, respectively. Genes are categorized based on the dependence of SIK2/3 for the ability of **YKL**-05-093 to regulate their expression. Genes that are SIK2/3-dependent show no **YKL** -05-093-induced regulation in SIK2/3-deficient cells. Genes that are partially SIK2/3-dependent show blunted regulation by **YKL** -05-093 in SIK2/3-deficient cells. Genes that are SlK2/3-independent show normal **YKL**-05-093-induced regulation in SIK2/3-

deficient cells. Therefore, the regulation of these genes is likely due to cellular targets of YKL-05-093 other than SIK2/3.

[00124] Figure 16: The half-life (in minute) of the indicated compound was measured in murine hepatic microsomes. Note the improved half-life of YKL-05-093 compared to YKL-04-114 and HG-9-91-01.

[00125] **Figure 17:** Western blots showing the results of the Ocy454 osteocyte cell line treated for 90 minutes with a 10 μM dose of the indicated compound.

[00126] **Figure 18:** Western blot showing the results exemplary analogs of YKL-04-114. "04-114" denotes YKL-04-114. "05-068" denotes YKL-05-068. "05-077" denotes YKL-05-077. "05-093" denotes YKL-05-093. "05-094" denotes YKL-05-094. "05-098" denotes YKL-05-098. "cmpd" denotes compound. "90"' denotes 90 minutes.

[00127] **Figure 19:** Western blots showing the results of exemplary analogs of YKL-05-093. "05-068" denotes YKL-05-068. "05-093" denotes YKL-05-093. "05-096" denotes YKL-05-096. "05-099" denotes YKL-05-099. "06-031" denotes YKL-06-031. "06-038" denotes YKL-06-038. "06-040" denotes YKL-06-040. "06-051" denotes YKL-06-051. "06-061" denotes YKL-06-061. "cmpd" denotes compound.

[00128] **Figure 20:** Western blot showing the effect of YKL-05-093, and exemplary analogs thereof, on HDAC4 S246 phosphorylation. "cmpd" denotes compound.

[00129] **Figure 21:** Graphs showing gene expression of Ocy454 cells treated with the indicated compounds analyzed by RT-qPCR. "exp" denotes expression.

[00130] **Figure 22A:** Graphs showing gene expression YKL-05-093 analogs treated with the indicated compounds was analyzed by RT-qPCR.

[00131] **Figure 22B:** SIK2 IC_{50} data generated from an *in vitro* kinase assay. In Figures 22A and 22B: "05-093" denotes YKL-05-093; "05-068" denotes YKL-05-068; "05-096" denotes YKL-05-096; "06-031" denotes YKL-06-031; "06-038" denotes YKL-06-038; "06-040" denotes YKL-06-040; "06-051" denotes YKL-06-051; "06-061" denotes YKL-06-061; "Dastnb" denotes dasatinib; and "cmpd" denotes compound.

[00132] **Figure 23:** Graphs showing the gene expression of YKL-05-093, and exemplary analogs thereof, versus SIK2 IC_{50}.

[00133] Figure 24: 8 week old male mice were treated for 2 weeks with the indicated doses of YKL-Q5-G99. Histomorphometry of the proximal tibia was performed.

[00134] Figure **25:** Bone marrow macrophages were differentiated into osteoclasts in the prescence of the indicated doses of YKL-Q5-099.

[00135] **Figure 26:** Quantification of tartrate resistant acid phosphatase (TRAP) secretion (see left panel) and TRAP+ multinucleated cells (see right panel). "uM" refers to μM.

[00136] **Figure 27:** DiscoverX profiling data revealed that YKL-G5-099 inhibited multiple tyrosine kinases *in vitro,* including CSFRl (see left panel). Bone marrow macrophages were pre-treated with either vehicle or YKL-05-099. 60 minutes later, cells were treated with M-CSF for the indicated time. YKL-05-099 pre-treatment blocked M-CSF induced receptor auto-phosphorylation and downstream ERK1/2 phosphorylation (see right panel).

[00137] Figure 28: Overview of the experimental conditions employed for Figures 29A to 35.

[00138] Figures 29A **to 29F:** Graphs showing effects of OVX and drug (PTH or YKL) treatments assessed by of micro-CT of the distal femur metaphysis. OVX had no effect on BV/TV, but led to reduced Tb.BMD.

100139] Figure 30: Graph showing effects of OVX and drug (PTH or YKL) treatments assessed by of micro-CT of the femur. OVX: 18.4% bone loss, p=0.041 vs SHAM; PTH: 31.5% bone gain, p-0.0047 vs OVX/VEH; YKL: 44.9% bone gain, p=0.00036 vs OVX/VEH.

100140] Figures 31A to **31E:** Graphs showing effects of OVX and drug (PTH or YKL) treatments assessed by micro-CT of the L5 vertebrae. OVX: 19.6% bone loss, p=0.00043 vs SHAM; PTH: 12.4% bone gain, p=0.084 vs OVX/VEH; YKL: 11.9% bone gain, p=0.036 vs OVX/VEH.

100141] Figures 32A to **32C:** Graphs showing that both treatments (treatment comprising PTH and treatment comprising YKL) increased osteoblasts, but showed different effects on osteoclasts.

100142] Figures 33A **to 33D:** Histomorphometry: both treatments (treatment comprising PTH and treatment comprising YKL) increased BFR, but only PTH increases osteoid.

[00143] Figures 34A to **34B:** Bone turnover markers: both treatments (treatment comprising PTH and treatment comprising YKL) increased P1NP, only the treatment comprising PTH increased CTX.

[00144] **Figure 35:** Tibial histomorphometry results. YKL treatment may have reduced marrow adiposity.

[00145] **Figures 36A** to **36D:** the hematology data showed no signal.

[00146] **Figures 37A to 37D:** Serum toxicology data showed increased glucose and BUN.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

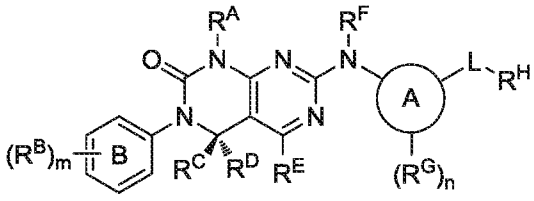
[00147] Described herein are uses of SIK inhibitors *(e.g.*, SIK1 inhibitors, SIK2 inhibitors,SIK3 inhibitors) and pharmaceutical compositions that include SIK inhibitors in the treatment and/or prevention of osteoporosis. SIK inhibitors may be able to treat osteoporosis, prevent osteoporosis, increase the function of osteocytes, increase the number of osteoblasts, increase the activity of osteoblasts, inhibit the resorption of a bone, decrease the number of osteoclasts, inhibit the activity of osteoclasts, increase the mass of a bone, down-regulate the expression of the gene SOST, inhibit the activity of sclerostin, and/or reduce the production of sclerostin in a subject in need thereof.

[00148] Osteocytes orchestrate bone formation and resorption. Parathyroid hormone (PTH) activates receptors on osteocytes to accomplish both goals. PTH inhibition of SOST, a WNT antagonist, may require HDAC4 and HDAC5, while PTH stimulation of RANKL, a stimulator of bone resorption, may require CRTC2. Salt inducible kinases (SIKs) may control subcellular localization of both HDAC4/5 and CRTC2. PTH may regulate both HDAC4/5 and CRTC2 localization via phosphorylation and inhibition of SIK2. Like PTH, SIK inhibitors may cause dephosphoryiation and nuclear translocation of HDAC4/5 and CRTC2. SIK inhibition may mimic many of the effects of PTH in osteocytes as assessed by RNA-seq in cultured osteocytes and following *in vivo* administration. Once daily treatment with the SIK inhibitor YKL-05-099 increased bone formation and bone mass. Therefore, a major arm of PTH signaling in osteocytes may involve SIK inhibition, and SIK inhibitors may be a useful strategy to mimic skeletal effects of PTH.

Compounds for Use in the Invention

Compounds of Formula (I)

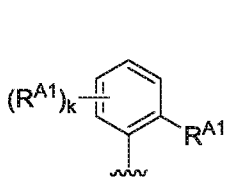
[00149] In one aspect, the present disclosure provides bicyclic urea compounds of Formula (I) for use in the present disclosure:



(I),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

R^A is substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,



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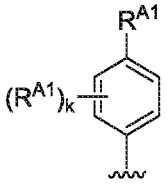


, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl;

each instance of R^{A1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, --SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

each instance of R^b is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^b are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, or 4;

each instance of R^B is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=())R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-N0_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

m is 0, 1, 2, 3, 4, or 5;

R^C is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^D is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^E is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-N0_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

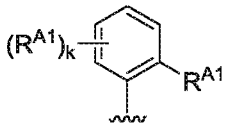
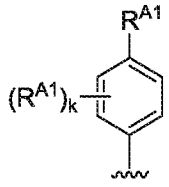
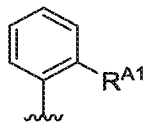
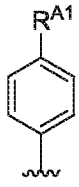
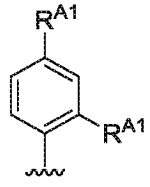
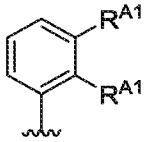
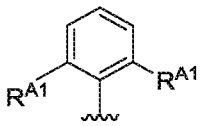
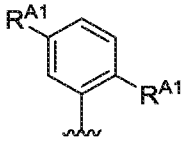
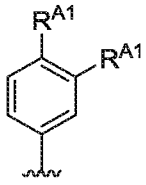
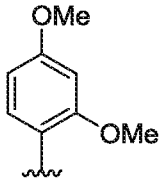
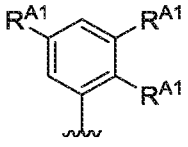
n is 0, 1, 2, 3, or 4, as valency permits;

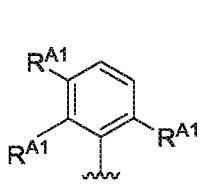
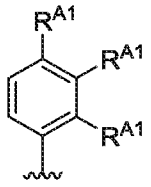
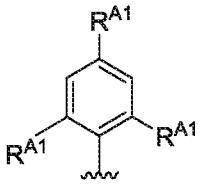
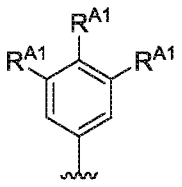
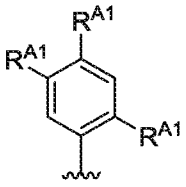
L is a bond or a substituted or unsubstituted, C_{1-6} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -C(=0)-, -0-, -S-, $-NR^b-$, -N=, or =N-; and

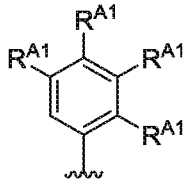
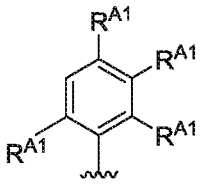
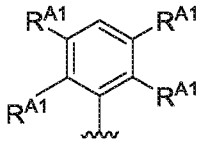
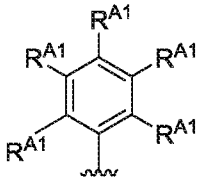
R^H is substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted heterocyclyl, -OH, or $-N(R^c)_2$, wherein each instance of R^c is independently

hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

100150] Unless expressly provided otherwise, the moieties and variables described in the subsection **Compounds of Formula** (I) apply only to Formula (I).

[00151] Formula (I) includes substituent R^A. In certain embodiments, R^A is substituted alkenyl. In certain embodiments, R^A is unsubstituted alkenyl. In certain embodiments, R^A is substituted alkynyl. In certain embodiments, R^A is unsubstituted alkynyl. In certain embodiments, R^A is substituted phenyl. In certain embodiments, R^A is of the formula:  or  . In certain embodiments, k is 0. In certain embodiments, R^A is of the formula:  or  . In certain embodiments, k is 1. In certain embodiments, R^A is of the formula:  ,  ,  , or  . In certain embodiments, R^A is of the formula:  . In certain embodiments, R^A is  . In certain embodiments, k is 2. In certain embodiments, R^A is of the formula:  ,

 ,  ,  ,  , or  . In certain embodiments, k is 3. In certain embodiments, R^A is of the formula:

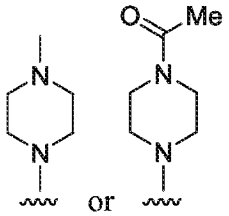
 ,  , or  . In certain embodiments, k is 4. In certain embodiments, R^A is of the formula:  .

[00152] In certain embodiments, when R^A is substituted phenyl, R^A includes one or more R^{A1} substituents. In certain embodiments, at least one instance of R^{A1} is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one R^{A1} is substituted or unsubstituted alkyl *(e.g.,* substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkynyl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments , at least one instance of R^{A1} is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A1} is benzyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted phenyl. In certain

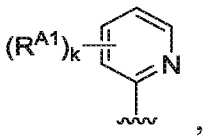
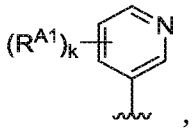
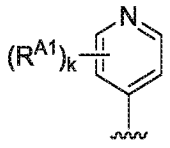
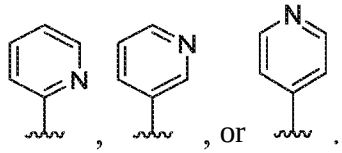
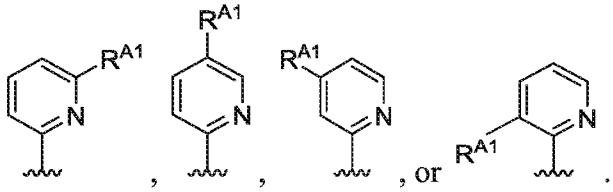
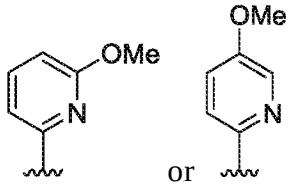
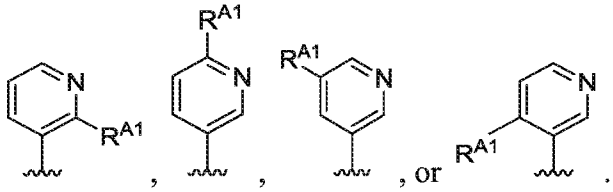
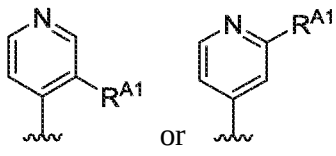
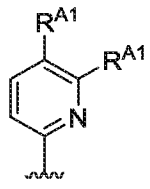
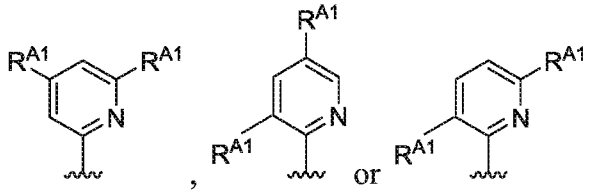
embodiments, at least one instance of R^{A1} is substituted or unsubstituted heteroaryl *(e.g.,* substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A1} is $-OR^a$ *(e.g.,* –OH or –OMe). In certain embodiments, at least one instance of R^{A1} is $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

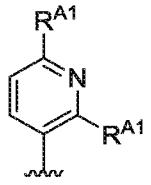
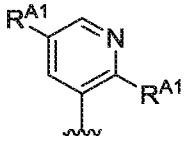
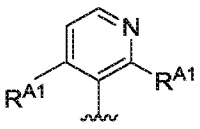
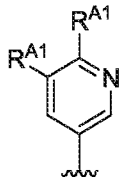
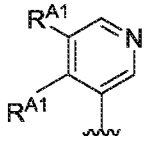
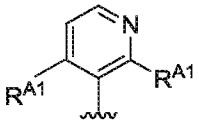
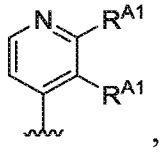
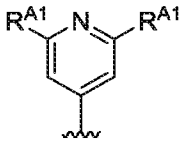
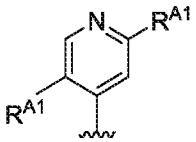
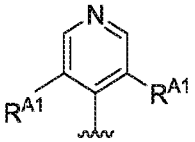
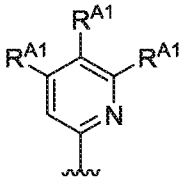
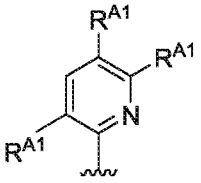
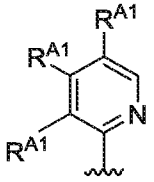
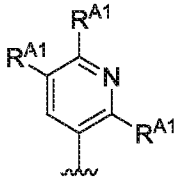
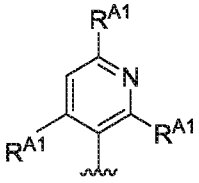
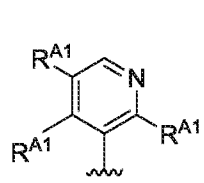
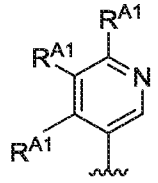
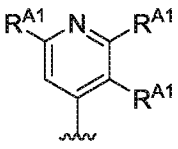
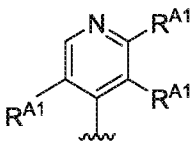
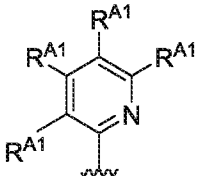
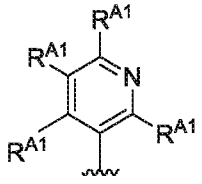
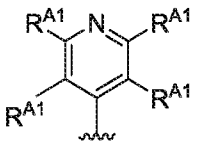
[00153] In certain embodiments, at least one instance of R^a is hydrogen. In certain embodiments, at least one instance of R^a is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkyl *(e.g.,* substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkenyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkynyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, 5- to 1G-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments , at least one instance of R^a is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A1} is benzyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl *(e.g.* , substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or

unsubstituted, 9- to 10-membered, bieyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, at least one instance of R^a is a sulfur protecting group when attached to a sulfur atom.

[00154] In certain embodiments, at least one instance of R^b is hydrogen. In certain embodiments, at least one instance of R^b is substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* substituted or unsubstituted methyl, ethyl, or propyl). In certain embodiments, at least one instance of R^b is a nitrogen protecting group *(e.g.,* benzyl (Bn), t-butyl carbonate (BOC or Boc), benzyl carbamate (Cbz), 9-fluorenylmethyl carbonate (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl, or p-toluenesulfonamide (Ts)). In certain embodiments, two instances of R^b are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring *(e.g.,* substituted or unsubstituted, 5- to 10-membered monocyclic or bieyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^b are taken together with their intervening atoms to form substituted or unsubstituted piperazinyl. In certain embodiments, two instances of R^b are taken together with their intervening atoms to form  or .

[00155] In certain embodiments, R^A is substituted or unsubstituted heteroaryl. In certain embodiments, R^A is substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur *(e.g.,* furanyl, thiophenyl, pyridinyl, or pyrimidinyl, *etc.)* In certain embodiments, R^A is substituted or unsubstituted furanyl. In certain embodiments, R^A is substituted or unsubstituted thiophenyl. In certain embodiments, R^A is substituted or unsubstituted pyridinyl. In

certain embodiments, R^A is of the formula:  ,  , or  . In certain embodiments, k is 0. In certain embodiments, R^A is of the formula:  . In certain embodiments, k is 1. In certain embodiments, R^A is of the formula:  . In certain embodiments, R^A is of the formula:  . In certain embodiments, R^A is of the formula:  . In certain embodiments, R^A is of the formula:  . In certain embodiments, k is 2. In certain embodiments, R^A is of the formula:  ,  . In certain embodiments, R^A is of the

formula:  ,  ,  ,  ,  , or  . In certain embodiments, R^A is of the formula:  ,  ,  , or  . In certain embodiments, k is 3. In certain embodiments, R^A is of the formula:  ,  , or  . In certain embodiments, R^A is of the formula:  ,  ,  , or  . In certain embodiments, R^A is of the formula:  , or  . In certain embodiments, k is 4. In certain embodiments, R^A is of the formula:  ,  , or  . In certain embodiments, R^A is not substituted or unsubstituted pyridinyl. In certain embodiments, R^A is not substituted or unsubstituted 2-pyridinyl. In certain embodiments, R^A is not substituted 2-pyridinyl. In certain embodiments, R^A

is substituted or unsubstituted pyrimidinyl. In certain embodiments, R^A is substituted or unsubstituted pyrazinyl. In certain embodiments, R^A is substituted or unsubstituted triazinyl. In certain embodiments, R^A is substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^A is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur), provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl. In certain embodiments, R^A is substituted or unsubstituted tetrahydropyranyl. In certain embodiments, R^A is unsubstituted tetrahydropyranyl. In certain embodiments, R^A is piperidinyl. In certain embodiments, R^A is substituted or unsubstituted morpholinyl. In certain embodiments, R^A is substituted or unsubstituted piperazinyl.

[00156] Formula (I) includes Ring B. Ring B is as described herein for Formula **(II).**

[00157] Formula **(I)** includes substituents R^C, R^D, R^E, and R^F. R^C, R^D, R^E, and R^F are as described herein for Formula **(III).**

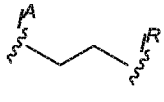
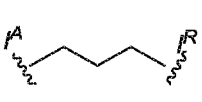
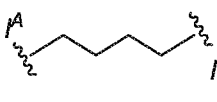
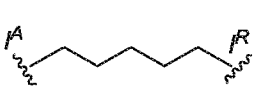
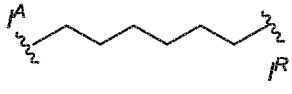
[00158) Formula **(I)** includes Ring A and one or more instances of substituent R^G. Ring A and substituent R^G are as described herein for Formula (III).

[00159] Formula **(I)** includes linker L that connects Ring A to substituent R^H. In certain embodiments, L is a substituted or unsubstituted, C_{1-6} hydrocarbon chain. In certain embodiments, one or more *(e.g., 2,* 3, 4, 5, or 6) chain atoms of the hydrocarbon chain of L are independently replaced with -C(=G)-, -0-, -S-, $-NR^b-$, -N=, or =N--. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain.

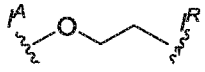
100160] In certain embodiments, L is of the formula: 

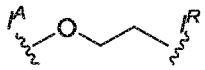
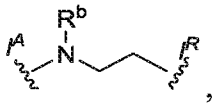
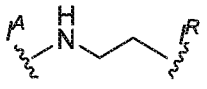
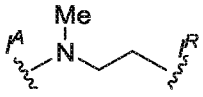
, wherein a is 0, 1, 2, 3, 4, 5, or 6. In certain embodiments, a is 0. In certain embodiments, L is a bond. In certain embodiments, a is 1. In certain embodiments, a is *2.* In certain embodiments, a is 3. In certain embodiments, a is 4. In certain embodiments, a is 5. In certain embodiments, a is 6. In certain embodiments, L is of the formula: 

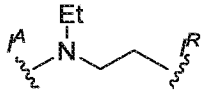
,

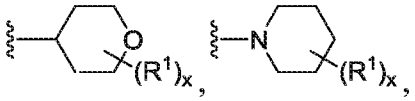
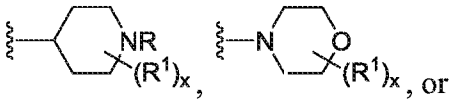
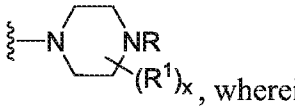
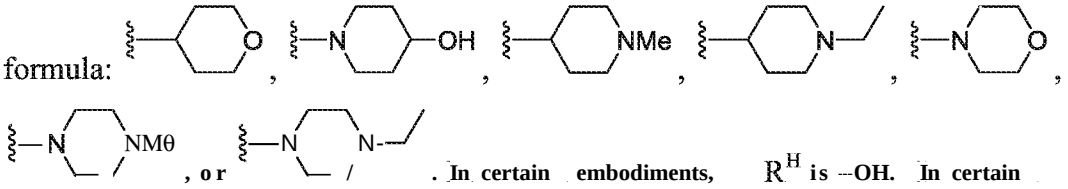
 , or  ,  ,  , or  , wherein l^A indicates the point of attachment to Ring A, and l^R indicates the point of attachment to R^H.

1001611 In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one or more *(e.g.,* 2, 3, 4, 5, or 6) chain atoms of the hydrocarbon chain are independently replaced with --0 -- or -NR^b- . In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with -0-. In certain embodiments, L is of the formula:

 , wherein l^A indicates the point of attachment to Ring A, and l^R indicates the point of attachment to R^A. In certain embodiments, L is of the formula:

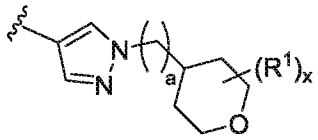
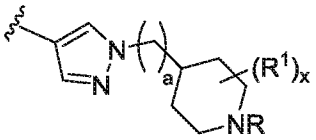
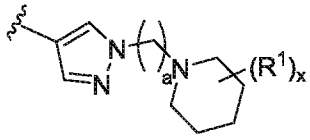
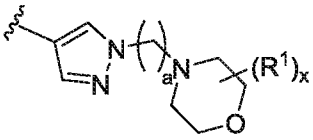
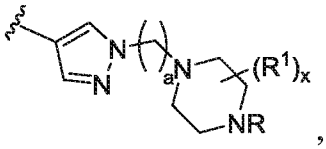
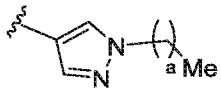
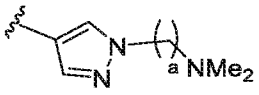
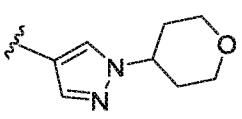
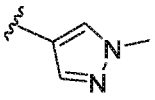
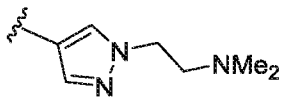
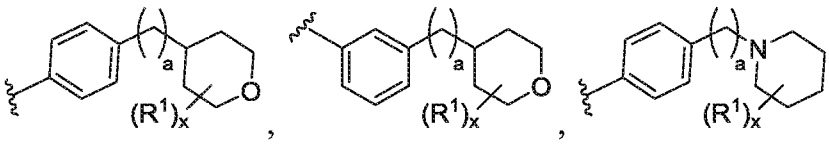
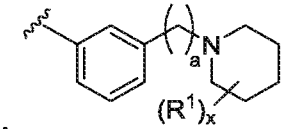
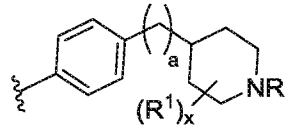
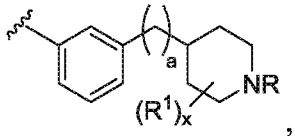
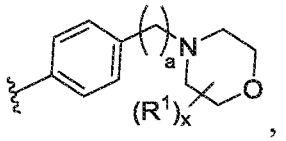
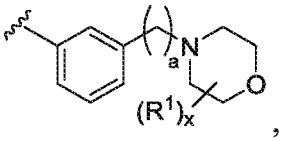
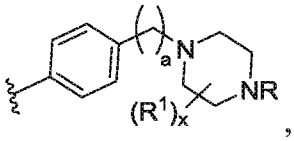
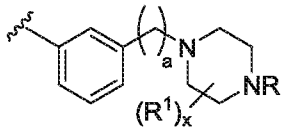
 . In certain embodiments, L is a substituted C_{1-6} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with --N- . In certain embodiments, L is of the formula:  , wherein l^A indicates the point of attachment to Ring A, and l^R indicates the point of attachment to R^H. In certain embodiments, L is of the formula:  . In certain embodiments, L is of the formula:  . In certain embodiments, L is of the formula:

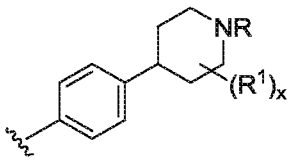
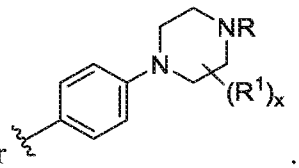
 . In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with --C(=0) --. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with --S-. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with -NR^b- . In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with -N=. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with =N-.

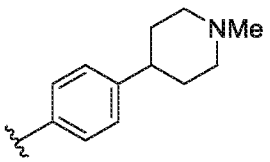
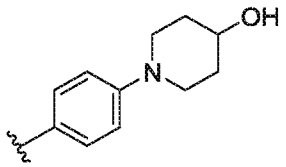
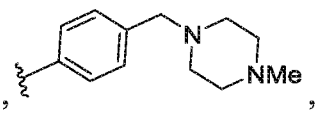
[00162] Formula (I) includes substituent R^H. In certain embodiments, R^H is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^H is methyl. In certain embodiments, R^H is ethyl. In certain embodiments, R^H is propyl. In certain embodiments, R^H is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^H is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl. In certain embodiments, R^H is of the formula:  ,  , or  , wherein R^1 is substituted or unsubstituted, C_{1-6} alkyl or $-OR^{x1}$, wherein R is hydrogen, substituted or unsubstituted, C_{1-6} alkyl or nniittrrooggeenn pprrootteeccttiinngg ggrroouupp;; R^{x1} iiss hhyyddrrooggeenn oorr substituted or unsubstituted, C_{1-6} alkyl; and x is 0, 1, 2, or 3. In certain embodiments, R^H is of the formula:  . In certain embodiments, R^H is –OH. In certain embodiments, R^H is $-N(R^c)_2$.

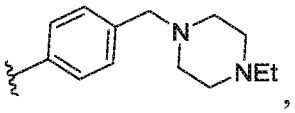
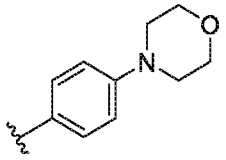
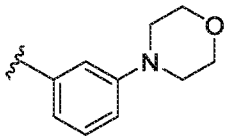
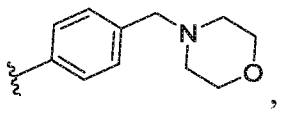
[00163] R^H may include substituent R^c. In certain embodiments, R^c is hydrogen. In certain embodiments, R^c is substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, R^c is substituted or unsubstituted, C_{1-3} alkyl. In certain embodiments, R^c is substituted or unsubstituted methyl. In certain embodiments, R^c is methyl. In certain embodiments, R^c is substituted or unsubstituted ethyl. In certain embodiments, R^c is substituted or unsubstituted methyl. In certain embodiments, R^c is a nitrogen protecting group. In certain embodiments, R^H is $-NMe_2$. In certain embodiments, two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic ring (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heteroaryl ring (*e.g.*,

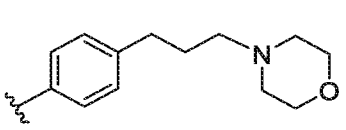
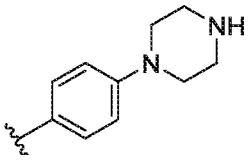
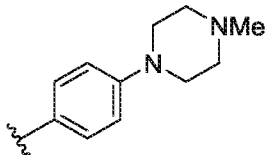
substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

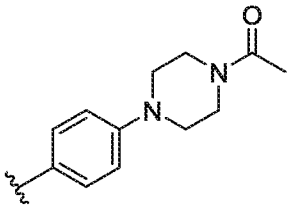
[00164] In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  ,  ,  ,  ,  , or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  , or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  ,  ,  ,  ,  ,  , or  . In certain embodiments, Ring A with linker L and substituent

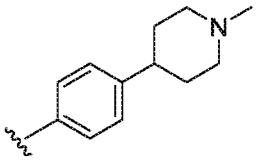
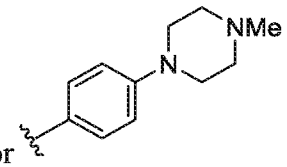
R^H is not of the formula:  or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

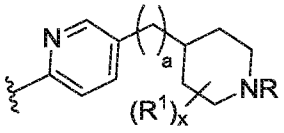
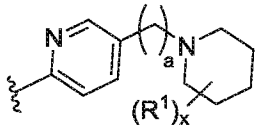
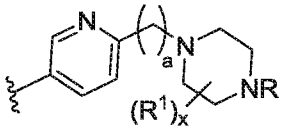
 ,  ,  ,

 ,  ,  ,  ,

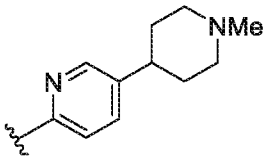
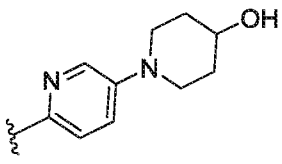
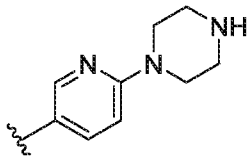
 ,  ,  , or

 . In certain embodiments, Ring A with linker L and substituent R^H is not of the formula:

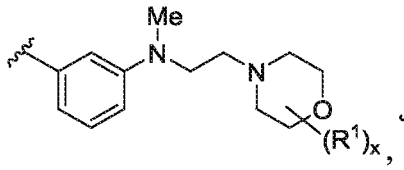
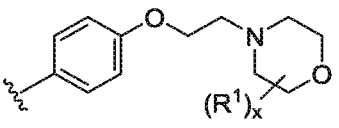
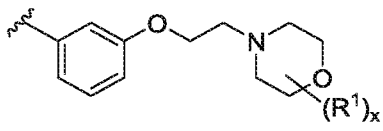
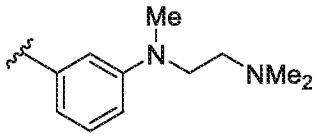
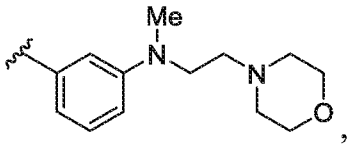
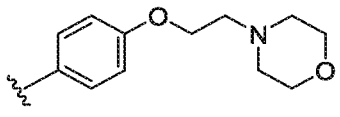
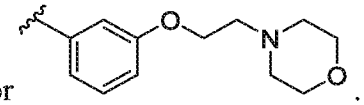
 or  .

[00165] In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  , or  .

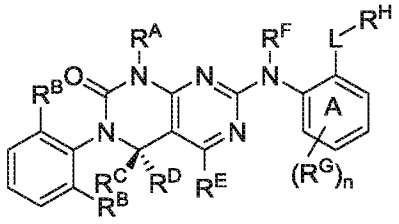
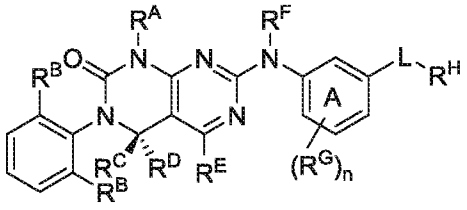
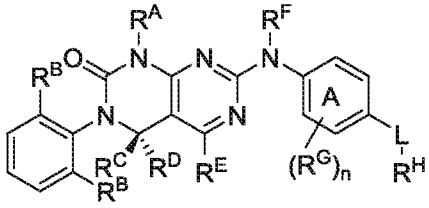
In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

 ,  , or  .

In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

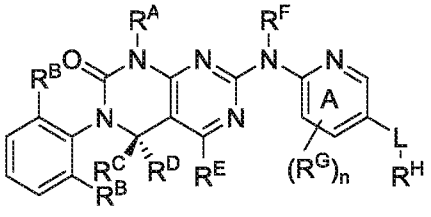
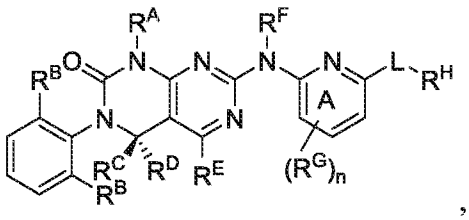

, 
, or 
. In certain embodiments, Ring A with linker L and substituent R^H is of the formula: 
, 
, 
, or 
.

[00166] In certain embodiments, the compound of Formula **(I)** is of the formula:


, 
, or 
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00167] In certain embodiments, the compound of Formula **(I)** is of the formula:


, 
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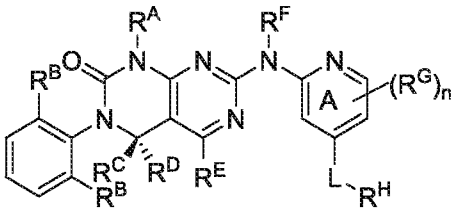
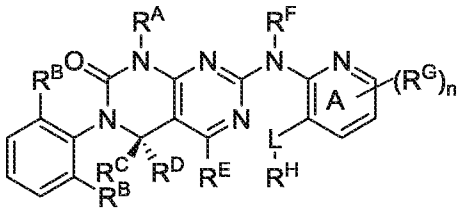
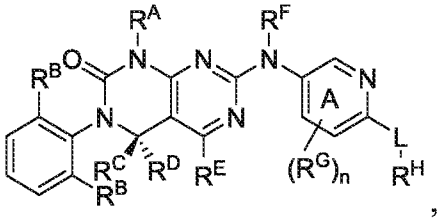
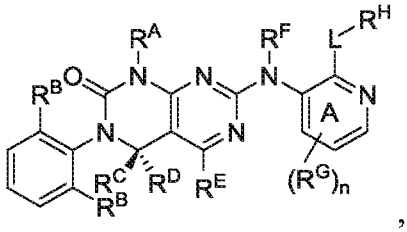
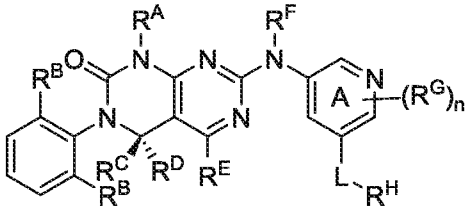
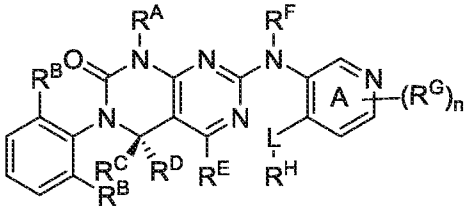
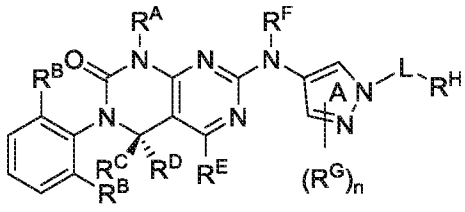

,

,or

,

,

,

,

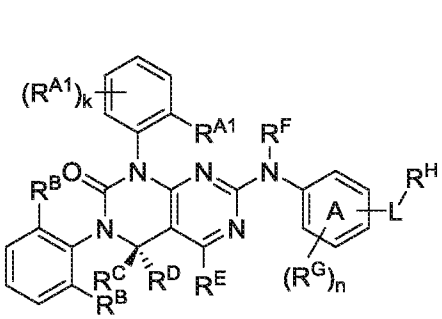
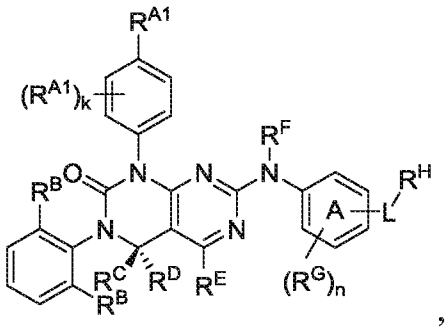
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00168] In certain embodiments, the compound of Formula **(I)** is of the formula:


,

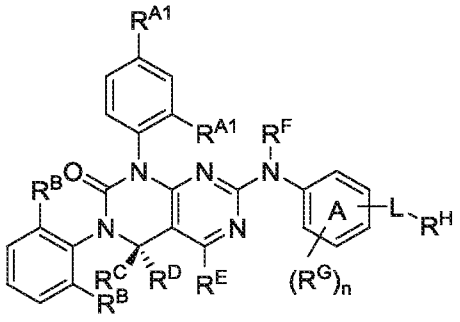
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

1001691 In certain embodiments, the compound of Formula **(I)** is of the formula:


,

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

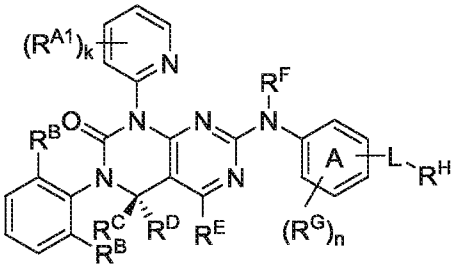
[00170] In certain embodiments, the compound of Formula (I) is of the formula:



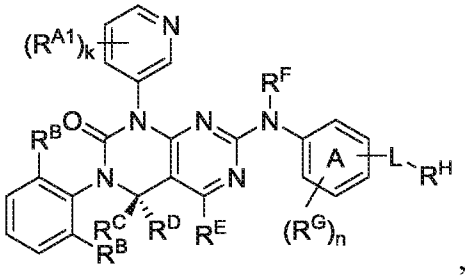
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

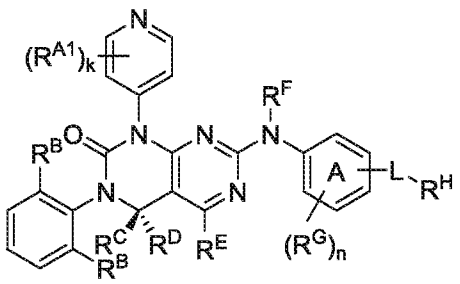
[00171] In certain embodiments, the compound of Formula (I) is of the formula:



,



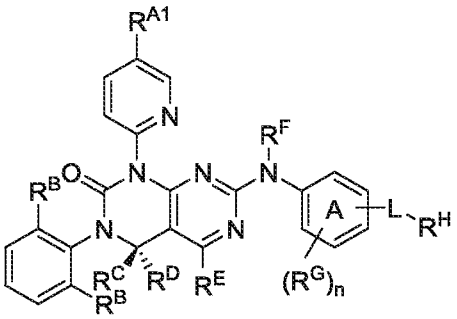
,



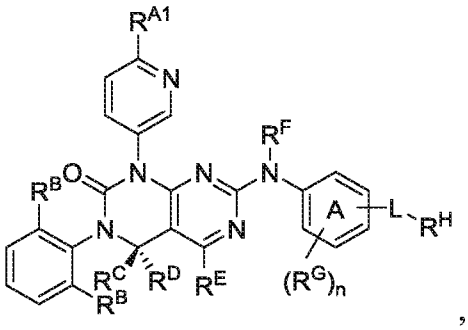
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

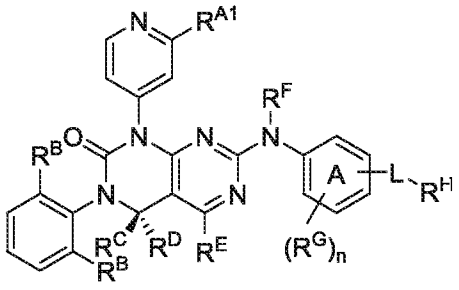
[00172] In certain embodiments, the compound of Formula (I) is of the formula:



,



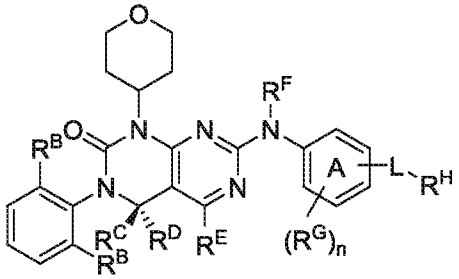
,



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

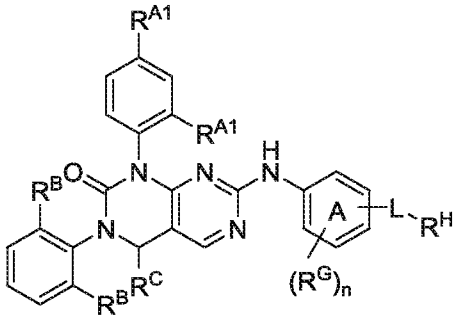
[00173] In certain embodiments, the compound of Formula **(I)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

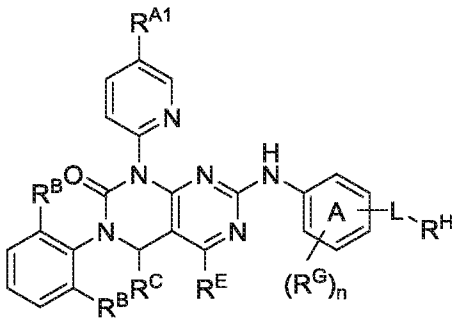
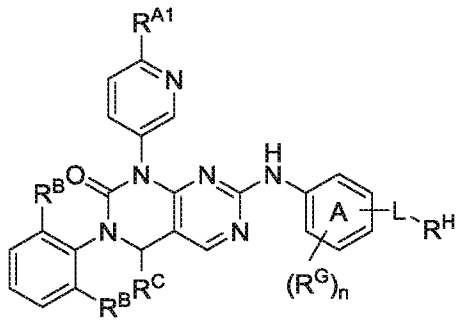
[00174] In certain embodiments, the compound of Formula **(I)** is of the formula:



,

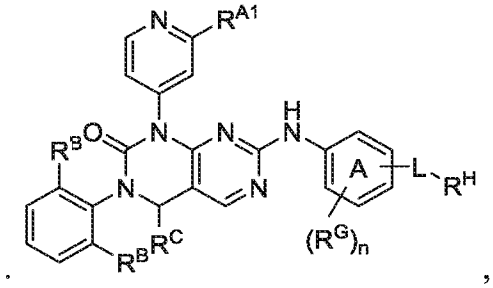
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00175] In certain embodiments, the compound of Formula **(I)** is of the formula:

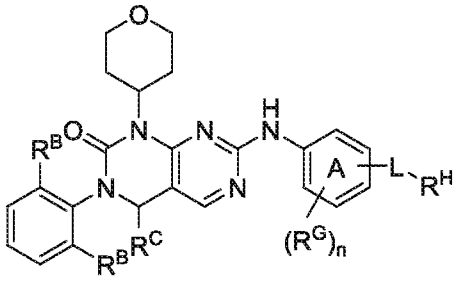
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00176] In certain embodiments, the compound of Formula (I) is of the formula:



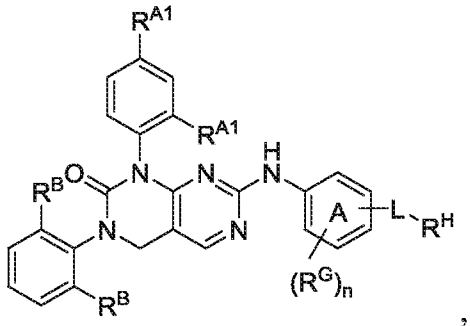
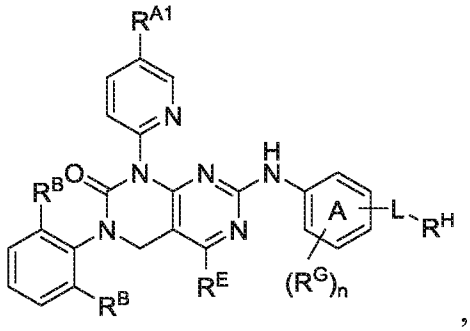
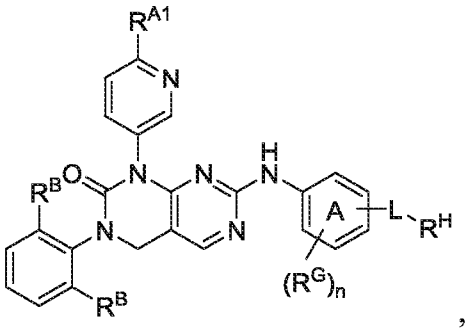
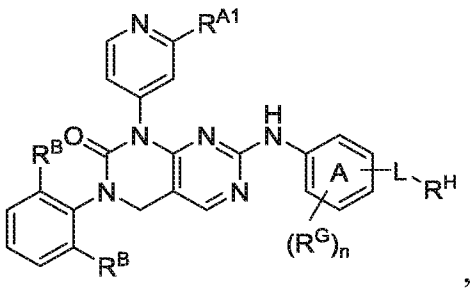
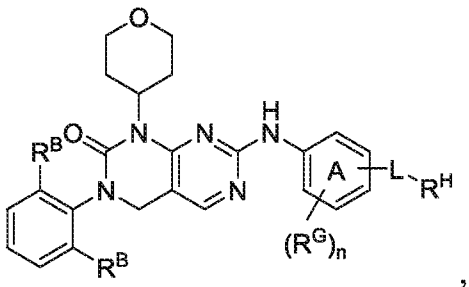
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00177] In certain embodiments, the compound of Formula (I) is of the formula:



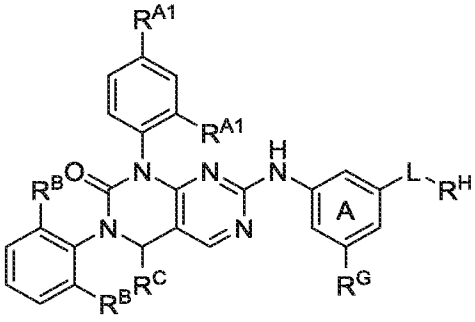
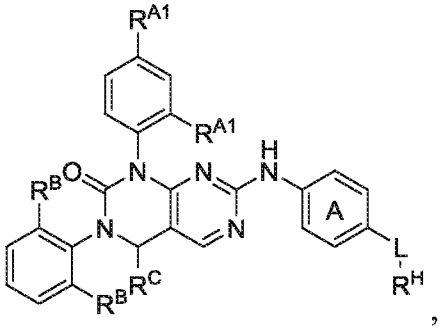
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00178] In certain embodiments, the compound of Formula (I) is of the formula:


,

,

,

,

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00179] In certain embodiments, the compound of Formula (I) is of the formula:


,

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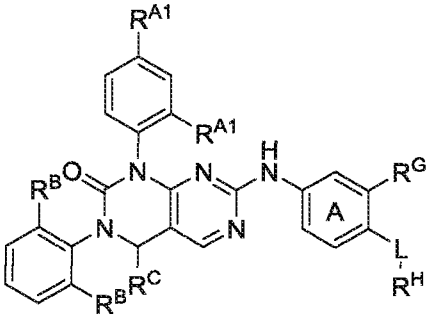
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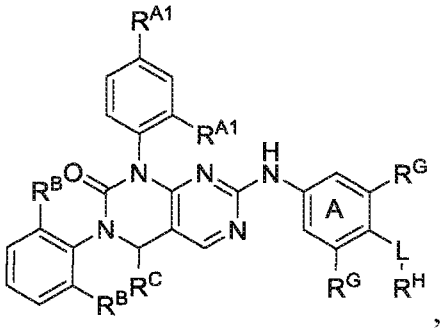
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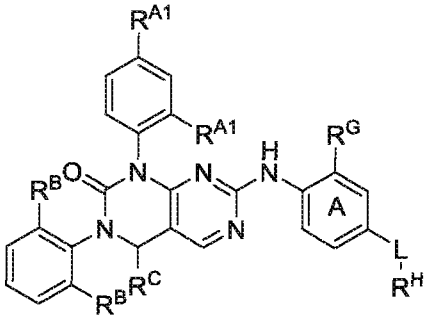
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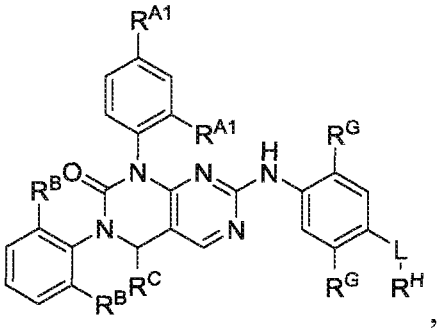
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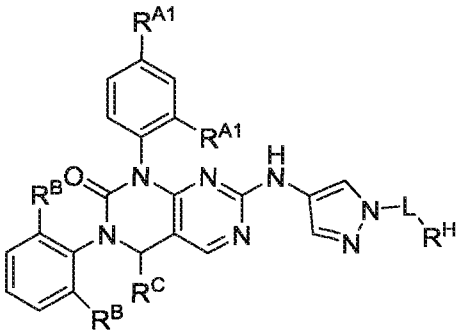
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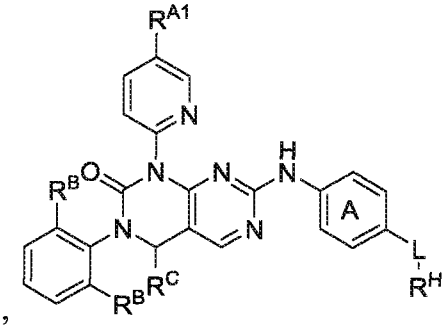
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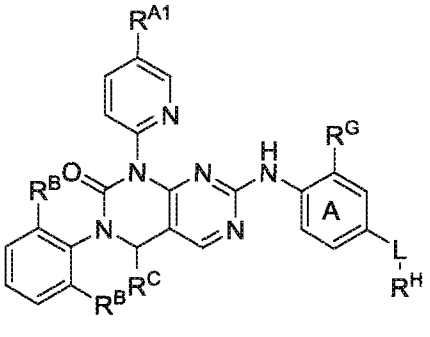
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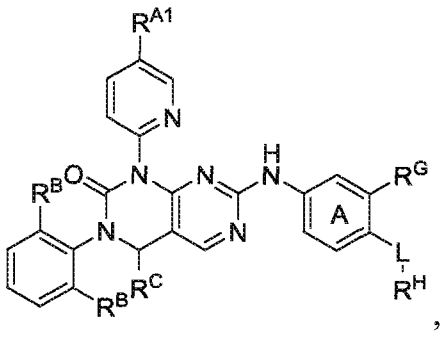
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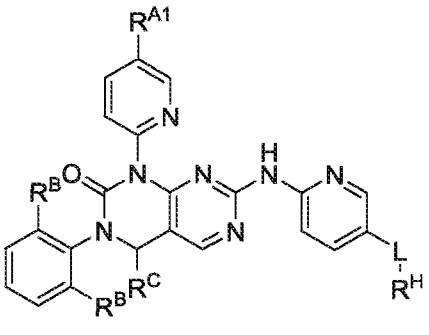
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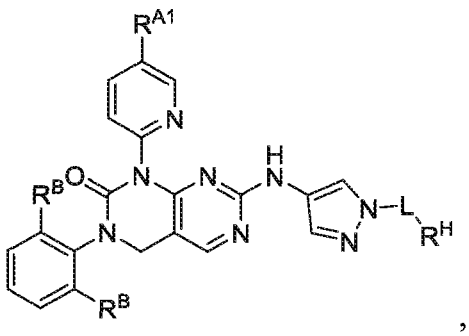
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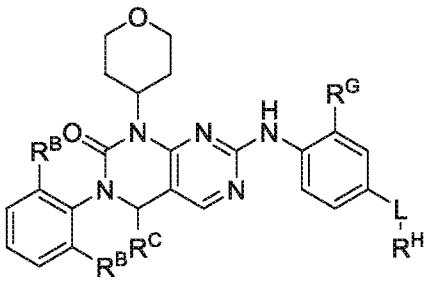
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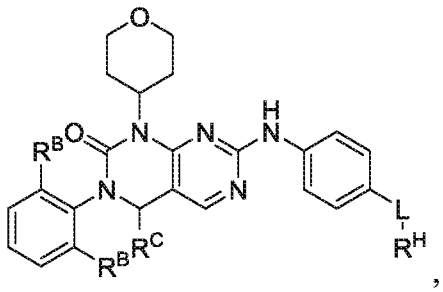
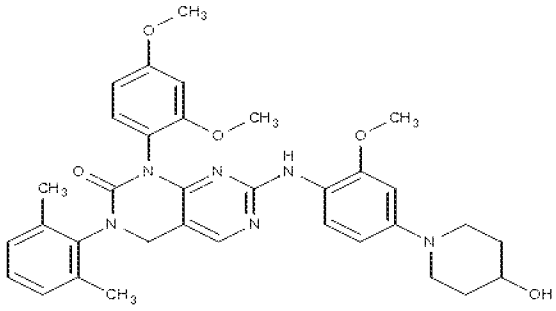

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00180] In certain embodiments, the compound of Formula (I) is of the formula:



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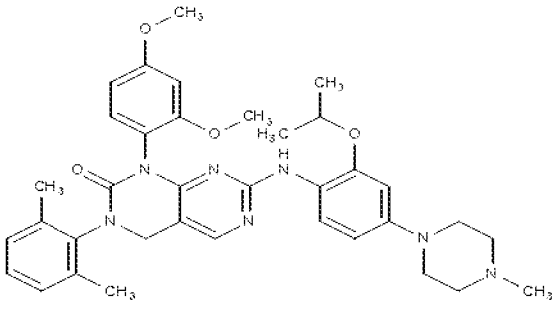

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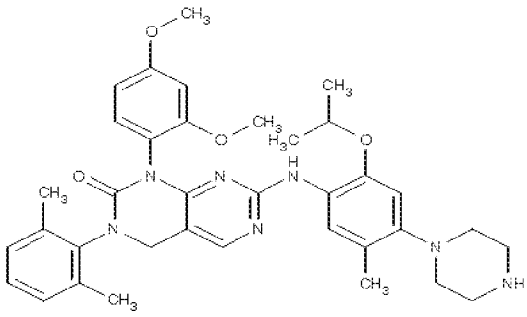
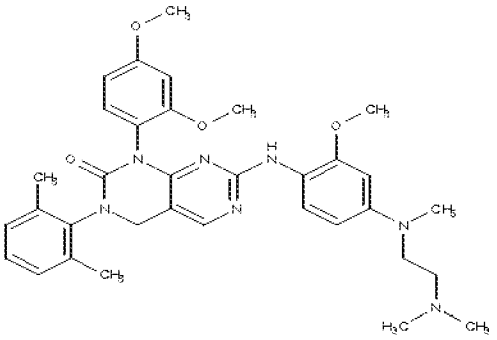


(YKL-05-59),



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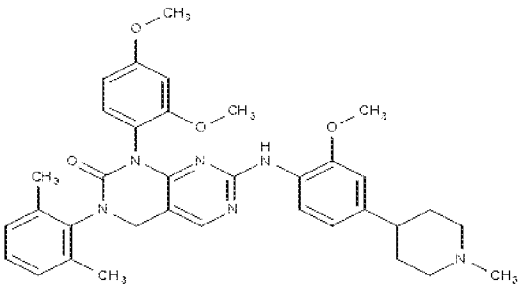
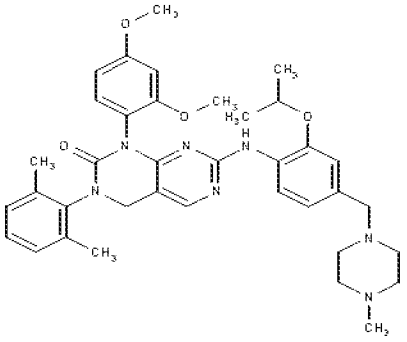
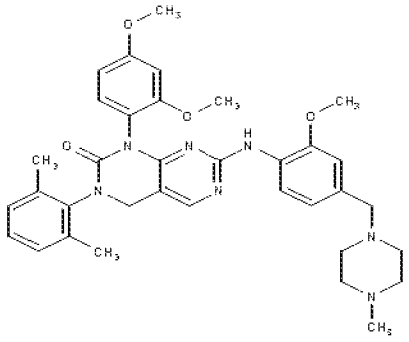


(YKL-05-68 or YKL-05-068),



(YKL-05-69),



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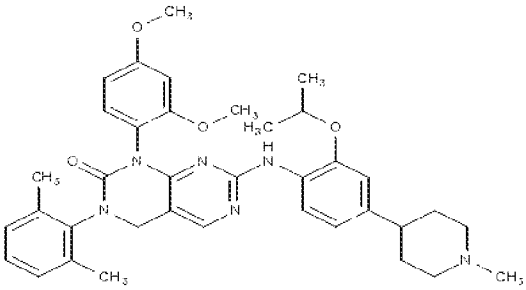

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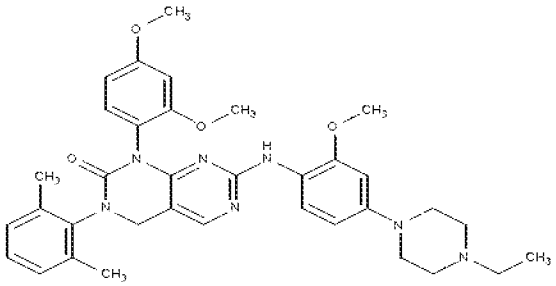

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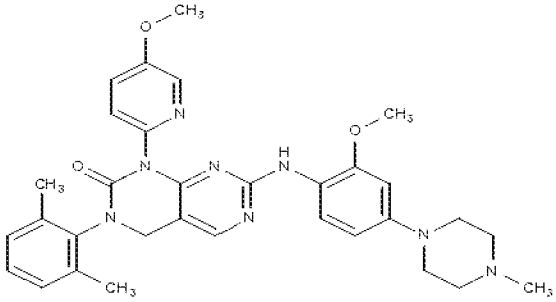

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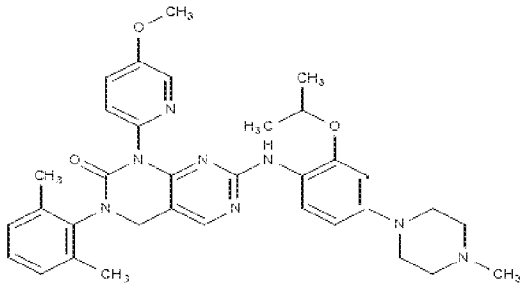

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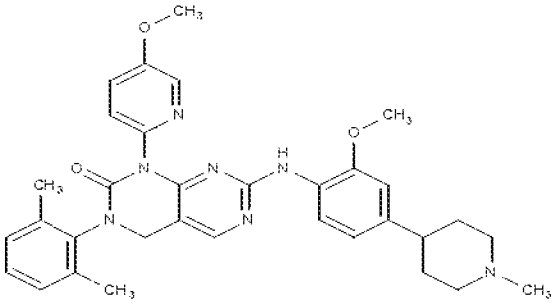

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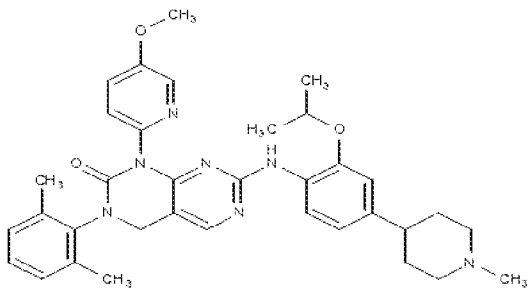

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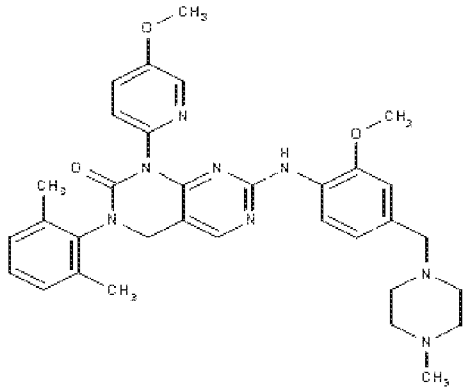

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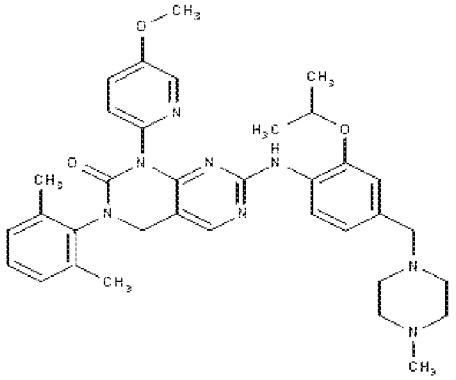

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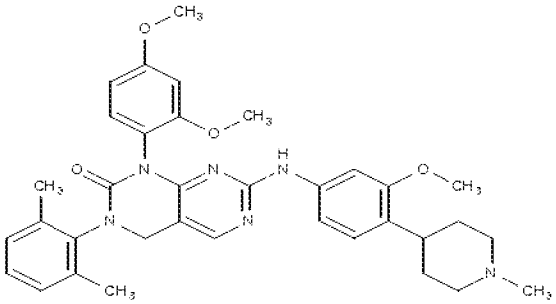

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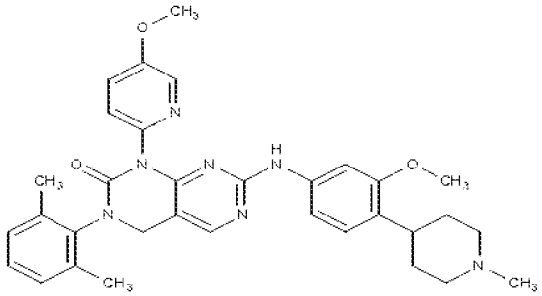

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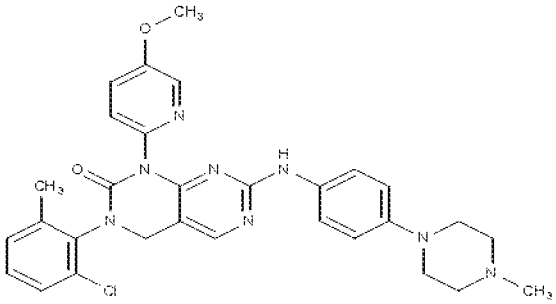

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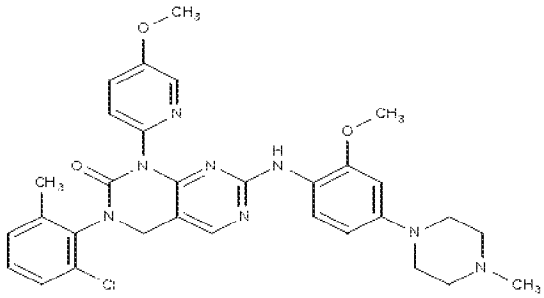

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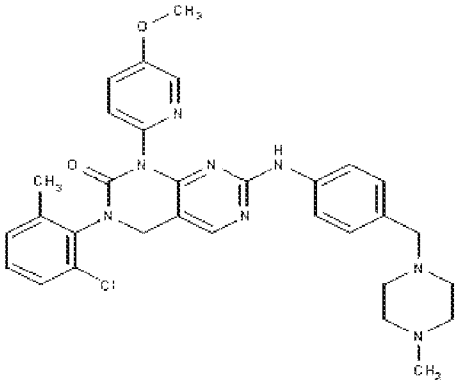

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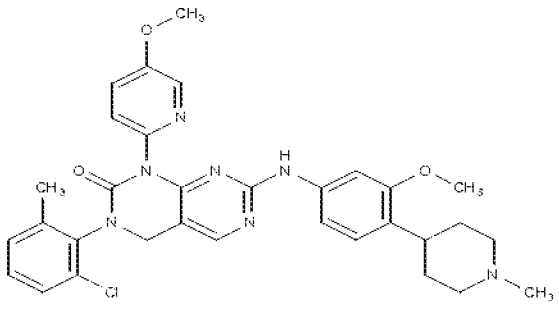
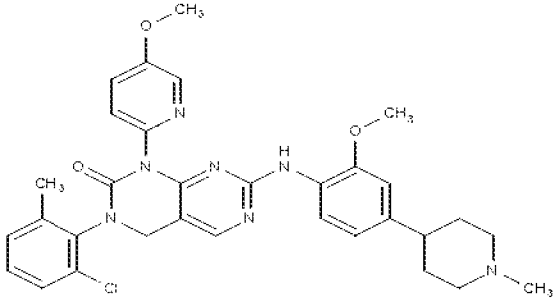


(YKL-05-98 or YKL-05-098),



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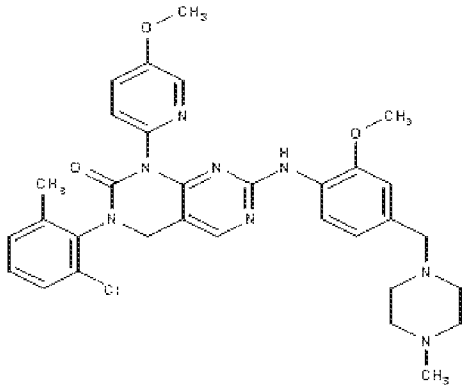

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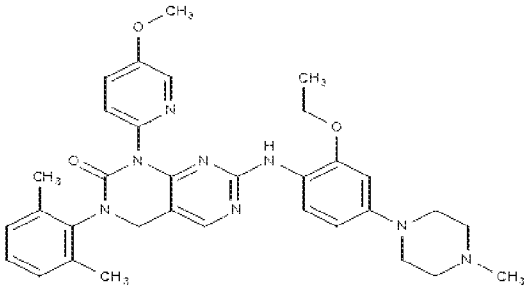

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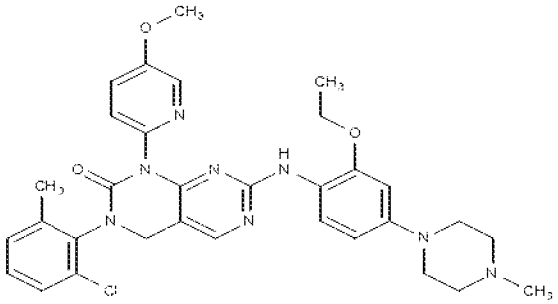

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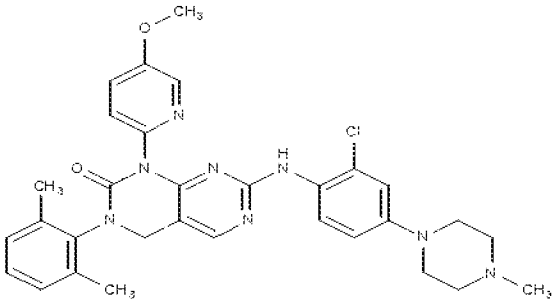

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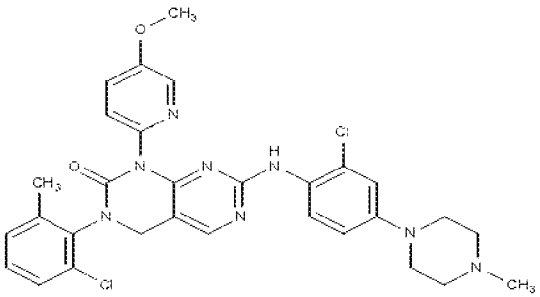

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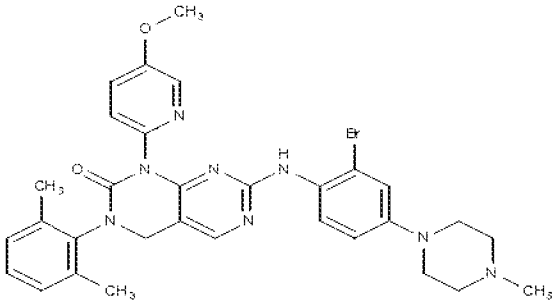

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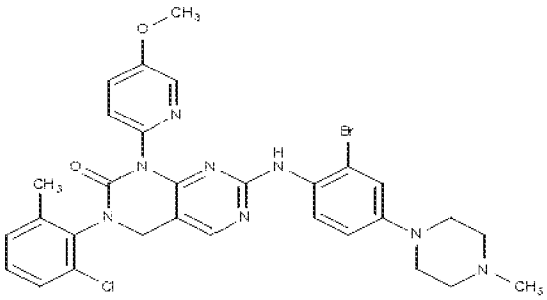

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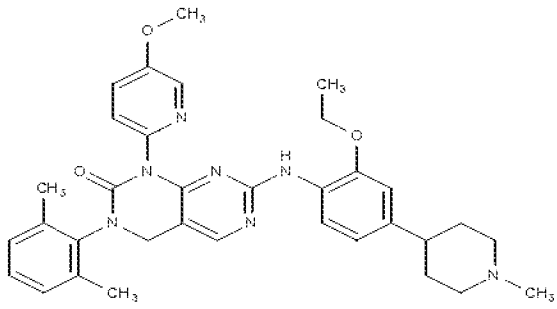

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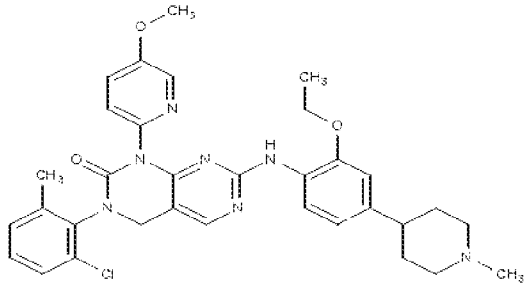
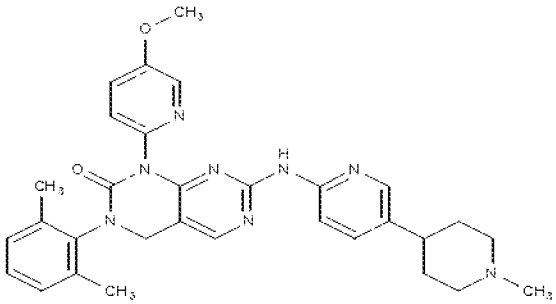


(YKL-05-164),



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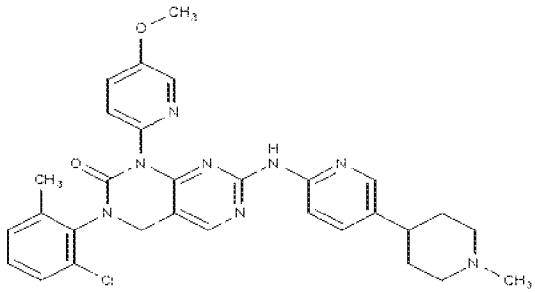

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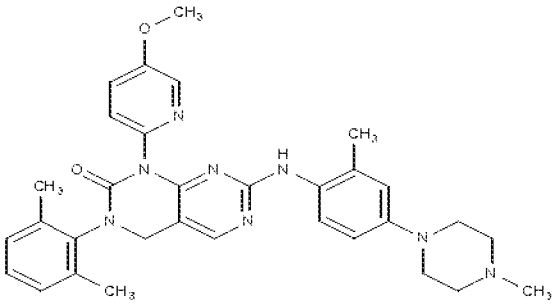

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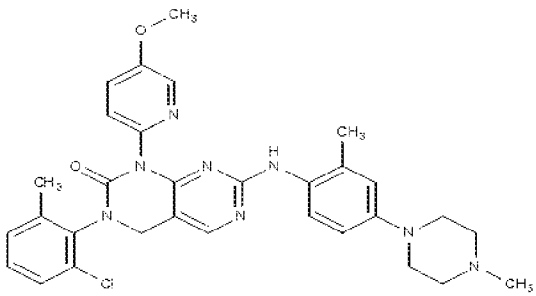

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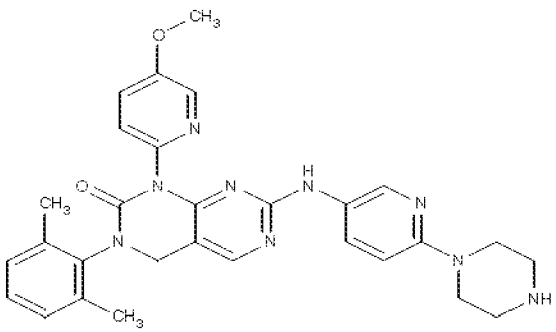
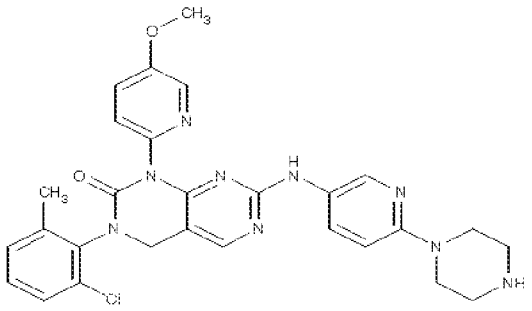
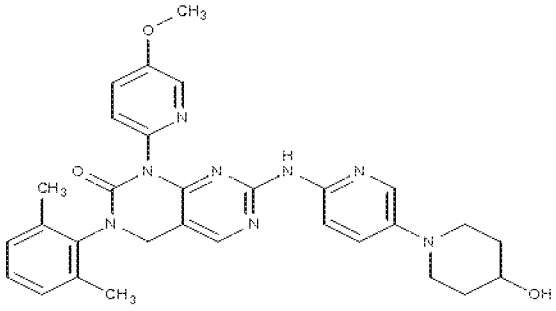


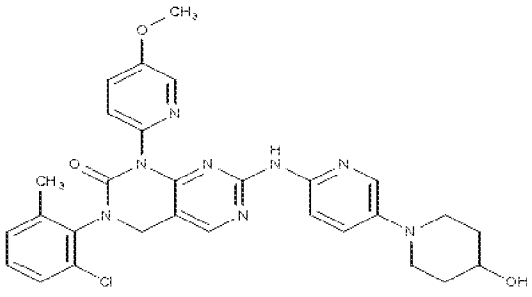
(YKL-05-180),



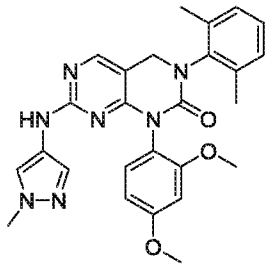
(YKL-05-181),



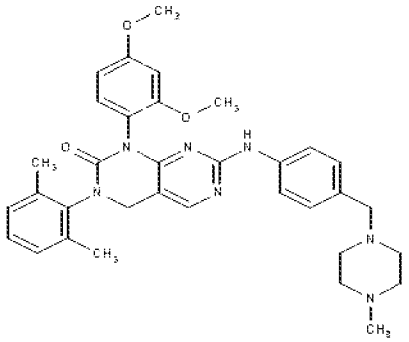
(YKL-05-182),



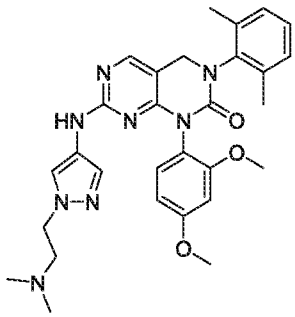
(YKL-05-183),



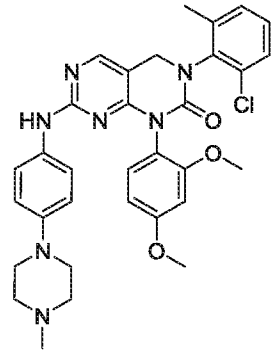
(Example 2),



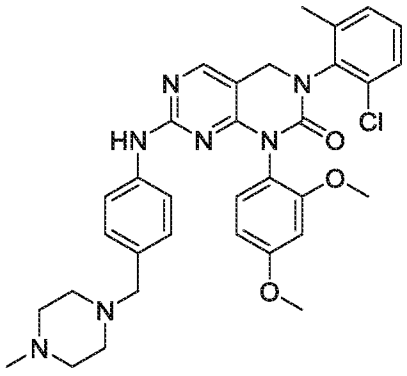
(YKL-04-136-1 or SBl-D-01),

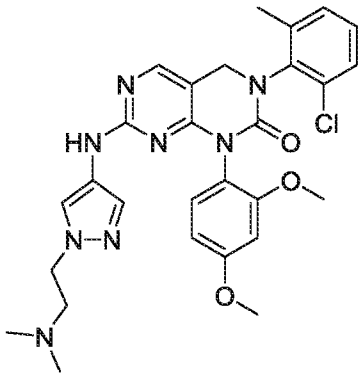


(YKL-04-136-2 or SB1-D-02),

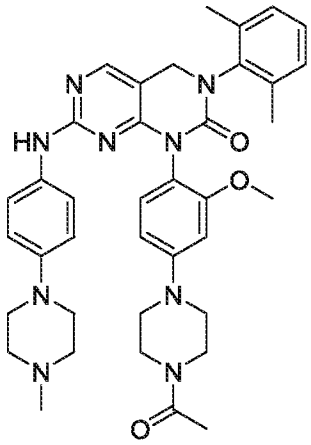


(YKL-04-136-3 or SBl-D-03),

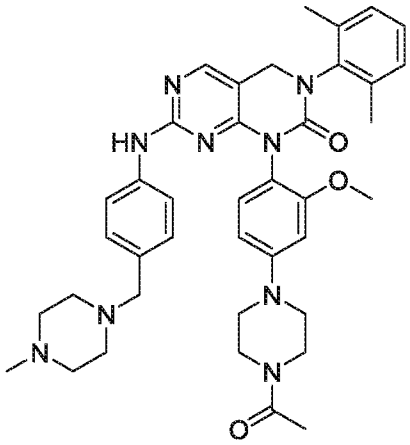




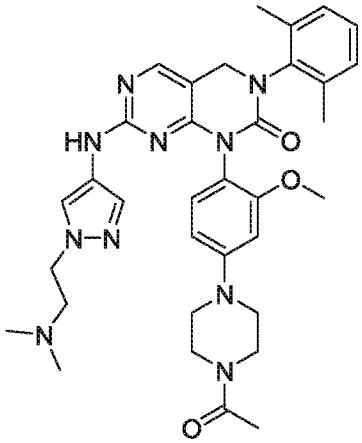
(YKL-04-**136-9** or SBl-D-04),



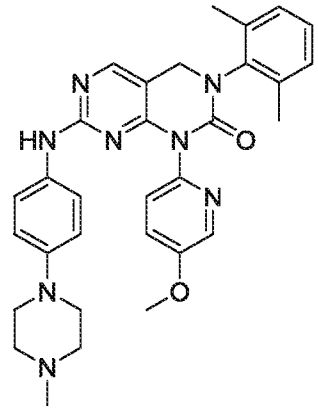
(YKL-04- 136-4 or SB1-D-05),



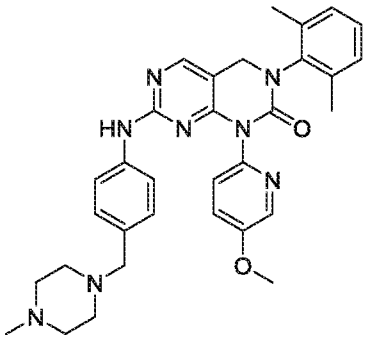
(YKL-04-136-5 or SB1-D-06),



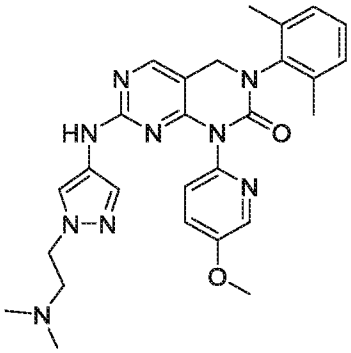
(YKL-04-136-11 or SB1-D-07),

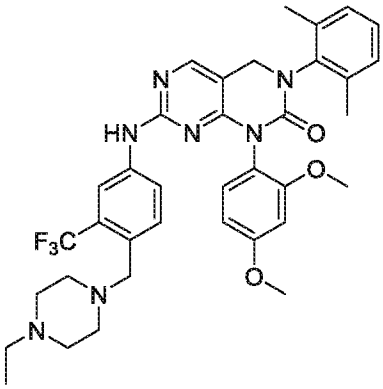


(YKL-04- 136-7 or SBl-D-08),

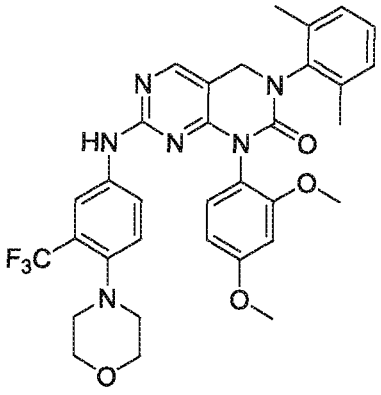


(YKL-04- 136-6 or SBl-D-09),

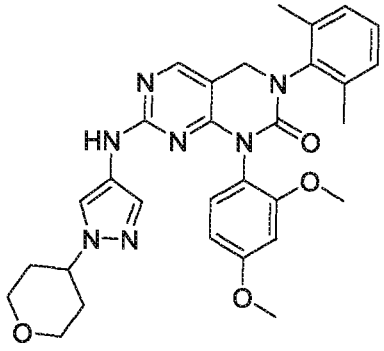




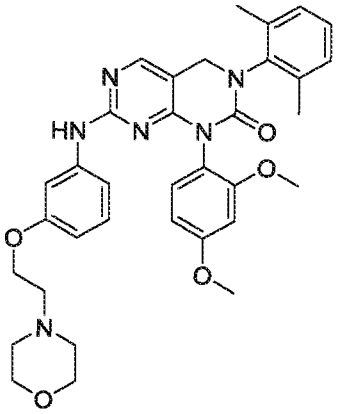
(YKL-04-136-10 or SBl-D-10), (YKL-04-136-8 or SBl-D-l l), (YKL-04-103),



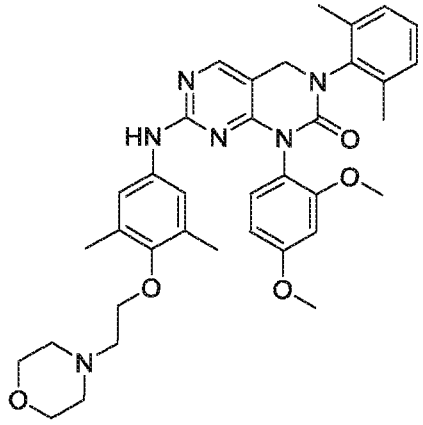
(YKL-04-104),



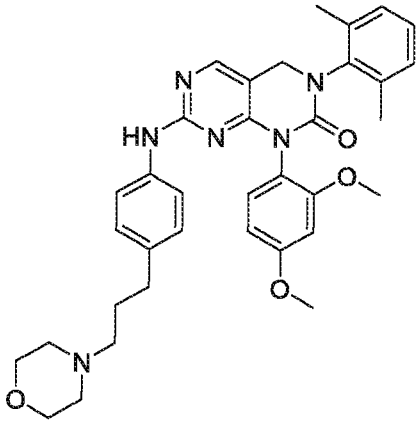
(YKL-04-105),



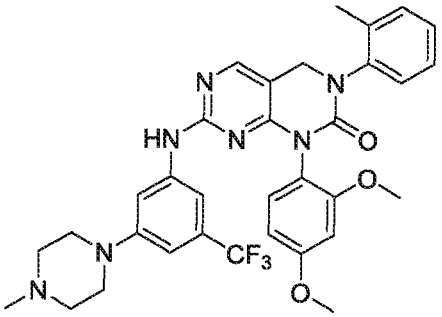
(YKL-04-106),



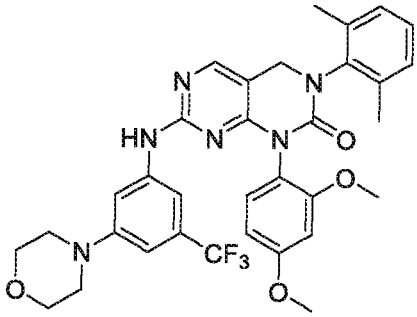
(YKL-04-107),



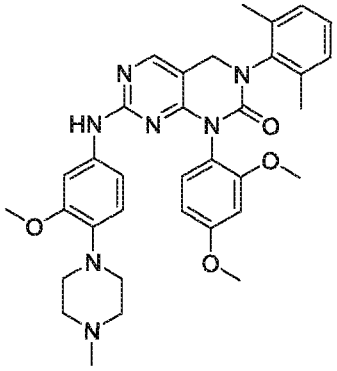
(YKL-04-108),



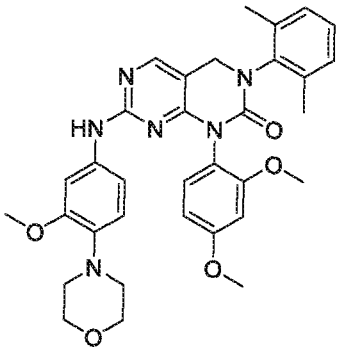
(YKL-04-112),



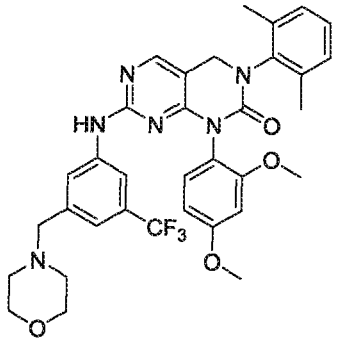
(YKL-04-113),



(YKL-04-1 14),



(YKL-04-1 15),



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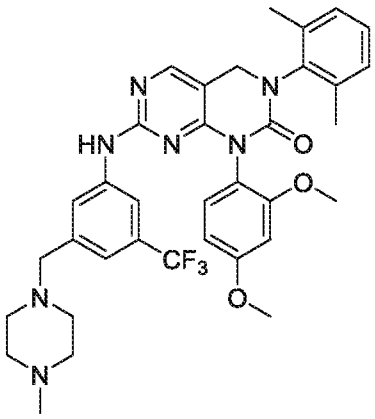
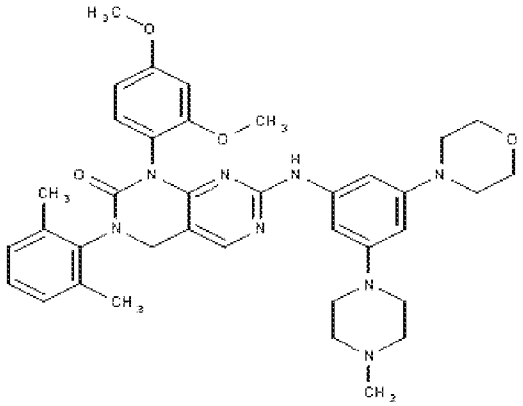
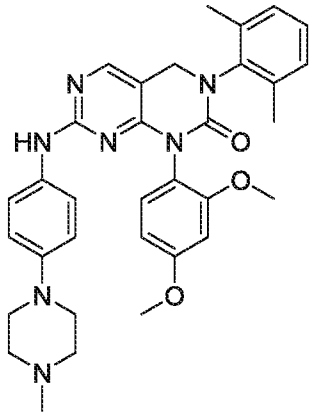


(YKL-04-125),



(HG-11-143-01),



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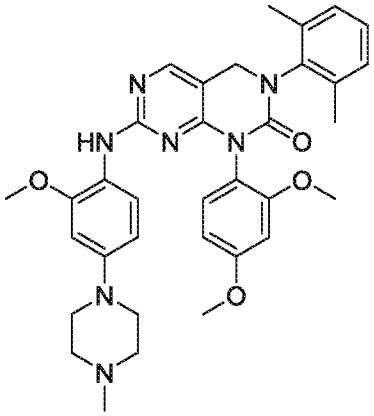
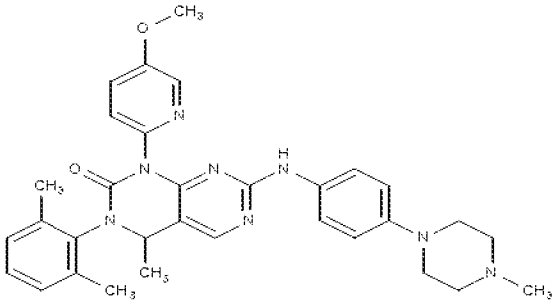
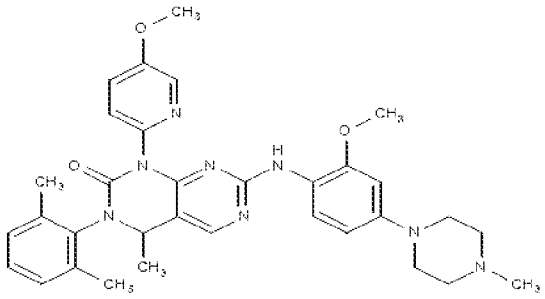


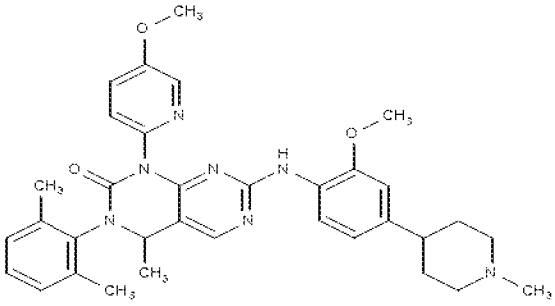
(HG-11-139-01),



(YKL-06-038, YKL 06-038, or SB1-D-40),



(YKL-06-039 or SBl-D-42),



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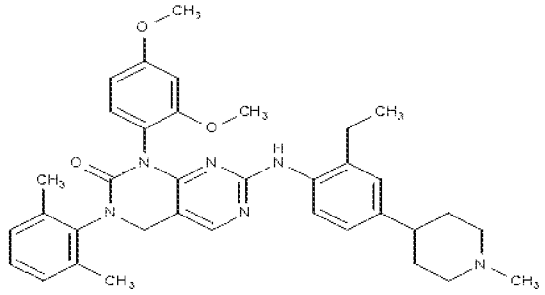

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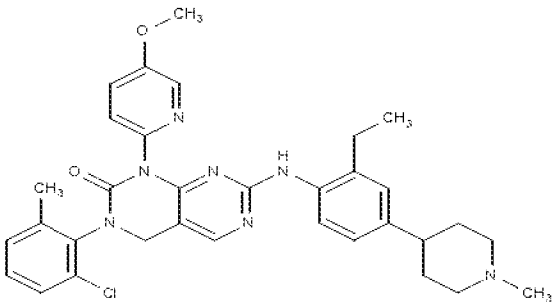
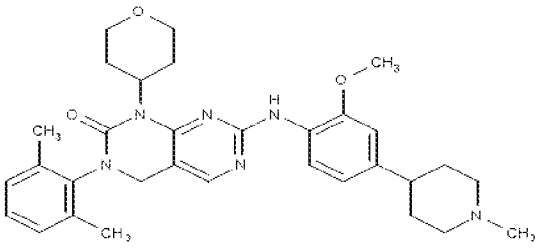


(YKL-Q6-Q45),



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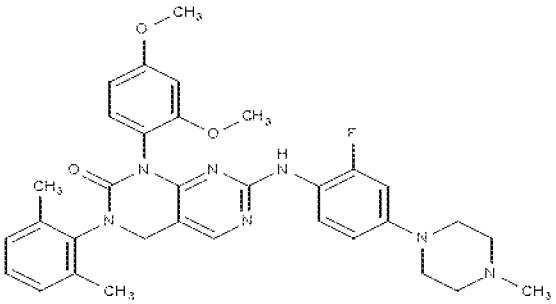
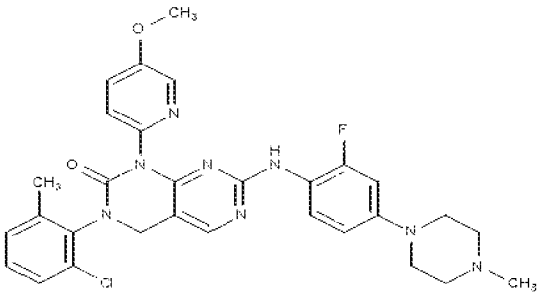


(YKL-06-054),



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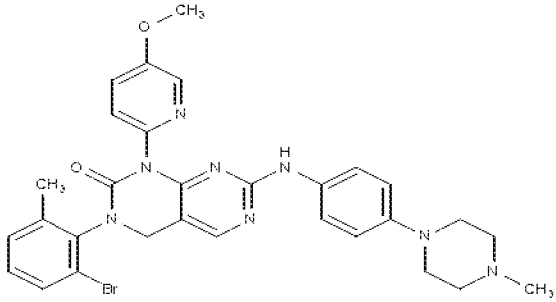
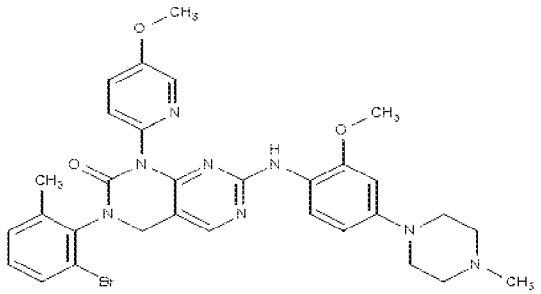
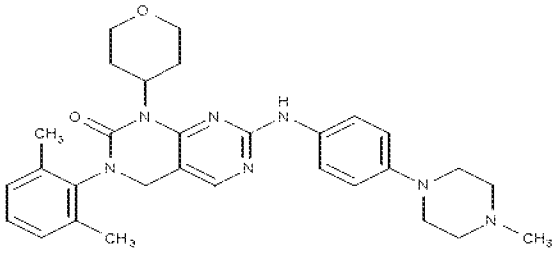


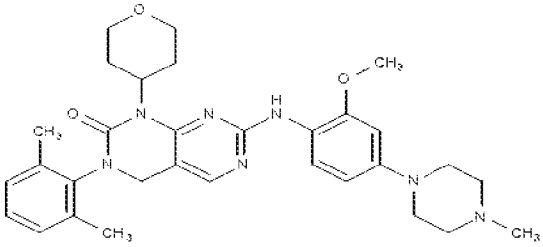
(YKL-06-056),



(YKL-06-057 or SBl -D-43),



(YKL-06-077 or SBl-D-57),



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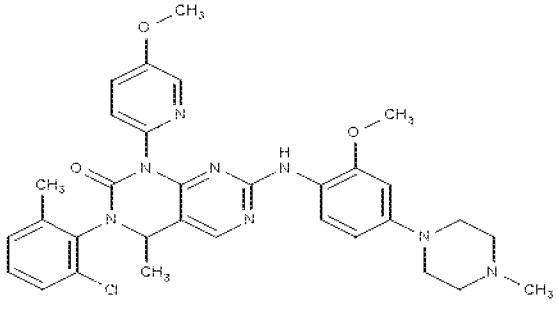
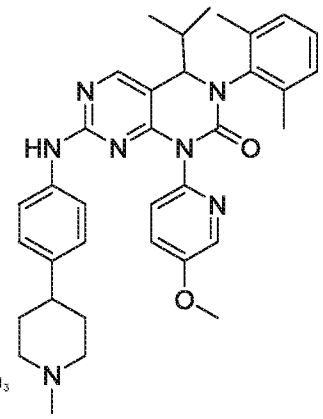
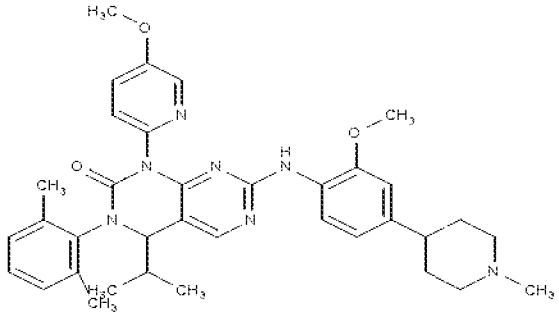


(YKL-06-080-1 or SB1-D-60),



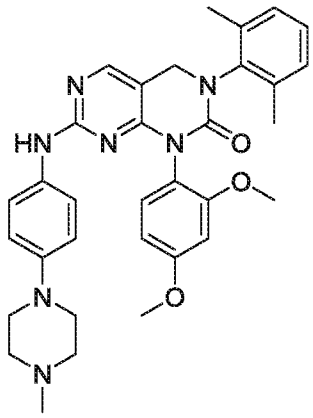
(YKL-06-081-1 or SB1-D-61),



(YKL-06-082 or SB1-D-62),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00181] In certain embodiments, the compound of Formula **(I)** is of the formula:



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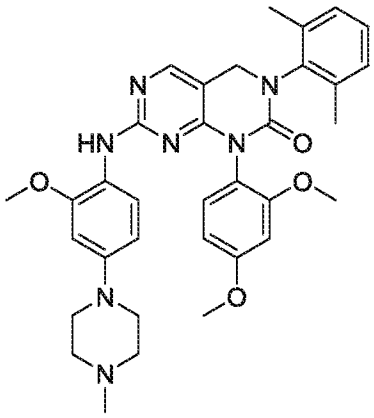

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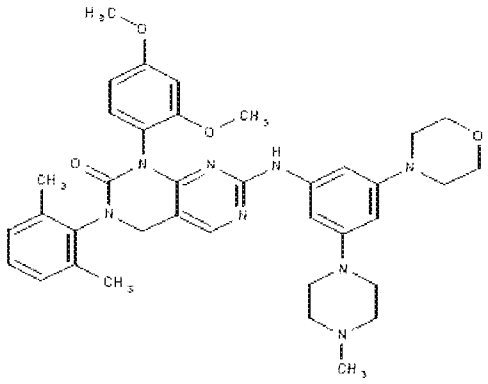

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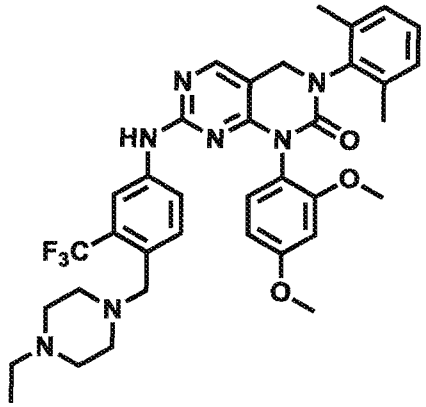

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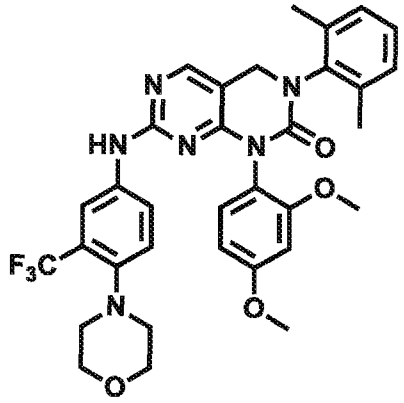

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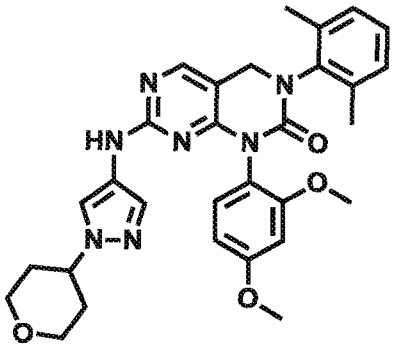

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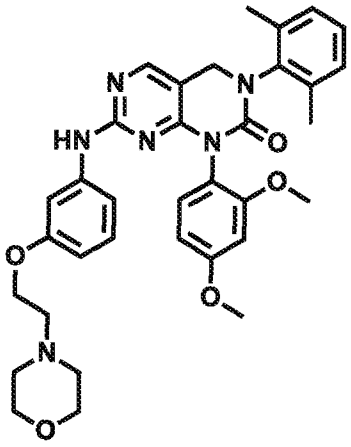

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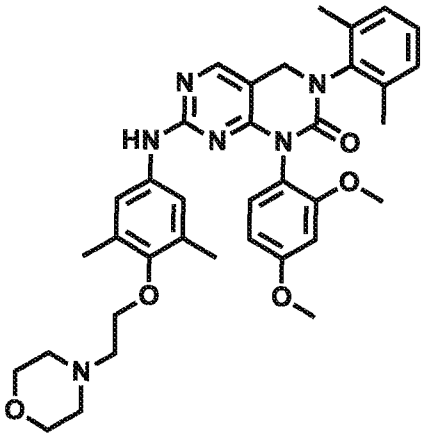

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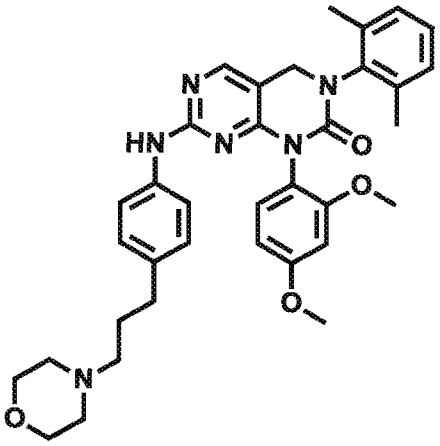

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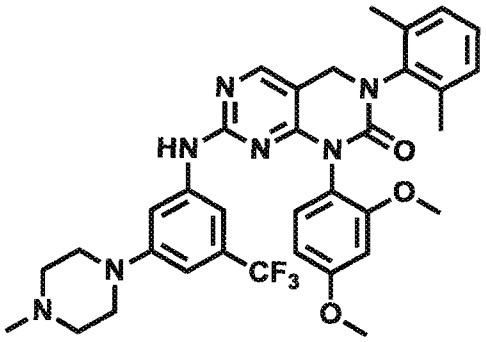

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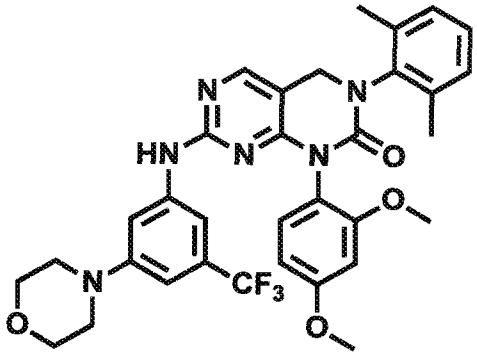

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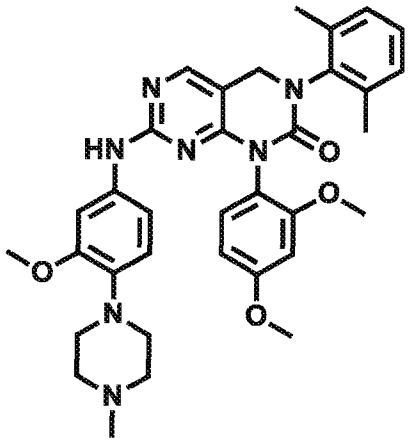
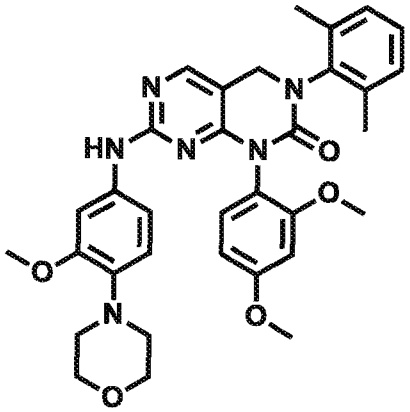
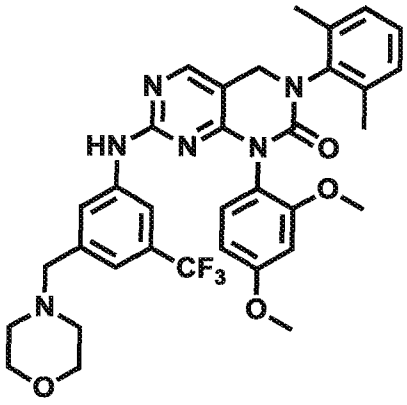


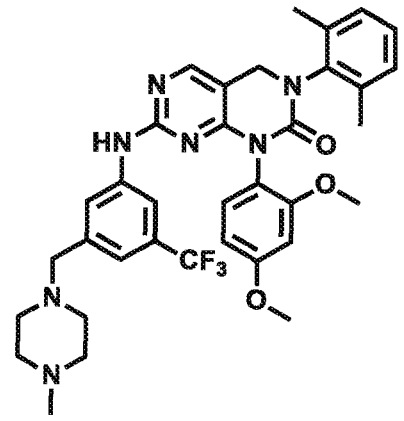
(YKL-04-114),



(YKL-04-115),



(YKL-04-118),



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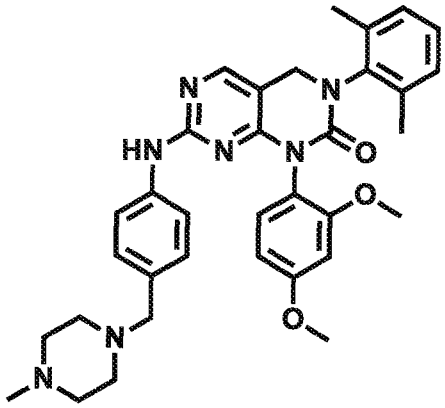

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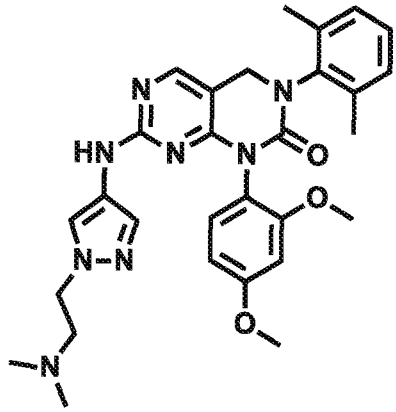

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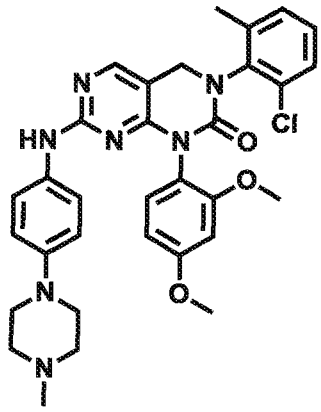

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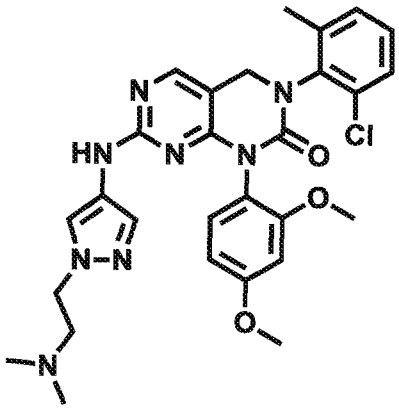

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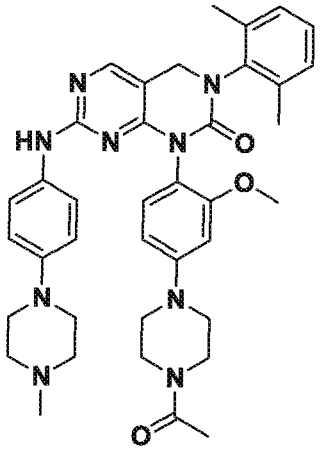

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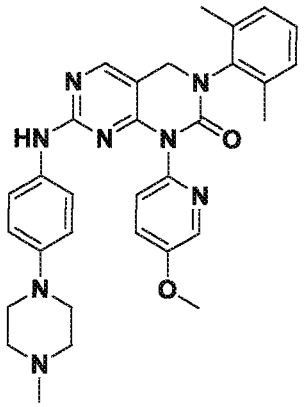

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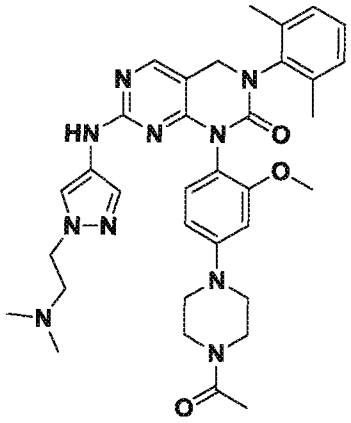

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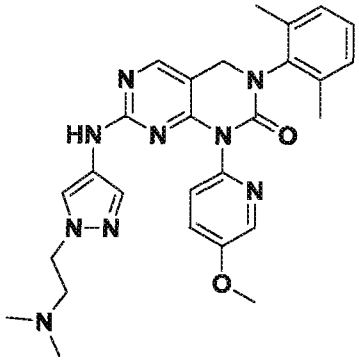

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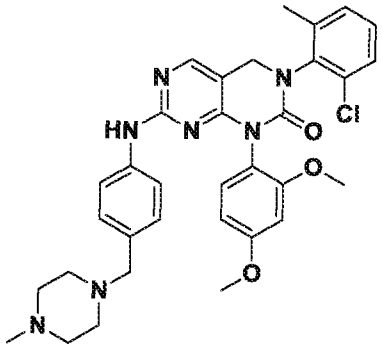

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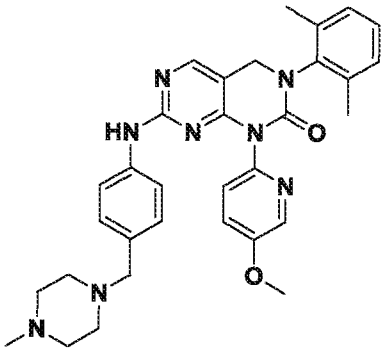

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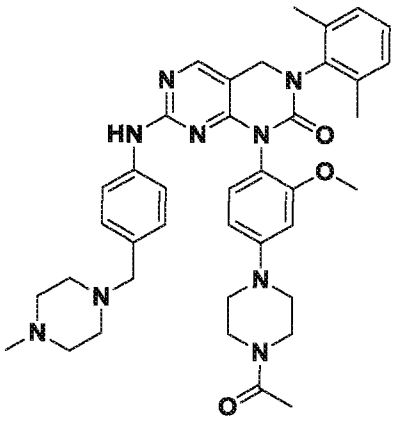

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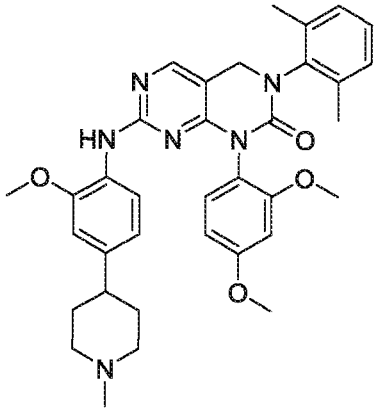

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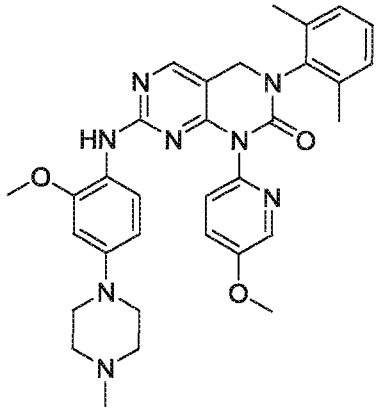

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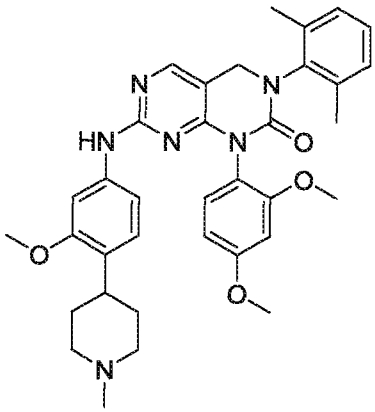

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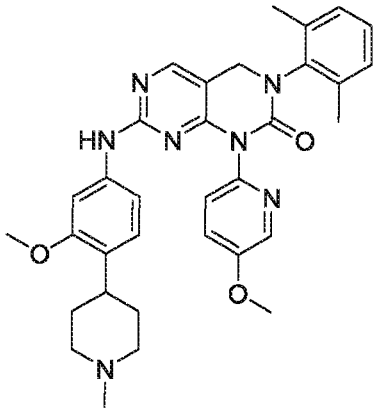

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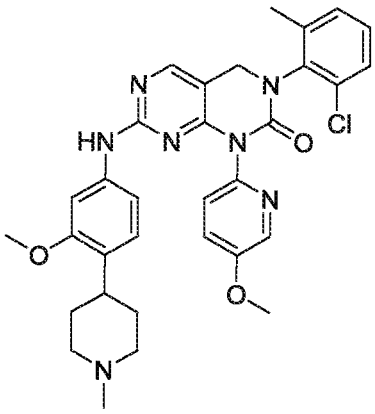

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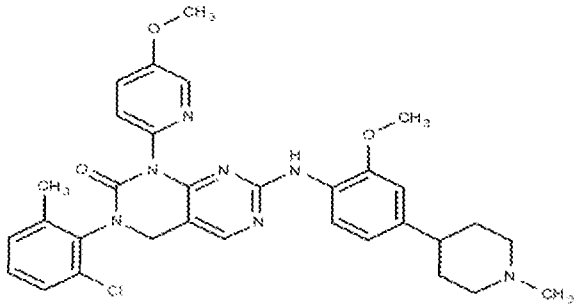

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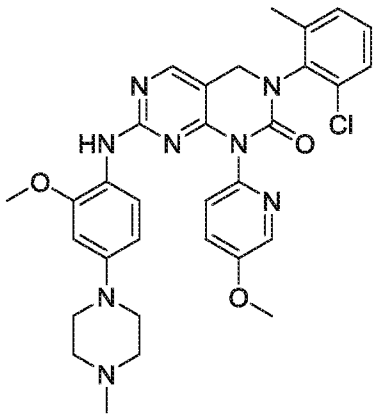

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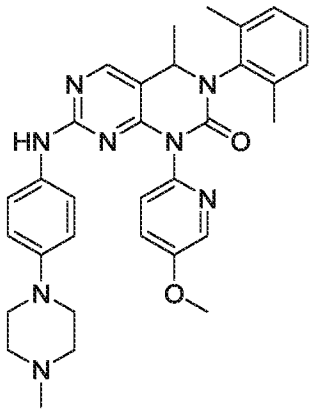

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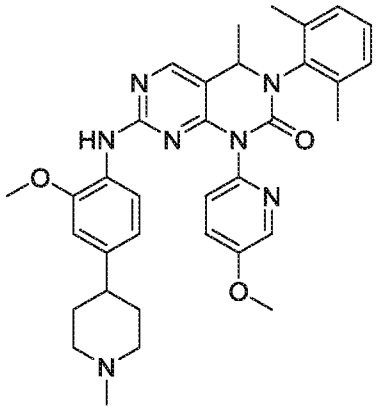
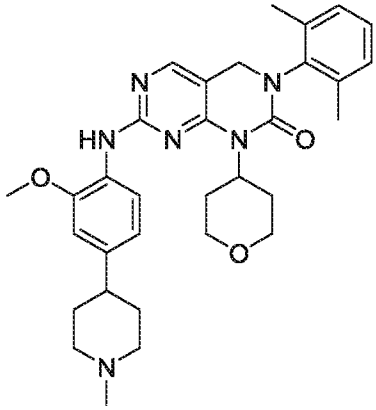


(YKL-06-040),



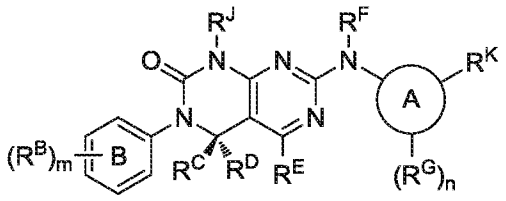
(YKL-06-051 or YKL 06-05 1),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00182] In certain embodiments, the compound of Formula (I) is YKL-05-99, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof *(e.g.*, a pharmaceutically acceptable salt thereof). In certain embodiments, the compound of Formula (I) is YKL-05-093, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof *(e.g.*, a pharmaceutically acceptable salt thereof). In certain embodiments, the compound of Formula (I) is YKL-04-1 14, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof *(e.g.*, a pharmaceutically acceptable salt thereof).

Compounds of Formula (II)

[00183] In another aspect, the present disclosure provides bicyclic urea compounds of Formula (**II**) for use in the present disclosure:



(**II**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

$\mathbf{R}^J$ is substituted or unsubstituted carbocyclyl;

each instance of R^B is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\mathbf{OR}^a$, $-\mathbf{N(R}^b\mathbf{)_2}$, $-\mathbf{SR}^a$, -CN, **-SCN,** $-C(=NR^b)R^a$, $-\mathbf{C(=NR}^b\mathbf{)OR}^a$, $-C(-NR^b)N(R^b)_2$, $-\mathbf{C(=O)R}^a$, $-\mathbf{C(=O)OR}^a$, $-\mathbf{C(=O)N(R}^b\mathbf{)_2}$, $-\mathbf{N0}_2$, $-\mathbf{NR}^b\mathbf{C(=O)R}^a$, $-\mathbf{NR}^b\mathbf{C(=O)OR}^a$, $-\mathbf{NR}^b\mathbf{C(=O)N(R}^b\mathbf{)_2}$, $-\mathbf{OC(=O)R}^a$, $-\mathbf{OC(=O)OR}^a$, or $-\mathbf{OC(=O)N(R}^b\mathbf{)_2}$;

each instance of $\mathbf{R}^a$ is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

each instance of $\mathbf{R}^b$ is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of $\mathbf{R}^b$ are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

m is 0, 1, 2, 3, 4, or 5;

$\mathbf{R}^C$ is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

$\mathbf{R}^D$ is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

$\mathbf{R}^E$ is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

n is 0, 1, 2, 3, or 4, as valency permits; and

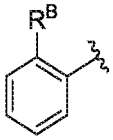
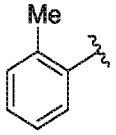
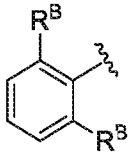
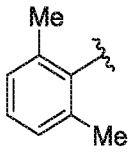
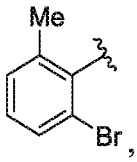
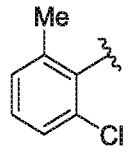
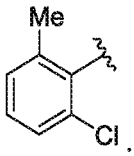
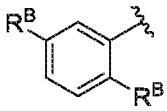
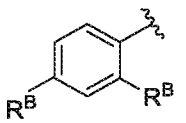
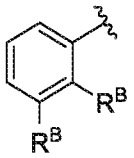
R^K is unsubstituted methyl, substituted or unsubstituted heterocyclyl, $-OR^a$, or $-N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

100184] Unless expressly provided otherwise, the moieties and variables described in the subsection **Compounds of Formula (II)** apply only to Formula **(II).** The moieties and variables included but not described in detail in the subsection **Compounds of Formula (II)** are as described in detail in other subsections.

100185] Formula **(II)** includes substituent R^J. In certain embodiments, R^J is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^J is substituted or unsubstituted, C_{3-6} carbocyclyl. In certain embodiments, R^J is substituted or unsubstituted cyclopropyl. In certain embodiments, R^J is substituted or unsubstituted cyclobutyl. In certain embodiments, R^J is cyclobutyl. In certain embodiments, R^J is substituted or unsubstituted cyclopentyl. In certain embodiments, R^J is cyclopentyl. In certain embodiments, R^J is substituted or unsubstituted cyclohexyl. In certain embodiments, R^J is cyclohexyl.

100186] In Formulae **(I)** and **(II),** Ring B is an unsubstituted phenyl ring *(e.g.,* when m is 0) or a phenyl ring substituted with one or more substituents R^B *(e.g.,* when m is 1, 2, 3, 4, or 5). In certain embodiments, at least two instances of R^B are different. In certain embodiments, all instances of R^B are the same. In certain embodiments, m is

0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.

In certain embodiments, Ring B is of the formula:  . In certain embodiments, Ring B is of the formula:  . In certain embodiments, Ring B is of the formula:  . In certain embodiments, Ring B is of the formula:  ,  , or  . In certain embodiments, Ring B is not of the formula:  . In certain embodiments, Ring B is of the formula:  . In certain embodiments, Ring B is of the formula:  . In certain embodiments, Ring B is of the formula:  .

(001871 In certain embodiments, at least one instance of R^B is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one instance of R^B is F. In certain embodiments, at least one instance of R^B is CI. In certain embodiments, at least one instance of R^B is Br. In certain embodiments, at least one instance of R^B is I. In certain embodiments, at least one R^B is substituted or unsubstituted alkyl (e.g., substituted or unsubstituted, $C_{1\text{-}6}$ alkyl). In certain embodiments, at least one instance of R^B is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R^B is methyl. In certain embodiments, m is 2, and both instances of R^B are methyl. In certain embodiments, m is 2, and one instance of R^B is halogen, and the other instance of R^B is methyl. In certain embodiments, m is 2, and one instance of R^B is Cl, and the

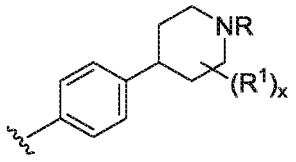
other instance of R^B is methyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkenyl). In certain embodiments, at least one instance of R^B is substituted or unsubstituted a!kynyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkynyl). In certain embodiments, at least one instance of R^B is substituted or unsubstituted carbocyclyl *(e.g.* , substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^B is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments , at least one instance of R^B is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^B is benzyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted heteroaryl *(e.g.,* substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^B is $-OR^a$ *(e.g.,* –OH or –OMe). In certain embodiments, at least one instance of R^B is $-N(R^b)_2$, $-SR^a$, -CN, –SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

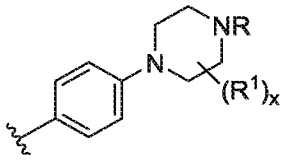
100188] Formula (II) includes substituents R^C, R^D, R^E, and R^F. R^C, R^D, R^E, and R^F are as described herein for Formula (III).

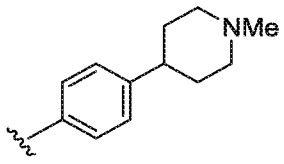
100189] Formula (II) includes Ring A and one or more instances of substituent R^G. Ring A and substituent R^G are as described herein for Formula (III).

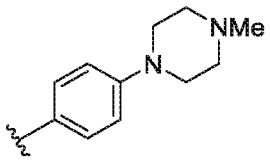
[00190] Formula (II) includes substituent R^K attached to Ring A. R^K is as described herein for Formula (III).

[00191] In certain embodiments, Ring A with substituent R^K is of the formula:



or


. In certain embodiments, Ring A with substituent R^K is of the formula:


or


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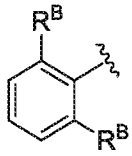
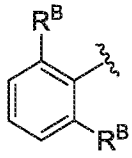
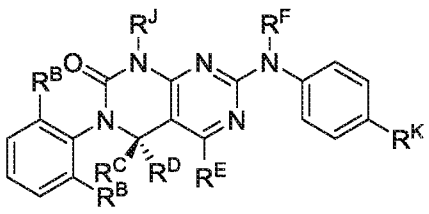
[00192] In certain embodiments, Ring B is of the formula:


; R^C, R^D, R^E, and R^F are each hydrogen; R^G is -OR a; R^J is substituted or unsubstituted, 4- to 6-membered carbocyclyl; and R^K is substituted or unsubstituted piperidinyl, or substituted or unsubstituted piperazinyl.

[00193] In certain embodiments, Ring B is of the formula:


; R^C, R^D, R^E, and R^F are each hydrogen; n is 0; R^J is substituted or unsubstituted, 4- to 6-membered carbocyclyl; and R^K is substituted or unsubstituted piperidinyl, or substituted or unsubstituted piperazinyl.

[00194] n certain embodiments, the compound of Formula **(II)** is of the formula:



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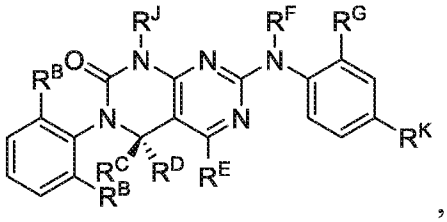
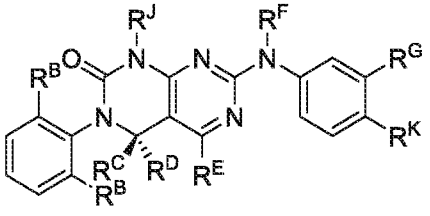
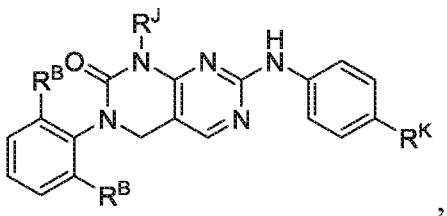
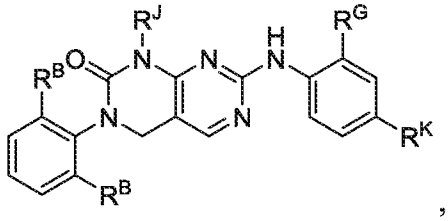
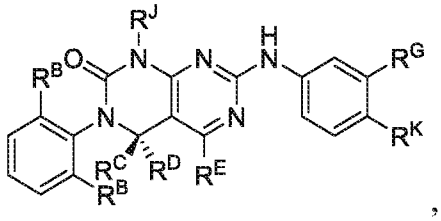


,


,

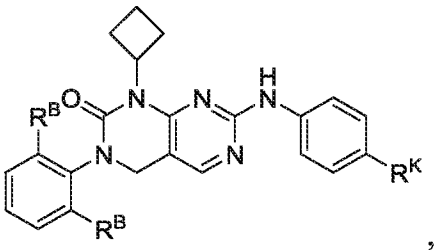
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00195] In certain embodiments, the compound of Formula (II) is of the formula:


,

,

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[001961 In certain embodiments, the compound of Formula **(II)** is of the formula: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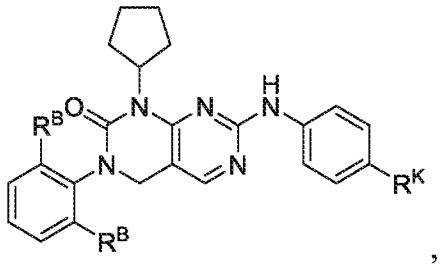
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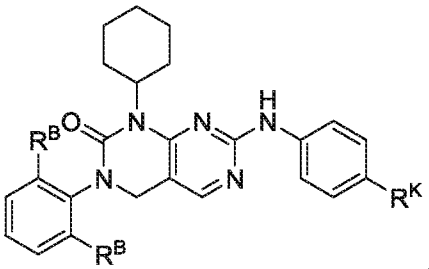
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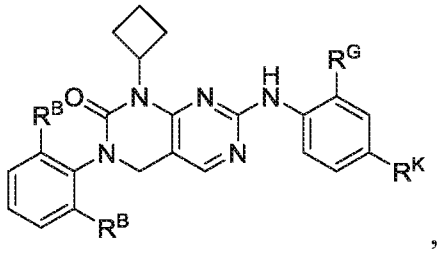
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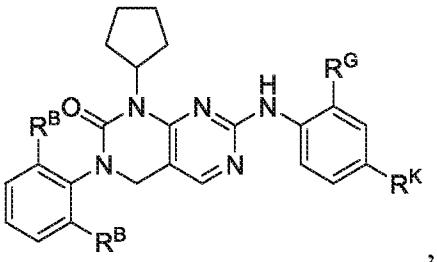
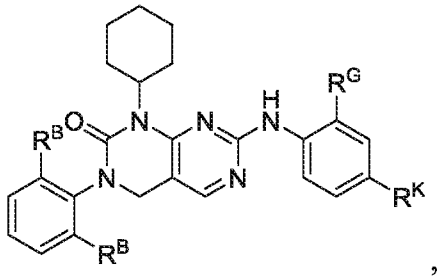
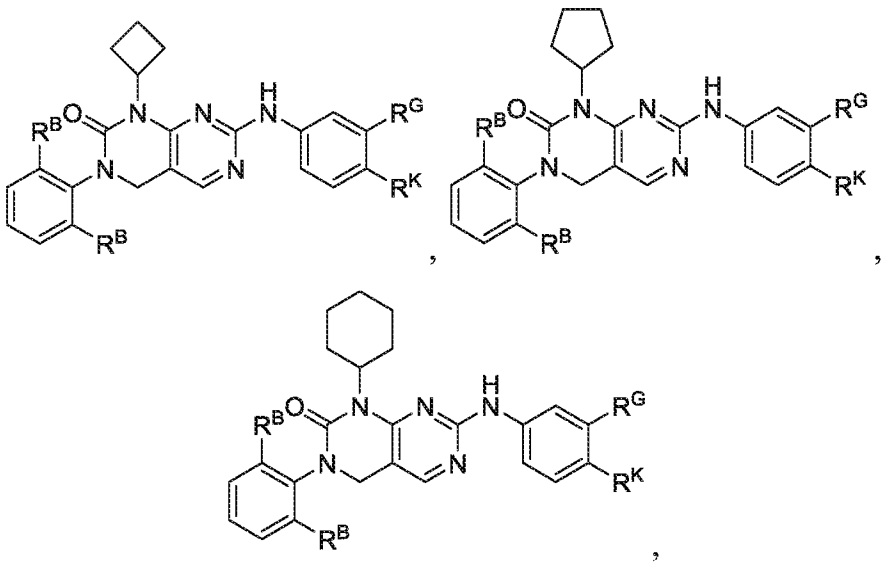
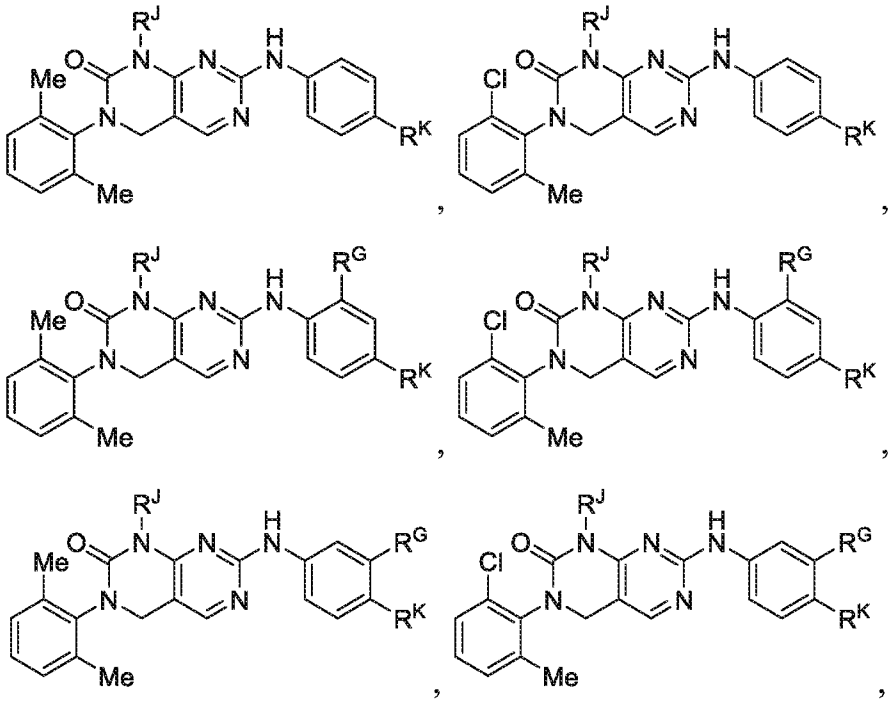

,

,



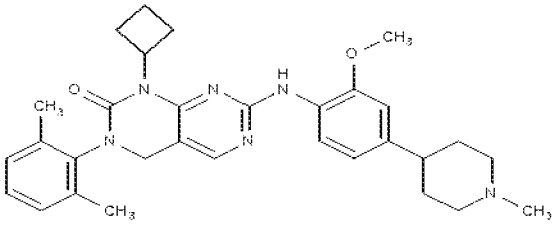
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00197] In certain embodiments, the compound of Formula (II) is of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00198] In certain embodiments, the compound of Formula (II) is of the formula:



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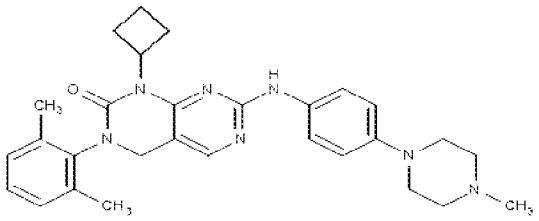

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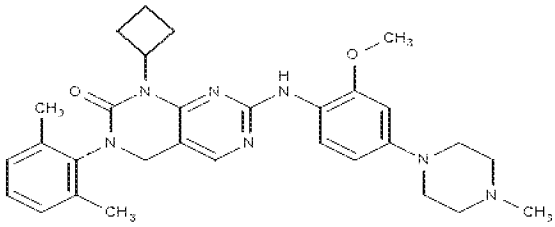
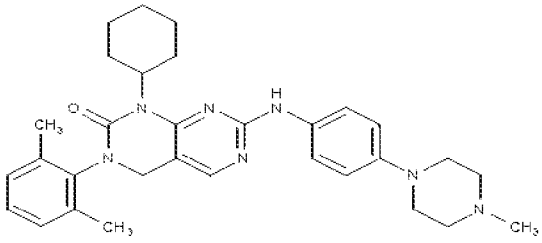


(YKL-06-061),



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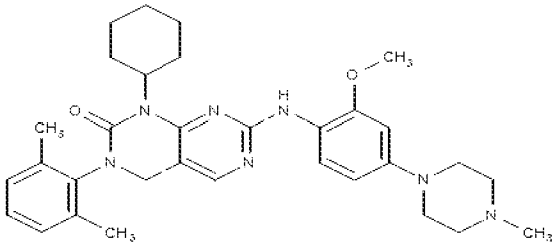

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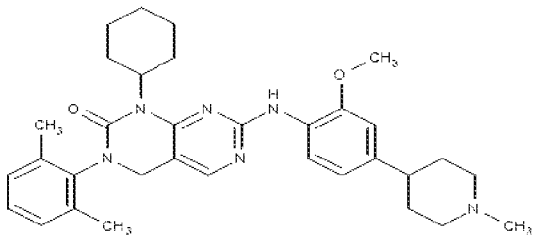

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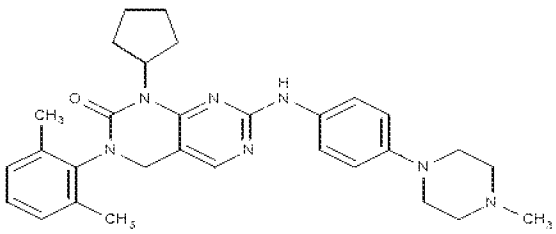

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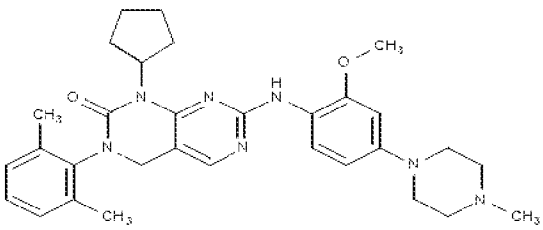

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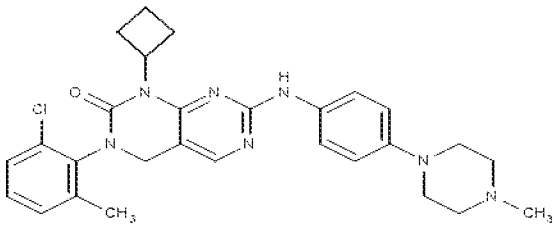

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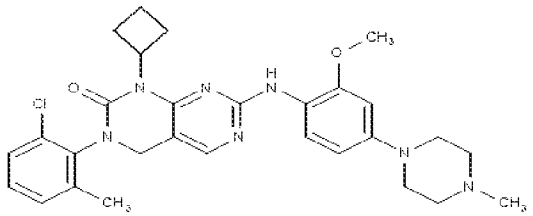
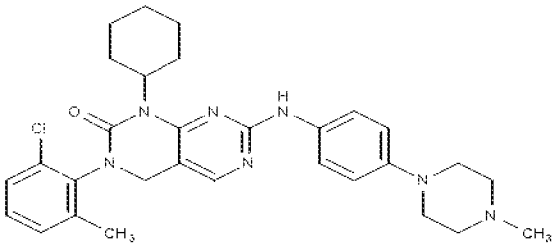
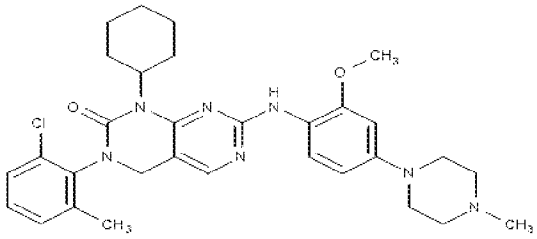


(YKL-06-089),



(YKL-06-G90),



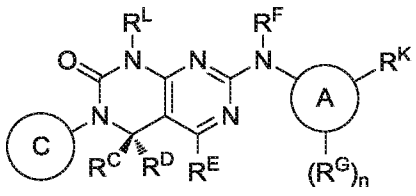
(YKL-G6-091),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[001991 In certain embodiments, the compound of Formula **(II)** is YKL-06-061, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

Compounds of Formula (III)

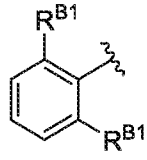
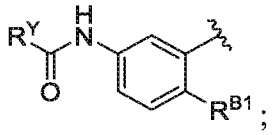
100200 1 In another aspect, the present disclosure provides bicyclic urea compounds of Formula **(III)** for use in the present disclosure:



(III),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

R^L is substituted or unsubstituted alkyl;

Ring C is unsubstituted phenyl or of the formula:  or  ;

each instance of R^{B1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^d)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^d)R^a$, $-C(=NR^d)OR^a$, $-C(=NR^d)N(R^d)_2$, $-C(=())R^a$, $-C(=O)OR^a$, $-C(=O)N(R^d)_2$, $-N0_2$, $-NR^dC(=O)R^a$, $-NR^dC(=O)OR^a$, $-NR^dC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^d)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

each instance of R^d is independently hydrogen, $-C(=0)R^a$, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^d are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

R^C is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^D is hydrogen, halogen, or substituted or unsubstituted, Ci_{-6} alkyl;

R^E is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, Ci_{-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)()R^a$, or $-OC(=O)N(R^b)_2$;

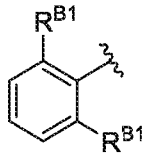
each instance of R^b is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^b are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

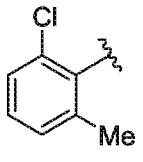
n is 0, 1, 2, 3, or 4, as valency permits;

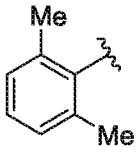
R^K is unsubstituted methyl, substituted or unsubstituted heterocyclyl, $-OR^a$, or $-N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; and

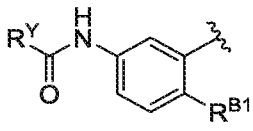
R^Y is substituted phenyl.

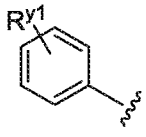
[00201] Unless expressly provided otherwise, the moieties and variables described in the subsection **Compounds of Formula (III)** apply only to Formula **(III).** The moieties and variables included but not described in detail in the subsection **Compounds of Formula (III)** are as described in detail in other subsections.

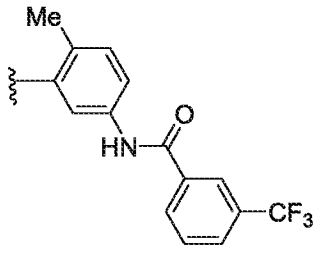
100202] Formula **(III)** includes Ring C. In certain embodiments, Ring C is unsubstituted phenyl. In certain embodiments, Ring C is of the formula:  . In certain embodiments, at least one instance of R^{B1} is halogen. In certain embodiments, at least one instance of R^{B1} is halogen. In certain embodiments, at least one instance of R^{B1} is F. In certain embodiments, at least one instance of R^{B1} is Cl. In certain embodiments, at least one instance of R^{B1} is Br. In certain embodiments, at least one instance of R^{B1} is I (iodine). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R^{B1} is methyl. In certain embodiments, at least one instance of R^{B1} is $-N(R^d)_2$, wherein each instance of R^d is hydrogen or $-C(=O)R^a$. In certain embodiments, at least one instance of R^{B1} is $-NH(C(=O)R^a)$. In

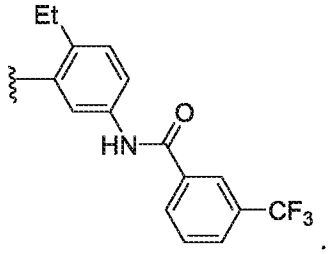
certain embodiments, at least one instance of R^{B1} is $-OR^a$ *(e.g.,* –OH or -OMe). In certain embodiments, at least one instance of R^{B1} is $-SR^a$, -CN, -SCN, $-C(=NR^d)R^a$, $-C(=NR^d)OR^a$, $-C(=NR^d)N(R^d)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^d)_2$, $-NO_2$, $-NR^dC(=O)R^a$, $-NR^dC(=O)OR^a$, $-NR^dC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^d)_2$. In certain embodiments, Ring C is of the formula: 

. In certain embodiments, Ring C is of the formula: 

. In certain embodiments, Ring C is of the formula: 

. In certain embodiments, R^Y is substituted phenyl. In certain embodiments, R^Y is substituted phenyl. In certain embodiments, R^Y is of the formula: 

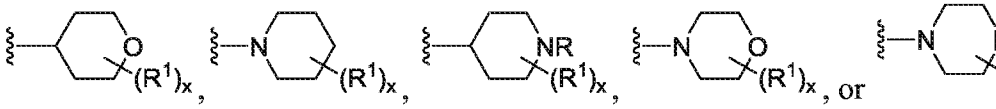
, wherein R^{y1} is halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, R^{y1} is halogen *(e.g.,* Br, CI, F). In certain embodiments, R^{y1} is substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* substituted or unsubstituted, methyl, ethyl, or propyl). In certain embodiments, R^{y1} is substituted or unsubstituted methyl. In certain embodiments, R^{y1} is substituted methyl. In certain embodiments, R^{y1} is methyl. In certain embodiments, R^{y1} is $-CF_3$. In certain embodiments, Ring C is of the formula: 

. In certain embodiments, Ring C is of the formula: 

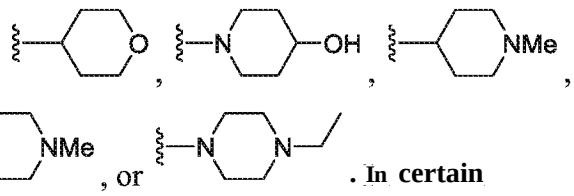
.

[00203] Formula **(III)** includes **substituent R^L.** In certain embodiments, **R^L** is **substituted or unsubstituted alkyl** *(e.g.,* **substituted or unsubstituted, C_{1-6} alkyl).** In **certain embodiments, R^L is substituted or unsubstituted methyl.** In **certain embodiments, R^L is methyl.** In **certain embodiments, R^L is substituted or unsubstituted ethyl.** In **certain embodiments, R^L is ethyl.** In **certain embodiments, R^L is substituted or unsubstituted propyl.** In **certain embodiments, R^L is propyl.** In **certain embodiments, R^L is isopropyl.** In **certain embodiments, R^L is substituted or unsubstituted butyl.**

[00204] **Formula (II) and (III) include substituent R^K attached to Ring A.** In **certain embodiments, R^K is unsubstituted methyl.** In **certain embodiments, R^K is substituted or unsubstituted heterocyclyl** *(e.g.,* **substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur).** In **certain embodiments, R^K is substituted or unsubstituted tetrahydropyranyl.** In **certain embodiments, R^K is substituted or unsubstituted piperidinyl.** In **certain embodiments, R^K is substituted or unsubstituted morpholinyl.** In **certain embodiments, R^K is substituted or unsubstituted** piperazinyl. In **certain embodiments, R^K is of the formula:**



wherein R^1 is substituted or unsubstituted, C_{1-6} alkyl or $-OR^{x1}$, wherein R is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or nitrogen protecting group; R^{x1} is hydrogen or substituted or unsubstituted, C_{1-6} alkyl; and x is 0, 1, 2, or 3. In **certain embodiments, R^K is of the formula:**



. In **certain embodiments, R^K is -QR [a]** *(e.g.,* **–OH or –OMe).** In **certain embodiments, R^K is -$N(R^c)_2$.** In **certain embodiments, two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic ring** *(e.g.,* **substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur).** In **certain embodiments, two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heteroaryl ring** *(e.g.,* **substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein**

one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^K is $-NMe_2$. In certain embodiments, R^K is $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

[00205] Formulae (I), (II), and (III) include substituent R^C. In certain embodiments, R^C is hydrogen. In certain embodiments, R^C is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^C is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^C is substituted or unsubstituted methyl. In certain embodiments, R^C is methyl. In certain embodiments, R^C is substituted or unsubstituted ethyl. In certain embodiments, R^C is ethyl. In certain embodiments, R^C is substituted or unsubstituted propyl. In certain embodiments, R^C is unsubstituted isopropyl.

[00206] Formulae (I), (II), and (III) include substituent R^D. In certain embodiments, R^D is hydrogen. In certain embodiments, R^D is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^D is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^D is substituted or unsubstituted methyl. In certain embodiments, R^D is methyl. In certain embodiments, R^D is substituted or unsubstituted ethyl. In certain embodiments, R^D is ethyl. In certain embodiments, R^D is substituted or unsubstituted propyl. In certain embodiments, R^D is isopropyl.

[00207] Formulae (I), (II), and (III) include substituent R^E. In certain embodiments, R^E is hydrogen. In certain embodiments, R^E is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^E is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^E is substituted or unsubstituted methyl. In certain embodiments, R^E is methyl. In certain embodiments, R^E is substituted or unsubstituted ethyl. In certain embodiments, R^E is ethyl. In certain embodiments, R^E is substituted or unsubstituted propyl. In certain embodiments, R^E is isopropyl.

[00208] Formulae (I), (II), and (III) include substituent R^F. In certain embodiments, R^F is hydrogen. In certain embodiments, R^E is substituted or

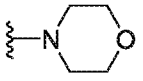
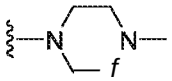
unsubstituted, C_{1-6} alkyl (e.g., methyl, ethyl, or propyl). In certain embodiments, R^F is substituted or unsubstituted methyl. In certain embodiments, R^F is methyl. In certain embodiments, R^F is substituted or unsubstituted ethyl. In certain embodiments, R^F is ethyl. In certain embodiments, R^F is substituted or unsubstituted propyl. In certain embodiments, R^F is isopropyl. In certain embodiments, R^F is a nitrogen protecting group *(e.g.*, a nitrogen protecting group *(e.g.*, benzyl (Bn), t-butyl carbonate (BOC or Boc), benzyl carbamate (Cbz), 9-fluorenylmethyl carbonate (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl, or /Moluenesulfonamide (Ts)).

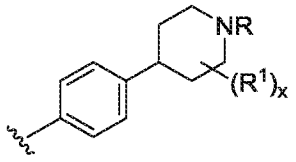
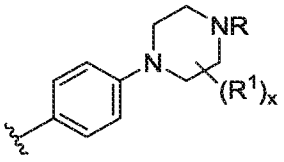
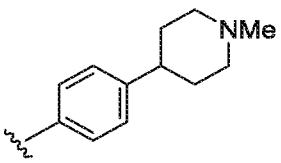
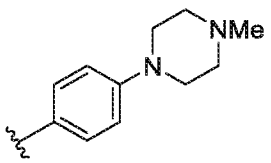
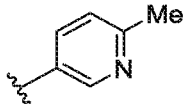
100209 1 In certain embodiments, R^C, R^D, R^E, and R^F are each hydrogen. In certain embodiments, at least one substituent selected from the group consisting of R^C, R^D, R^E, and R^F is substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, R^c is substituted or unsubstituted, C_{1-6} alkyl; and R^D, R^E, and R^F are each hydrogen. In certain embodiments, R^c is unsubstituted methyl; and R^D, R^E, and R^F are each hydrogen. In certain embodiments, R^C is unsubstituted isopropyl; and R^D, R^E, and R^F are each hydrogen. In certain embodiments, R^D is substituted or unsubstituted, C_{1-6} alkyl; and R^C, R^E, and R^F are each hydrogen. In certain embodiments, R^E is substituted or unsubstituted, C_{1-6} alkyl; and R^c, R^D, and R^F are each hydrogen. In certain embodiments, R^F is substituted or unsubstituted, C_{1-6} alkyl; and R^C, R^D, and R^E are each hydrogen.

100210] Formulae (I), (II), and (HI) include Ring A. In certain embodiments, Ring A is substituted or unsubstituted phenyl. In certain embodiments, Ring A is not substituted or unsubstituted phenyl. In certain embodiments, Ring A is not substituted phenyl. In certain embodiments, Ring A is not unsubstituted phenyl. In certain embodiments, Ring A is unsubstituted phenyl. In certain embodiments, Ring A is phenyl, and includes one or more R^G substituents. In certain embodiments. Ring A includes one R^G substituent. In certain embodiments, Ring A includes two R^G substituents. In certain embodiments, Ring A is substituted or unsubstituted polycyclic aryl *(e.g.*, naphthalene or anthracene). In certain embodiments, Ring A is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl *(e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, Ring A is substituted or unsubstituted furan. In certain embodiments, Ring A is substituted or unsubstituted thiophene. In certain embodiments. Ring A is substituted or unsubstituted pyrrole. In certain

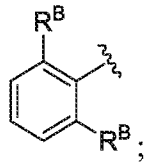
embodiments, Ring A is substituted or unsubstituted pyrazole. In certain embodiments, Ring A is pyrazole. In certain embodiments, Ring A is substituted or unsubstituted pyridinyl. In certain embodiments, Ring A is pyridinyl. In certain embodiments. Ring A is substituted or unsubstituted polycyclic heteroaryl *(e.g.,* substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[0021 11 Formulae (I), **(II),** and **(III)** include one or more instances of substituent R^G. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, at least one instance of R^G is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one instance of R^G is F. In certain embodiments, at least one instance of R^G is CI. In certain embodiments, at least one instance of R^G is Br. In certain embodiments, at least one instance of R^G is I. In certain embodiments, at least one R^G is substituted or unsubstituted alkyl *(e.g.,* substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^G is substituted or unsubstituted, C_{1-3} alkyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R^G is unsubstituted methyl. In certain embodiments, at least one instance of R^G is substituted methyl. In certain embodiments, at least one instance of R^G is $-CF_3$. In certain embodiments, at least one instance of R^G is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R^G is substituted ethyl. In certain embodiments, at least one instance of R^G is unsubstituted ethyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkenyl). In certain embodiments, at least one instance of R^G is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, C_{2-6} alkynyl). In certain embodiments, at least one instance of R^G is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^G is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain

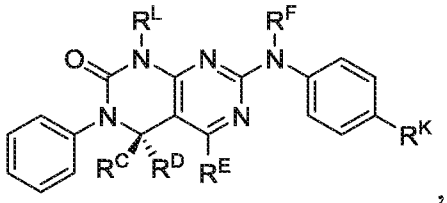
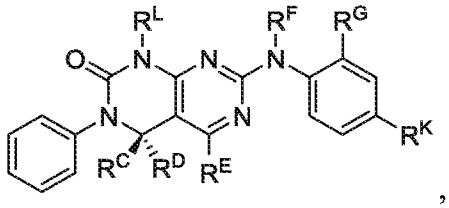
embodiments, at least one instance of R^G is substituted or unsubstituted morpholinyl. In certain embodiments, at least one instance of R^G is of the formula:  . In certain embodiments, at least one instance of R^G is substituted or unsubstituted piperazinyl. In certain embodiments, at least one instance of R^G is of the formula:  In certain embodiments , at least one instance of R^G is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^G is benzyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^B is substituted or unsubstituted heteroaryl *(e.g.,* substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 1()-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^G is $-OR^a$, wherein R^a is hydrogen or substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* -OH or -OMe). In certain embodiments, at least one instance of R^G is –OMe. In certain embodiments, at least one instance of R^G is –OEt. In certain embodiments, at least one instance of R^G is -O(Pr). In certain embodiments, at least one instance of R^G is –O(iPr). In certain embodiments, at least one instance of R^G is $-N(R^b)_2$, $-SR^a$, –CN, –SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(O)0R^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

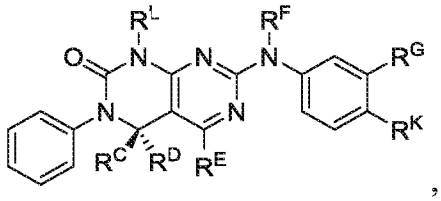
[00212] In certain embodiments, Ring A with substituent R^K is of the formula:  or  . In certain embodiments, Ring A with substituent R^K is of the formula:  ,  , or  .

[00213] In certain embodiments, Ring C is unsubstituted phenyl; R^C, R^D, R^E, and R^F are each hydrogen; n is 0; R^L is substituted or unsubstituted, C_{1-6} alkyl; and R^K is substituted or unsubstituted piperidinyl, or substituted or unsubstituted piperazinyl.

[00214] In certain embodiments, Ring C is of the formula:  ; R^C, R^D, R^E, and R^F are each hydrogen; R^G is $-OR^a$, $-CH_3$, or $-C_2H_5$; R^L is substituted or unsubstituted, C_{1-6} alkyl; and R^K is substituted or unsubstituted piperidinyl, or substituted or unsubstituted piperazinyl.

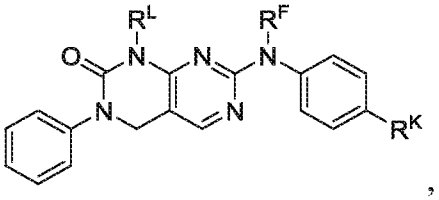
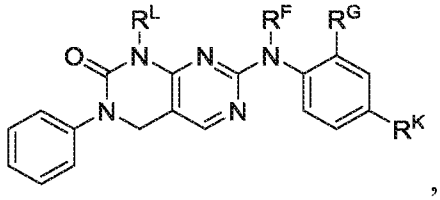
[00215] In certain embodiments, the compound of Formula **(HI)** is of the formula:

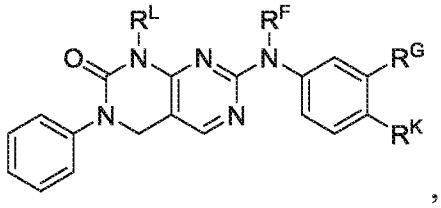
 ,  ,

 ,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

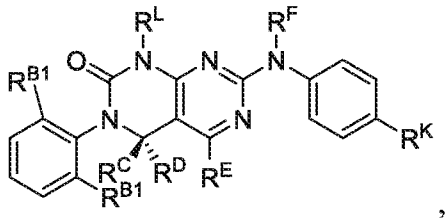
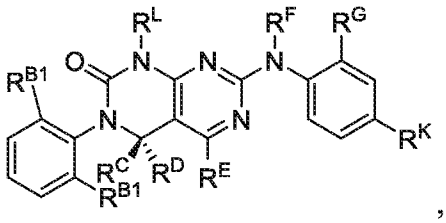
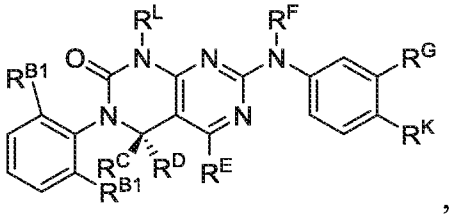
[00216] In certain embodiments, the compound of Formula (HI) is of the formula:

 ,  ,

 ,

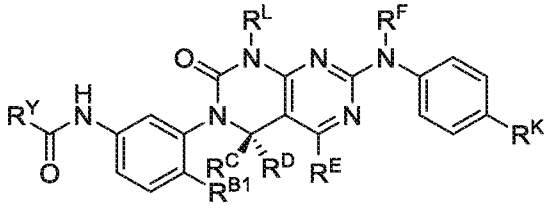
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00217] In certain embodiments, the compound of Formula (III) is of the formula:


,

,

,

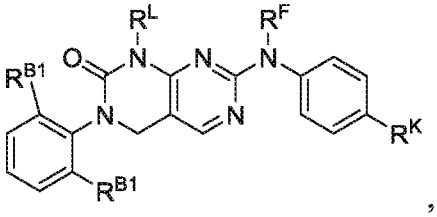
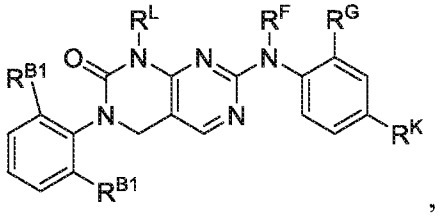
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00218] In certain embodiments, the compound of Formula (III) is of the formula:


,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00219] In certain embodiments, the compound of Formula (III) is of the formula:


,

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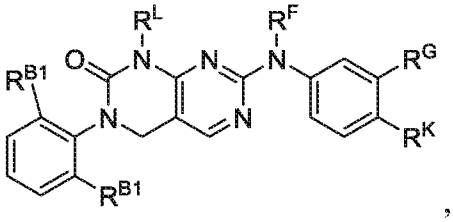
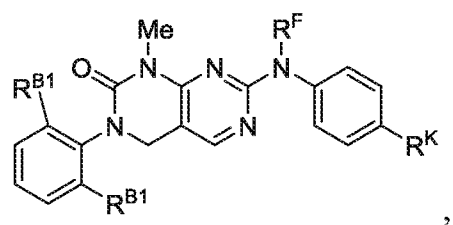
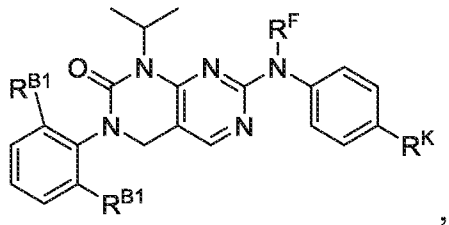

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00220] In certain embodiments, the compound of Formula (III) is of the formula:


,

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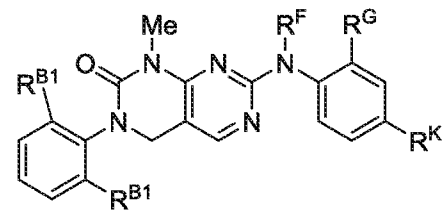
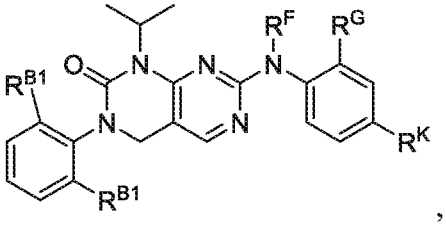
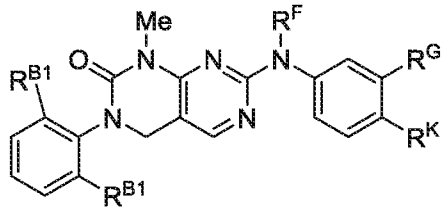

,

,

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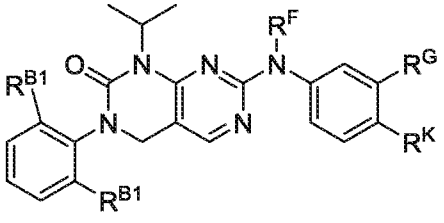
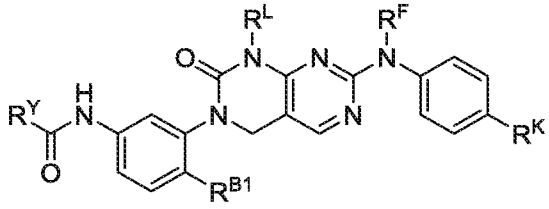

,

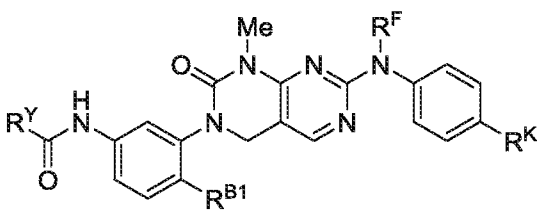
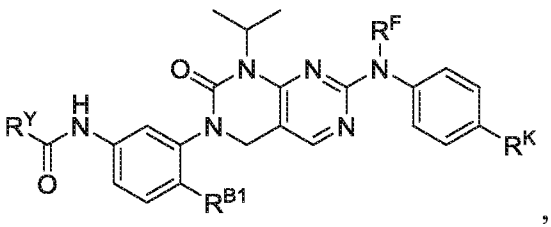
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

100221 1 In certain embodiments, the compound of Formula (III) is of the formula:


,

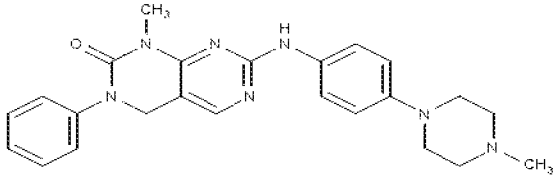
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[002221 In certain embodiments, the compound of Formula (III) is of the formula:

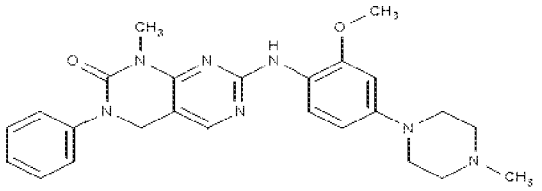

,

,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

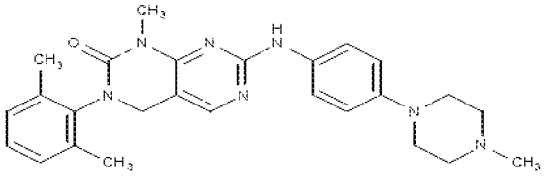
[00223] In certain embodiments, the compound of Formula (III) is of the formula:



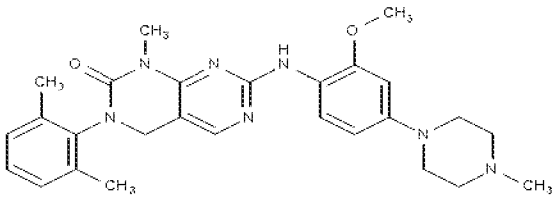
(HG-1 1-137-01),



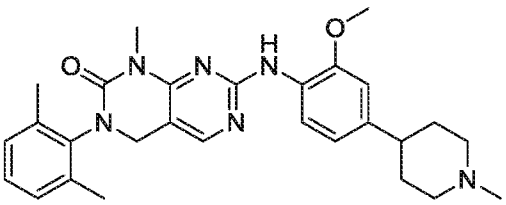
(HG-11-139-02),



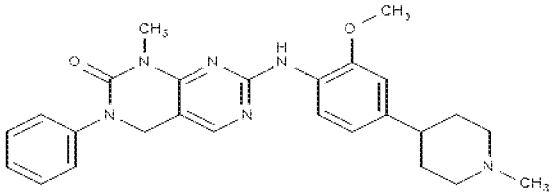
(YKL-06-029),



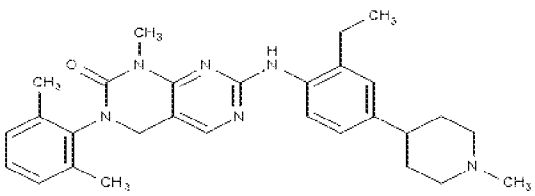
(YKL-06-030),



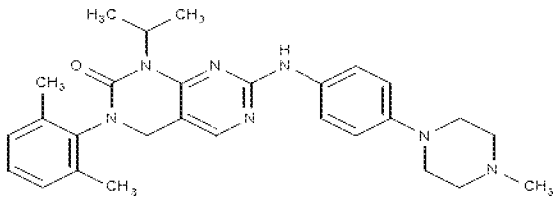
(YKL-06-031),



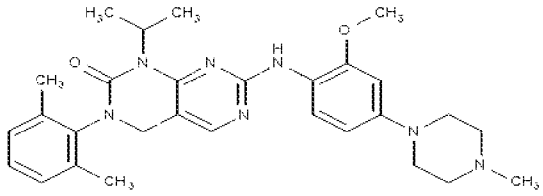
(YKL-06-033),



(YKL-06-046),



(YKL-06-058),



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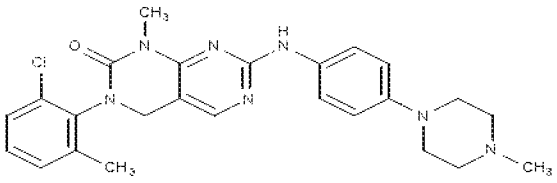
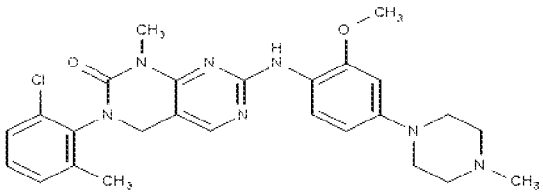
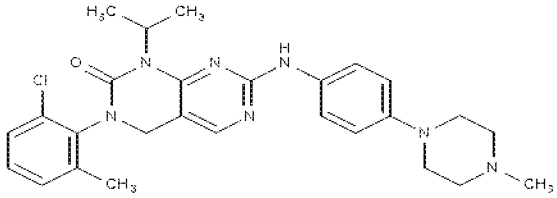


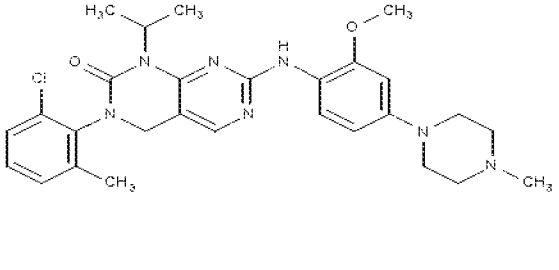
(YKL-G6-084),



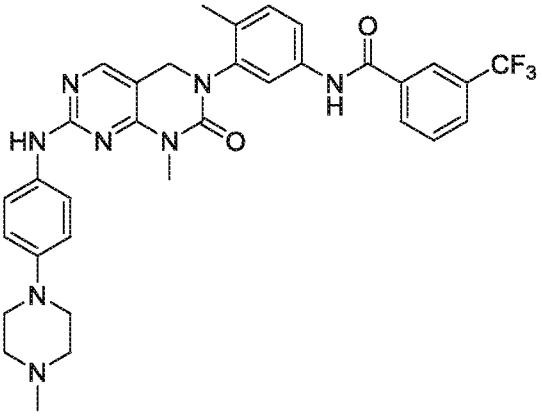
(YKL-06-085),



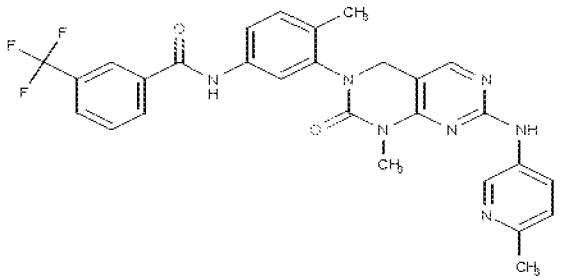
(YKL-06-086),



(YKL-06-087),



(HG-i **1-23-01),**



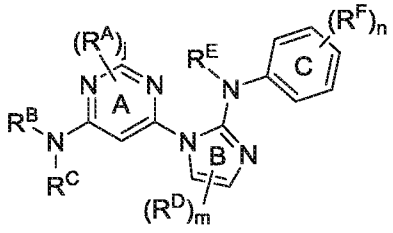
(HG-4-34-01),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00224] In certain embodiments, the compound of Formula (III) is YKL-06-031, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

Compounds of Formula (IV)

[00225] In another aspect, the present disclosure provides imidazolyl compounds of Formula (IV) for use in the invention:



(IV),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

j is 0, 1, or 2;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,

substituted or unsubstituted earbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

R^C is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^D is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted earbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

m is 0, 1, or 2;

R^E is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^F is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted earbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

n is 0, 1, 2, 3, 4, or 5.

[00226] Unless expressly provided otherwise, the moieties and variables described in the subsection **Compounds of Formula (IV)** apply only to Formula **(IV).** The moieties and variables included but not described in detail in the subsection **Compounds of Formula (IV)** are as described in detail in other subsections.

100227] Formula **(IV)** includes as Ring A a pyrimidinyl ring that is unsubstituted *(e.g.,* when j is 0) or substituted with one or two substituents R^A *(e.g.,* when j is 1 or 2). In certain embodiments, the two instances of R^A are different. In certain embodiments, both instances of R^A are the same. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instance of R^A is CI. In certain embodiments, at least one instance of R^A is Br. In certain embodiments, at least one

instance of R^A is I (iodine). In certain embodiments, at least one instance of R^A is substituted alkyl. In certain embodiments, at least one instance of R^A is unsubstituted alkyl. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, both instances of R^A are unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is substituted methyl. In certain embodiments, at least one instance of R^A is $-CH_2F$. In certain embodiments, at least one instance of R^A is $-CHF_2$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, at least one instance of R^A is ethyl. In certain embodiments, at least one instance of R^A is propyl. In certain embodiments, at least one instance of R^A is butyl. In certain embodiments, at least one instance of R^A is pentyl. In certain embodiments, at least one instance of R^A is hexyl. In certain embodiments, at least one instance of R^A is Bn. In certain embodiments, at least one instance of R^A is halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted alkenyl. In certain embodiments. at least one instance of R^A is unsubstituted alkenyl. In certain embodiments, at least one instance of R^A is substituted alkynyl. In certain embodiments, at least one instance of R^A is unsubstituted alkynyl. In certain embodiments, at least one instance of R^A is substituted carbocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^A is saturated carbocyclyl. In certain embodiments, at least one instance of R^A is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^A is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is substituted heterocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^A is saturated heterocyclyl. In certain embodiments, at least one instance of R^A is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^A is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heterocyclyl. In certain

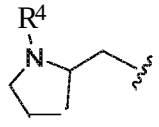
embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^A is substituted aryl. In certain embodiments, at least one instance of R^A is unsubstituted aryl. In certain embodiments, at least one instance of R^A is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^A is substituted phenyl. In certain embodiments, at least one instance of R^A is unsubstituted phenyl. In certain embodiments, at least one instance of R^A is substituted heteroaryl. In certain embodiments, at least one instance of R^A is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^A is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instaiice of R^A is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^A is $-OR^a$. In certain embodiments, at least one instance of R^A is -OH. In certain embodiments, at least one instance of R^A is –0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^A is –OMe. In certain embodiments, at least one instance of R^A is –OEt. In certain embodiments, at least one instance of R^A is –OPr. In certain embodiments, at least one instance of R^A is –OBu. In certain embodiments, at least one instance of R^A is –OBn. In certain embodiments, at least one instance of R^A is –OPh. In certain embodiments, at least one instance of R^A is $-SR^a$. In certain embodiments, at least one instance of R^A is -SH. In certain embodiments, at least one instance of R^A is -SMe. In certain embodiments, at least one instance of R^A is $-N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-NH_2$. In certain embodiments, at least one instance of R^A is –NHMe. In certain embodiments, at least one instance of R^A is $-NMe_2$. In certain embodiments, at least one instance of R^A is -CN. In certain embodiments, at least one instance of R^A is -SCN. In certain embodiments, at least one instance of R^A is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-C(=O)R^a$ or $-C(=O)OR^a$. In certain embodiments, at least one instance of R^A is $-C(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^A is

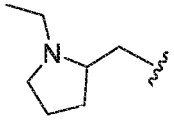
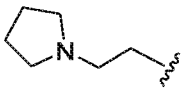
-C(=Q)NMe $_2$, -C(=0)NHMe, or -C(=Q)NH $_2$. In certain embodiments, at least one instance of R^A is -N0 $_2$. In certain embodiments, at least one instance of R^A is -NR^{a}C(=0)R ^{a}, -NR ^{a}C(=0)OR ^{a}, or -NR ^{a}C(=0)N(R ^{a})$_2$. In certain embodiments, at least one instance of R^A is -OC(=0)R^a, -OC(=0)OR ^{a}, or -OC(=0)N(R ^{a})$_2$.

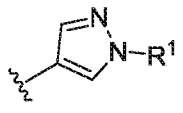
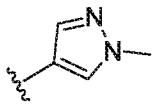
100228] Each instance of R^A, R^D, R^F, R^G, R^J, and R^K may independently include one or more substituents R^a. In certain embodiments, all instances of R^a are the same. In certain embodiments, at least two instances of R^a are different. In certain embodiments, at least one instance of R^a is H. In certain embodiments, each instance of R^a is H. In certain embodiments, at least one instance of R^a is substituted acyl. In certain embodiments, at least one instance of R^a is unsubstituted acyl. In certain embodiments, at least one instance of R^a is acetyl. In certain embodiments, at least one instance of R^a is substituted alkyl. In certain embodiments, at least one instance of R^a is unsubstituted alkyl. In certain embodiments, at least one instance of R^a is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^a is methyl. In certain embodiments, at least one instance of R^a is ethyl. In certain embodiments, at least one instance of R^a is propyl. In certain embodiments, at least one instance of R^a is butyl. In certain embodiments, at least one instance of R^a is pentyl. In certain embodiments, at least one instance of R^a is hexyl. In certain embodiments, at least one instance of R^a is Bn. In certain embodiments, at least one instance of R^a is substituted alkenyl. In certain embodiments, at least one instance of R^a is unsubstituted alkenyl. In certain embodiments, at least one instance of R^a is substituted alkynyl. In certain embodiments, at least one instance of R^a is unsubstituted alkynyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^a is saturated carbocyclyl. In certain embodiments, at least one instance of R^a is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^a is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^a is saturated heterocyclyl. In certain embodiments, at least one instance of R^a is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^a is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^a is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^a is substituted or

unsubstituted aryl. In certain embodiments, at least one instance of R^a is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^a is monocyclic aryl. In certain embodiments, at least one instance of R^a is substituted phenyl. In certain embodiments, at least one instance of R^a is unsubstituted phenyl. In certain embodiments, at least one instance of R^a is bicyclic aryl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^a is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^a is monocyclic heteroaryl. In certain embodiments, at least one instance of R^a is 5- or 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^a is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^a is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^a is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^a is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^a is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, ***t*-Bu,** Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^a is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^a is acetamidomethyl, ***t-Bu,*** 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a heterocyclic ring, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^a are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms of the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

[00229] In certain embodiments, j is 0. In certain embodiments,] is 1. In certain embodiments, j is 2.

[00230] Formula **(IV)** includes substituent R^B on a nitrogen atom. In certain embodiments, R^B is H. In certain embodiments, R^B is substituted acyl. In certain embodiments, R^B is unsubstituted acyl. In certain embodiments, R^B is acetyl. In certain embodiments, R^B is substituted alkyl. In certain embodiments, R^B is unsubstituted alkyl. In certain embodiments, R^B is unsubstituted C_{1-6} alkyl. In certain embodiments, R^B is substituted Ci_{-6} alkyl. In certain embodiments, R^B is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^B is $-CH_3$. In certain embodiments, R^B is substituted methyl. In certain embodiments, R^B is $-CH_2F$. In certain embodiments, R^B is $-CHF_2$. In certain embodiments, R^B is $-CF_3$. In certain embodiments, R^B is ethyl. In certain embodiments, R^B is propyl. In certain embodiments, R^B is butyl. In certain embodiments, R^B is pentyl. In certain embodiments, R^B is hexyl. In certain embodiments, R^B is Bn. In certain embodiments, R^B is $-(CH_2)_{1-4}-$(Ring F), wherein Ring F is a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, R^B is $-(CH_2)i_{-4}-$(substituted or unsubstituted pyrrolidinyl). In certain embodiments, R^B is of the formula:  , wherein R^4 is H, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, R^B is of the formula:

 or  . In certain embodiments, R^B is $-(CH_2)i_{-4}$-(Ring F), wherein Ring F is a substituted or unsubstituted oxetanyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl ring. In certain embodiments, R^B is substituted alkenyl. In certain embodiments, R^B is unsubstituted alkenyl. In certain embodiments, R^B is substituted alkynyl. In certain embodiments, R^B is unsubstituted alkynyl. In certain embodiments, R^B is substituted carbocyclyl. In certain embodiments, R^B is unsubstituted carbocyclyl. In certain embodiments, R^B is saturated carbocyclyl. In certain embodiments, R^B is unsaturated carbocyclyl. In certain embodiments, R^B is monocyclic carbocyclyl. In certain embodiments, R^B is 3-

to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^B is unsubstituted cyclopropyl. In certain embodiments, R^B is substituted cyclopropyl. In certain embodiments, R^B is substituted heterocyclyl. In certain embodiments, R^B is unsubstituted heterocyclyl. In certain embodiments, R^B is saturated heterocyclyl. In certain embodiments, R^B is unsaturated heterocyclyl. In certain embodiments, R^B is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^B is monocyclic heterocyclyl. In certain embodiments, R^B is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^B is substituted aryl. In certain embodiments, R^B is unsubstituted aryl. In certain embodiments, R^B is 6- to 10-membered aryl. In certain embodiments, R^B is substituted phenyl. In certain embodiments, R^B is unsubstituted phenyl. In certain embodiments, R^B is substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, R^B is substituted or unsubstituted pyrazolyl. In certain embodiments, R^B is of the formula:  , wherein R^1 is H, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, R^B is of the formula:  . In certain embodiments, R^B is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, or substituted or unsubstituted isothiazolyl. In certain embodiments, R^B is substituted or unsubstituted pyridyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl. In certain embodiments, R^B is substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, R^B is a nitrogen protecting group. In certain embodiments, R^B is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00231] Formula **(IV)** includes substituent R^C on a nitrogen atom. In certain embodiments, R^C is H. In certain embodiments, R^C is substituted acyl. In certain

embodiments, R^C is unsubstituted acyl. In certain embodiments, R^C is acetyl. In certain embodiments, R^C is unsubstituted C_{1-6} alkyl. In certain embodiments, R^C is substituted C_{1-6} alkyl. In certain embodiments, R^C is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^C is unsubstituted methyl. In certain embodiments, R^C is substituted methyl. In certain embodiments, R^C is $-CH_2F$. In certain embodiments, R^C is $-CHF_2$. In certain embodiments, R^C is $-CF_3$. In certain embodiments, R^C is ethyl. In certain embodiments, R^C is propyl. In certain embodiments, R^C is butyl. In certain embodiments, R^C is pentyl. In certain embodiments, R^C is hexyl. In certain embodiments, R^C is Bn. In certain embodiments, R^C is a nitrogen protecting group. In certain embodiments, R^C is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

100232] In certain embodiments, R^B is substituted or unsubstituted, C_{1-6} alkyl, and R^C is H. In certain embodiments, R^B is $-(CH_2)_{1-4}$-(Ring F), wherein Ring F is a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring; and R^C is H. In certain embodiments, R^B is substituted or unsubstituted phenyl (e.g., *para*-substituted phenyl), and R^C is H. In certain embodiments, R^B is substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; and R^C is H. In certain embodiments, R^B is substituted or unsubstituted pyrazolyl, and R^C is H. In certain embodiments, R^B is substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl; and R^C is H. In certain embodiments, R^B is substituted or unsubstituted cyclopropyl, and R^C is H.

100233 1 Formula **(IV)** includes as Ring B an imidazolyl ring that is unsubstituted (e.g., when m is 0) or substituted with one or two substituents R^D (e.g., when m is 1 or 2). In certain embodiments, Ring B does not include substituents R^D, that is, m is 0. In certain embodiments, the two instances of R^D are different. In certain embodiments, both instances of R^D are the same. In certain embodiments, at least one instance of R^D is halogen. In certain embodiments, at least one instance of R^D is F. In certain embodiments, at least one instance of R^D is CI. In certain embodiments, at least one instance of R^D is Br. In certain embodiments, at least one instance of R^D is I (iodine). In certain embodiments, at least one instance of R^D is substituted alkyl. In certain embodiments, at least one instance of R^D is unsubstituted alkyl. In certain embodiments, at least one instance of R^D is unsubstituted C_{1-6} alkyl. In certain embodiments, both instances of R^D are unsubstituted C_{1-6} alkyl. In certain

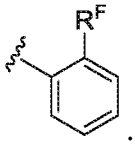
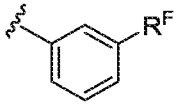
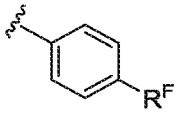
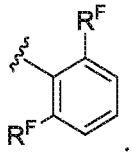
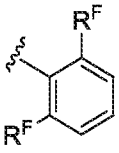
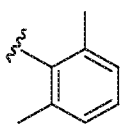
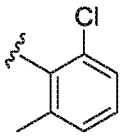
embodiments, at least one instance of R^D is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^D is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^D is -C¾. In certain embodiments, at least one instance of R^D is substituted methyl. In certain embodiments, at least one instance of R^D is $-CH_2F$. In certain embodiments, at least one instance of R^D is $-CHF_2$. In certain embodiments, at least one instance of R^D is $-CF_3$. In certain embodiments, at least one instance of R^D is ethyl. In certain embodiments, at least one instance of R^D is propyl. In certain embodiments, at least one instance of R^D is butyl. In certain embodiments, at least one instance of R^D is pentyl. In certain embodiments, at least one instance of R^D is hexyl. In certain embodiments, at least one instance of R^D is Bn. In certain embodiments, at least one instance of R^D is halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^D is substituted alkenyl. In certain embodiments, at least one instance of R^D is unsubstituted alkenyl. In certain embodiments, at least one instance of R^D is substituted alkynyl. In certain embodiments, at least one instance of R^D is unsubstituted alkynyl. In certain embodiments, at least one instance of R^D is substituted carbocyclyl. In certain embodiments. at least one instance of R^D is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^D is saturated carbocyclyl. In certain embodiments, at least one instance of R^D is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^D is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^D is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^D is substituted heterocyclyl. In certain embodiments, at least one instance of R^D is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^D is saturated heterocyclyl. In certain embodiments, at least one instance of R^D is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^D is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^D is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^D is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^D is substituted aryl. In certain embodiments, at least one instance of R^D is unsubstituted aryl. In certain embodiments, at least one instance of R^D is 6- to 10-membered aryl. In certain

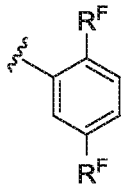
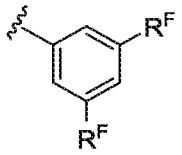
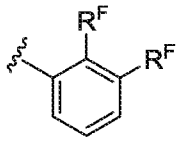
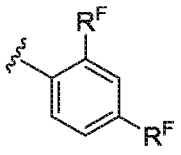
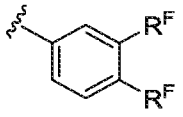
embodiments, at least one instance of R^D is substituted phenyl. In certain embodiments, at least one instance of R^D is unsubstituted phenyl. In certain embodiments, at least one instance of R^D is substituted heteroaryl. In certain embodiments, at least one instance of R^D is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^D is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^D is monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^D is 9- or 1Q-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^D is $-OR^a$. In certain embodiments, at least one instance of R^D is –OH. In certain embodiments, at least one instance of R^D is –**0** (substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^D is -OMe. In certain embodiments, at least one instance of R^D is -OEt. In certain embodiments, at least one instance of R^D is –OPr. In certain embodiments, at least one instance of R^D is -OBu. In certain embodiments, at least one instance of R^D is –OBn. In certain embodiments, at least one instance of R^D is –OPh. In certain embodiments, at least one instance of R^D is $-SR^a$. In certain embodiments, at least one instance of R^D is -SH. In certain embodiments, at least one instance of R^D is –SMe. In certain embodiments, at least one instance of R^D is $-N(R^a)_2$. In certain embodiments, at least one instance of R^D is $-NH_2$. In certain embodiments, at least one instance of R^D is –NHMe. In certain embodiments, at least one instance of R^D is $-NMe_2$. In certain embodiments, at least one instance of R^D is -CN. In certain embodiments, at least one instance of R^D is -SCN. In certain embodiments, at least one instance of R^D is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^D is –**C(=0)R**^{a} or –C**(=0**)OR^a. In certain embodiments, at least one instance of R^D is $-C(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^D is $-C(=O)NMe_2$, - **C(=0)NHMe,** or –$C(=O)NH_2$. In certain embodiments, at least one instance of R^D is –**N0 $_2$.** In certain embodiments, at least one instance of R^D is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^D is –O**C(=0**)R^a, –OC**(=0**)OR^a, or –OC**(=0**)$N(R^a)_2$.

[00234] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2.

[00235] Formula **(IV)** includes substituent R^E on a nitrogen atom. In certain embodiments, $\mathbf{R^E}$ is **H.** In certain embodiments, R^E is substituted acyl. In certain embodiments, R^E is unsubstituted acyl. In certain embodiments, R^E is acetyl. In certain embodiments, $\mathbf{R^E}$ is unsubstituted C_{1-6} alkyl. In certain embodiments, R^E is substituted C_{1-6} alkyl. In certain embodiments, R^E is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^E is unsubstituted methyl. In certain embodiments, R^E is substituted methyl. In certain embodiments, R^E is $-CH_2F$. In certain embodiments, R^E is $-CHF_2$. In certain embodiments, $\mathbf{R^E}$ is $-CF_3$. In certain embodiments, R^E is ethyl. In certain embodiments, R^E is propyl. In certain embodiments, R^E is butyl. In certain embodiments, R^E is pentyl. In certain embodiments, $\mathbf{R^E}$ is hexyl. In certain embodiments, $\mathbf{R^E}$ is Bn. In certain embodiments, $\mathbf{R^E}$ is a nitrogen protecting group. In certain embodiments, R^E is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

100236] In certain embodiments, each of R^C and R^E is H.

[00237] Formula **(IV)** includes as Ring C a phenyl ring that is unsubstituted *(e.g.,* when n is 0) or substituted with one or more substituents $\mathbf{R^F}$ (*e.g.*, when n is 1, 2, 3, 4, or 5**).** In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments. Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  , wherein each instance of R^F is independently halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments. Ring C is of the formula:  or  . In certain

embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  ,  , or  . In certain embodiments, at least two instances of R^F are different. In certain embodiments, all instances of R^F are the same. In certain embodiments, at least one instance of R^F is halogen. In certain embodiments, at least one instance of R^F is F. In certain embodiments, at least one instance of R^F is CI. In certain embodiments, at least one instance of R^F is Br. In certain embodiments, at least one instance of R^F is I (iodine). In certain embodiments, at least one instance of R^F is substituted alkyl. In certain embodiments, at least one instance of R^F is unsubstituted alkyl. In certain embodiments, at least one instance of R^F is unsubstituted C_{1-6} alkyl. In certain embodiments, all instances of R^F are unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is Ci_{-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^F is $–CH_3$. In certain embodiments, all instances of R^F are $-CH_3$. In certain embodiments, at least one instance of R^F is substituted methyl. In certain embodiments, at least one instance of R^F is $-CH_2F$. In certain embodiments, at least one instance of R^F is $–CHF_2$. In certain embodiments, at least one instance of R^F is $–CF_3$. In certain embodiments, at least one instance of R^F is ethyl. In certain embodiments, at least one instance of R^F is propyl. In certain embodiments, at least one instance of R^F is butyl. In certain embodiments, at least one instance of R^F is pentyl. In certain embodiments, at least one instance of R^F is hexyl. In certain embodiments, at least one instance of R^F is Bn. In certain embodiments, at least one instance of R^F is substituted alkenyl. In certain embodiments, at least one instance of R^F is unsubstituted alkenyl. In certain embodiments, at least one instance of R^F is substituted alkynyl. In certain embodiments, at least one instance of R^F is

unsubstituted alkynyl. In certain embodiments, at least one instance of R^F is substituted carbocyclyl. In certain embodiments, at least one instance of R^F is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^F is saturated carbocyclyl. In certain embodiments, at least one instance of R^F is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^F is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^F is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^F is substituted heterocyclyl. In certain embodiments, at least one instance of R^F is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^F is saturated heterocyclyl. In certain embodiments, at least one instance of R^F is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^F is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^F is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^F is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^F is substituted aryl. In certain embodiments, at least one instance of R^F is unsubstituted aryl. In certain embodiments, at least one instance of R^F is 6- to 1G-membered aryl. In certain embodiments, at least one instance of R^F is substituted phenyl. In certain embodiments, at least one instance of R^F is unsubstituted phenyl. In certain embodiments, at least one instance of R^F is substituted heteroaryl. In certain embodiments, at least one instance of R^F is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^F is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^F is monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^F is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^F is $-OR^a$. In certain embodiments, at least one instance of R^F is -OH. In certain embodiments, at least one instainee of R^F is -0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one

instance of R^F is -QMe. In certain embodiments, at least one instance of R^F is –OEt. In certain embodiments, at least one instance of R^F is –OPr. In certain embodiments, at least one instance of R^F is -OBu. In certain embodiments, at least one instance of R^F is –OBn. In certain embodiments, at least one instance of R^F is –OPh. In certain embodiments, at least one instance of R^F is -SR^a. In certain embodiments, at least one instance of R^F is -SH. In certain embodiments, at least one instance of R^F is -SMe. In certain embodiments, at least one instance of R^F is –$N(R^a)_2$. In certain embodiments, at least one instance of R^F is -NH_2. In certain embodiments, at least one instance of R^F is –NHMe. In certain embodiments, at least one instance of R^F is –NMe_2. In certain embodiments, at least one instance of R^F is -CN. In certain embodiments, at least one instance of R^F is -SCN. In certain embodiments, at least one instance of R^F is –$C(=NR^a)R^a$, –$C(=NR^a)OR^a$, or –$C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^F is –$C(=O)R^a$ or –$C(=O)OR^a$. In certain embodiments, at least one instance of R^F is -$C(=O)N(R^a)_2$.

[00238] In certain embodiments, at least one instance of R^F is -$C(=O)N(R^a)_2$, wherein each instance of R^a is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted phenyl, or a nitrogen protecting group. In certain embodiments, at least one instance of R^F is –$C(=O)NHR^a$, wherein R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^F is –$C(=O)NHR^a$, wherein R^a is phenyl substituted with one, two, three, four, or five substituents independently selected from the group consisting of halogen and substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is -$C(=O)NMeR^a$, wherein R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^F is –$C(=O)NMeR^a$, wherein R^a is phenyl substituted with one, two, three, four, or five substituents independently selected from the group consisting of halogen and substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is –$C(=O)NMe_2$, –C(=O)NHMe, or –C(=O)NH_2. In certain embodiments, at least one instance of R^F is -NO_2. In certain embodiments, at least one instance of R^F is –$NR^aC(=O)R^a$, –$NR^aC(=O)OR^a$, or -$NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^F is –$OC(=O)R^a$, -$OC(=O)OR^a$, or –$OC(=O)N(R^a)_2$.

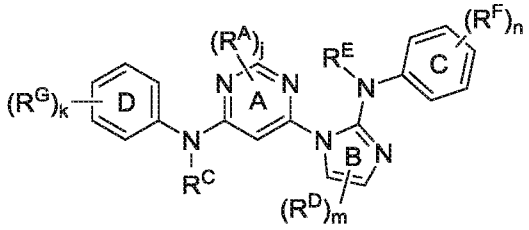
[00239] In certain embodiments, at least one instance of R^F is halogen, substituted or unsubstituted, C_{1-6} alkyl, or -OR^a. In certain embodiments, at least one instance of R^F is halogen, substituted or unsubstituted, C_{1-6} alkyl, or -OR^a, wherein R^a

is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or an oxygen protecting group. In certain embodiments, at least one instance **of** R^F is halogen, unsubstituted C_{1-6} alkyl, or -OR^a, wherein R^a is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is $-CH_3$ or Cl.

[00240] In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, n is 5.

100241 In certain embodiments, n is 1; and R^F is - **C(=0)N(R a)$_2$.** In certain embodiments, n is 1; and R^F is - **C(=0)N(R a)$_2$,** wherein each instance **of** R^a is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted phenyl, or a nitrogen protecting group. In certain embodiments, n is 2; and each instance of R^F is independently halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, n is 2; and each instance of R^F is independently halogen or unsubstituted, C_{1-6} alkyl *(e.g.,* -CH_3). In certain embodiments, n is 2; and each instance **of** R^F is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, $-OR^a$, or - **C(=0)N(R a)$_2$.** In certain embodiments, n is 2; and each instance of R^F is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, **-OR a,** or - **C(=0)N(R a)$_2$,** wherein each instance of R^a is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted phenyl, an oxygen protecting group when attached to an oxygen atom, or a nitrogen protecting group when attached to a nitrogen atom.

100242 In certain embodiments, the compound of Formula **(IV)** is of Formula **(IV-A):**



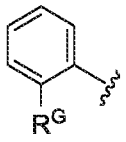
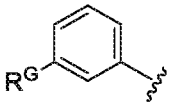
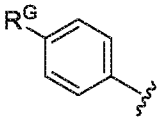
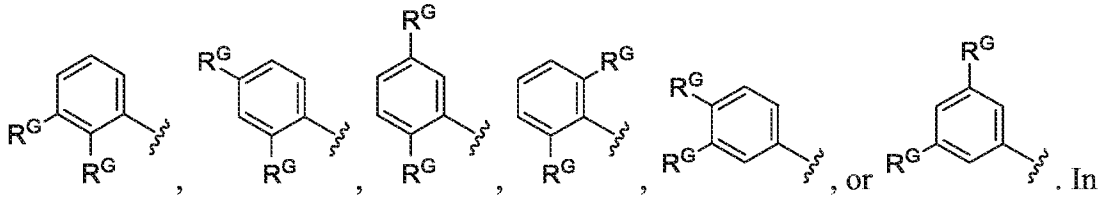
(IV-A),

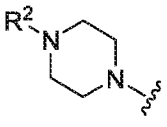
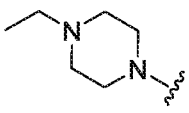
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein:

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, - -

$N(R^a)_2$, $-SR^a$, –CN, –SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=0)OR^a$, $-C(=0)N(R^a)_2$, **-NO2,** $-NR^aC(=0)R^a$, $-NR^aC(O)0R^a$, $-NR^aC(=0)N(R^a)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$; and

k is 0, 1, 2, 3, 4, or 5.

[00243] Formula (IV-A) includes as Ring D a phenyl ring that is unsubstituted (*e.g.*, when k is 0) or substituted with one or more substituents R^G (*e.g.*, when k is 1, 2, 3, 4, or 5). In certain embodiments, Ring D is of the formula:  . In certain embodiments, Ring D is of the formula:  . In certain embodiments, Ring D is of the formula:  . In certain embodiments, Ring D is of the formula:  . In certain embodiments, at least two instances of R^G are different. In certain embodiments, all instances of R^G are the same. In certain embodiments, at least one instance of R^G is halogen. In certain embodiments, at least one instance of R^G is F. In certain embodiments, at least one instance of R^G is CI. In certain embodiments, at least one instance of R^G is Br. In certain embodiments, at least one instance of R^G is I (iodine). In certain embodiments, at least one instance of R^G is substituted alkyl. In certain embodiments, at least one instance of R^G is unsubstituted alkyl. In certain embodiments, at least one instance of R^G is unsubstituted C_{1-6} alkyl. In certain embodiments, all instances of R^G are unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^G is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^G is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^G is $-CH_3$. In certain embodiments, all instances of R^G are $-CH_3$. In certain embodiments, at least one instance of R^G is substituted methyl. In certain embodiments, at least one instance of R^G is $-CH_2F$. In certain embodiments, at least one instance of R^G is $-CHF_2$. In certain embodiments, at least one instance of R^G is $-CF_3$. In certain embodiments, at least one instance of R^G

is ethyl. In certain embodiments, at least one instance of R^G is propyl. In certain embodiments, at least one instance of R^G is butyl. In certain embodiments, at least one instance of R^G is pentyl. In certain embodiments, at least one instance of R^G is hexyl. In certain embodiments, at least one instance of R^G is Bn. In certain embodiments, at least one instance of R^G is substituted alkenyl. In certain embodiments, at least one instance of R^G is unsubstituted alkenyl. In certain embodiments, at least one instance of R^G is substituted alkynyl. In certain embodiments, at least one instance of R^G is unsubstituted alkynyl. In certain embodiments, at least one instance of R^G is substituted carbocyclyl. In certain embodiments, at least one instance of R^G is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^G is saturated carbocyclyl. In certain embodiments, at least one instance of R^G is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^G is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^G is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^G is substituted heterocyclyl. In certain embodiments, at least one instance of R^G is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^G is saturated heterocyclyl. In certain embodiments, at least one instance of R^G is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^G is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^G is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^G is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted piperazinyl. In certain embodiments, at least one instance of R^G is of the formula:  , wherein R^2 is H, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, at least one instance of R^G is of the formula:  . In certain embodiments, at least one instance of R^G is substituted aryl. In certain embodiments, at least one instance of R^G is unsubstituted aryl. In certain embodiments, at least one instance of R^G is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^G is substituted phenyl. In certain embodiments, at least one instance of R^G is unsubstituted phenyl. In certain

embodiments, at least one instance of R^G is substituted heteroaryl. In certain embodiments, at least one instance of R^G is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^G is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^G is monocyclic heteroaryl. In certain embodiments, at least one instance of R^G is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^G is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^G is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^G is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^G is $-OR^a$. In certain embodiments, at least one instance of R^G is -OH. In certain embodiments, at least one instance of R^G is –Ofsubstituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^G is $-O-(CH_2)_{2-4}-0-$(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^G is $-O-(CH_2)_2-OMe$. In certain embodiments, at least one instance of R^G is -OMe. In certain embodiments, at least one instance of R^G is –OEt. In certain embodiments, at least one instance ofR^G is –OPr. In certain embodiments, at least one instance of R^G is -OBu. In certain embodiments, at least one instance of R^G is -OBn. In certain embodiments, at least one instance of R^G is -OPh. In certain embodiments, at least one instance of R^G is $-SR^a$. In certain embodiments, at least one instance of R^G is –SH. In certain embodiments, at least one instance of R^G is –SMe. In certain embodiments, at least one instance of R^G is $-N(R^a)_2$. In certain embodiments, at least one instance of R^G is $-N(R^a)_2$, wherein each instance of R^a is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or two instances of R^a are joined to form a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, at least one instaiice of R^G is $-NH_2$. In certain embodiments, at least one instance of R^G is –NHMe. In certain embodiments, at least one instance of R^G is $-NMe_2$. In certain embodiments, at least one instance of R^G is -CN. In certain embodiments, at least one instance of R^G is -SCN. In certain embodiments, at least one instance of R^G is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^G is $-C(=0)R^a$ or $-C(=0)OR^a$. In certain embodiments, at least one instance of R^G is $-C(=0)N(R^a)_2$. In

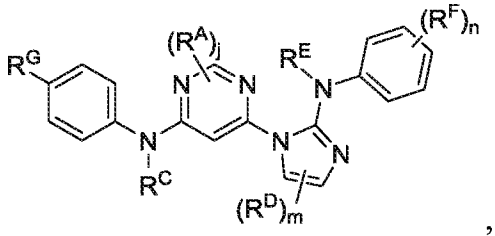
certain embodiments, at least one instance of R^G is -C(=0)NMe $_2$, –C(=O)NHMe, or -C(=0)NH $_2$. in certain embodiments, at least one instance of R^G is --N0 $_2$. In certain embodiments, at least one instance of R^G is -NR ^{a}C(=0)R ^{a}, -NR ^{a}C(=0)OR ^{a}, or -NR^{a}C(=0)N(R ^{a})$_2$. In certain embodiments, at least one instance of R^G is –OC(=0)R ^{a}, -OC(=0)OR ^{a}, or -OC(=0)N(R ^{a})$_2$.

100244] In certain embodiments, at least one instance of R^G is -QR ^{a}, -N(R ^{a})$_2$, or substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

100245] In certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, k is 3. In certain embodiments, k is 4. In certain embodiments, k is 5.

100246 1 In certain embodiments, k is 1; and R^G is –OR^a, -N(R ^{a})$_2$, or substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, k is 1; and R^G is –O R^a, –N(R^a)$_2$, or substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently nitrogen, oxygen, or sulfur; and each instance of R^a is independently H, substituted or unsubstituted, C_{1-6} alkyl, an oxygen protecting group when attached to an oxygen atom, or a nitrogen protecting group when attached to a nitrogen group.

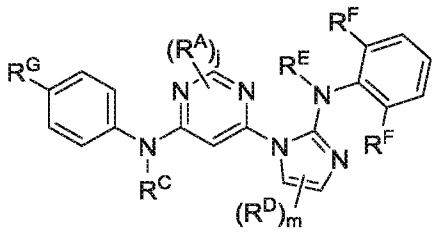
[00247 1 In certain embodiments, the compound of Formula **(IV)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

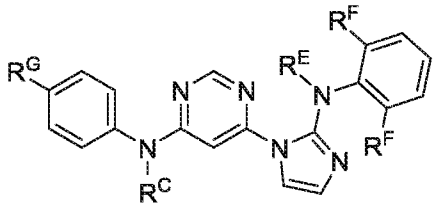
[00248] In certain embodiments, the compound of Formula **(IV)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

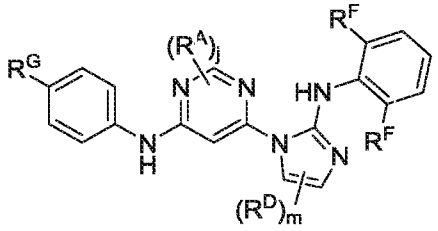
[00249] In certain embodiments, the compound of Formula **(IV)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

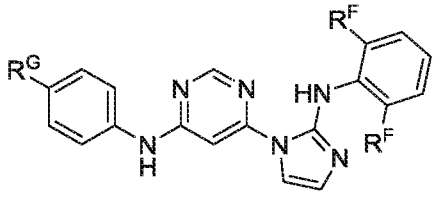
[00250] In certain embodiments, the compound of Formula **(IV)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

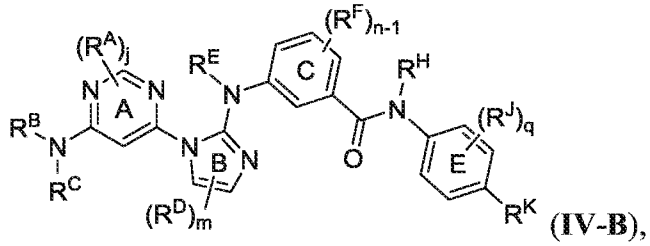
[00251] In certain embodiments, the compound of Formula **(IV)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00252] In certain embodiments, the compound of Formula (IV) is of Formula (IV-B):



(IV-B),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein:

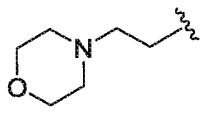
R^H is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^J is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

q is 0, 1, 2, 3, or 4; and

R^K is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

100253] In certain embodiments, a compound of Formula (IV) is of Formula (IV-B), wherein when R^c is hydrogen, R^B is not unsubstituted cyclopropyl or



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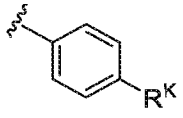
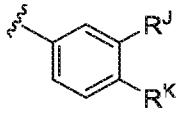
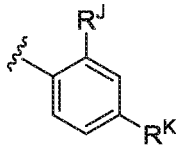
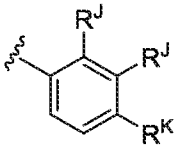
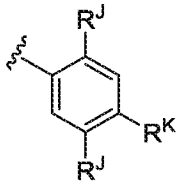
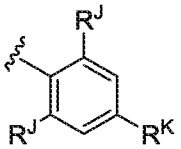
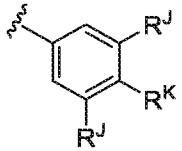
1002541 Formula (IV-B) includes substituent R^H on a nitrogen atom. In certain embodiments, R^H is H. In certain embodiments, R^H is not H. In certain embodiments, R^H is substituted acyl. In certain embodiments, R^H is unsubstituted acyl. In certain

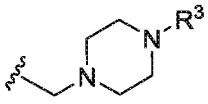
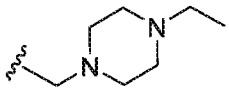
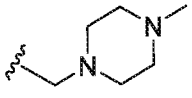
embodiments, R^H is acetyl. In certain embodiments, R^H is unsubstituted C_{1-6} alkyl. In certain embodiments, R^H is substituted C_{1-6} alkyl. In certain embodiments, R^H is C1-6 alkyl substituted with at least one halogen. In certain embodiments, R^H is unsubstituted methyl. In certain embodiments, R^H is substituted methyl. In certain embodiments, R^H is $-CH_2F$. In certain embodiments, R^H is $-CHF_2$. In certain embodiments, R^H is $-CF_3$. In certain embodiments, R^H is ethyl. In certain embodiments, R^H is propyl. In certain embodiments, R^H is butyl. In certain embodiments, R^H is pentyl. In certain embodiments, R^H is hexyl. In certain embodiments, R^H is Bn. In certain embodiments, R^H is a nitrogen protecting group. In certain embodiments, R^H is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts. In certain embodiments, R^H is hydrogen or unsubstituted, C_{1-6} alkyl.

100255] Formula **(IV-B)** includes as Ring E a phenyl ring that is substituted with R^K and optionally one or more substituents R^J. In certain embodiments, Ring E is of the formula:  . In certain embodiments, Ring E is of the formula:

 . In certain embodiments, Ring E is of the formula:  . In certain embodiments, Ring E is of the formula:  . In certain embodiments, Ring E is of the formula:  . In certain embodiments, Ring E is of the formula:  . In certain embodiments, Ring E is of the formula:  . In certain embodiments, R^K is H. In certain embodiments, R^K is halogen. In certain embodiments, R^K is F. In certain embodiments, R^K is Cl. In certain

embodiments, R^K is Br. In certain embodiments, R^K is I (iodine). In certain embodiments, R^K is substituted alkyl. In certain embodiments, R^K is unsubstituted alkyl. In certain embodiments, R^K is unsubstituted C_{1-6} alkyl. In certain embodiments, R^K is substituted C_{1-6} alkyl. In certain embodiments, R^K is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^K is $-CH_3$. In certain embodiments, R^K is substituted methyl. In certain embodiments, R^K is $-CH_2F$. In certain embodiments, R^K is $-CHF_2$. In certain embodiments, R^K is $-CF_3$. In certain embodiments, R^K is ethyl. In certain embodiments, R^K is propyl. In certain embodiments, R^K is butyl. In certain embodiments, R^K is pentyl. In certain embodiments, R^K is hexyl. In certain embodiments, R^K is Bn. In certain embodiments, R^K is substituted alkenyl. In certain embodiments, R^K is unsubstituted alkenyl. In certain embodiments, R^K is substituted alkynyl. In certain embodiments, R^K is unsubstituted alkynyl. In certain embodiments, R^K is substituted carbocyclyl. In certain embodiments, R^K is unsubstituted carbocyclyl. In certain embodiments, R^K is saturated carbocyclyl. In certain embodiments, R^K is unsaturated carbocyclyl. In certain embodiments, R^K is monocyclic carbocyclyl. In certain embodiments, R^K is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^K is substituted heterocyclyl. In certain embodiments, R^K is unsubstituted heterocyclyl. In certain embodiments, R^K is saturated heterocyclyl. In certain embodiments, R^K is unsaturated heterocyclyl. In certain embodiments, R^K is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^K is monocyclic heterocyclyl. In certain embodiments, R^K is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^K is substituted aryl. In certain embodiments, R^K is unsubstituted aryl. In certain embodiments, R^K is 6- to 10-membered aryl. In certain embodiments, R^K is substituted phenyl. In certain embodiments, R^K is unsubstituted phenyl. In certain embodiments, R^K is substituted heteroaryl. In certain embodiments, R^K is unsubstituted heteroaryl. In certain embodiments, R^K is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^K is monocyclic heteroaryl. In certain embodiments, R^K is 5-membered, monocyclic heteroaryl. In certain embodiments, R^K is not substituted imidazolyl. In certain embodiments, R^K is 6-membered, monocyclic heteroaryl. In certain embodiments, R^K is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the

bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^K is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, R^K is $-OR^a$. In certain embodiments, R^K is -OH. In certain embodiments, R^K is -0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, R^K is –OMe. In certain embodiments, R^K is -OEt. In certain embodiments, R^K is -OPr. In certain embodiments, R^K is -OBu. In certain embodiments, R^K is –OBn. In certain embodiments, R^K is –OPh. In certain embodiments, R^K is $-SR^a$. In certain embodiments, R^K is -SH. In certain embodiments, R^K is -SMe. In certain embodiments, R^K is $-N(R^a)_2$. In certain embodiments, R^K is $-NH_2$. In certain embodiments, R^K is -NHMe. In certain embodiments, R^K is $-NMe_2$. In certain embodiments, R^K is -CN. In certain embodiments, R^K is --SCN. In certain embodiments, R^K is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^K is $-C(=O)R^a$ or $-C(=O)OR^a$. In certain embodiments, R^K is $-C(=O)N(R^a)_2$. In certain embodiments, R^K is $-C(=O)NMe_2$, $-C(=O)NHMe$, or $-C(=O)NH_2$. In certain embodiments, R^K is $-NO_2$. In certain embodiments, R^K is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, R^K is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00256] In certain embodiments, R^K is $-(CH_2)_{1-3}-$(Ring G), wherein Ring G is a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, R^K is $-(CH_2)_{1-3}-$(substituted or unsubstituted piperazinyl). In certain embodiments, R^K is of the formula:  , wherein R^3 is H, substituted or unsubstituted, C_{2-6} alkyl, substituted methyl, or a nitrogen protecting group. In certain embodiments, R^K is of the formula:  . In certain embodiments, R^K is not of the formula:  . In certain embodiments, R^K is $-(CH_2)_{1-3}-$(Ring G), wherein Ring G is a substituted or unsubstituted oxetanyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, or substituted or unsubstituted morpholinyl ring.

[00257] Ring E of Formula (1V-B) may include one or more substituents R^J. In certain embodiments, at least two instances of R^J are different. In certain embodiments, all instances of R^J are the same. In certain embodiments, at least one instance of R^J is halogen. In certain embodiments, at least one instance of R^J is F. In certain embodiments, at least one instance of R^J is CI. In certain embodiments, at least one instance of R^J is Br. In certain embodiments, at least one instance of R^J is I (iodine). In certain embodiments, at least one instance of R^J is substituted alkyl. In certain embodiments, at least one instance of R^J is unsubstituted alkyl. In certain embodiments, at least one instance of R^J is unsubstituted Ci^ alkyl. In certain embodiments, all instances of R^J are unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^J is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^J is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^J is $-CH_3$. In certain embodiments, all instances of R^J are $-CH_3$. In certain embodiments, at least one instance of R^J is substituted methyl. In certain embodiments, at least one instance of R^J is $-CH_2F$. In certain embodiments, at least one instance of R^J is $-CHF_2$. In certain embodiments, at least one instance of R^J is $-CF_3$. In certain embodiments, at least one instance of R^J is ethyl. In certain embodiments, at least one instance of R^J is propyl. In certain embodiments, at least one instance of R^J is butyl. In certain embodiments, at least one instance of R^J is pentyl. In certain embodiments, at least one instance of R^J is hexyl. In certain embodiments, at least one instance of R^J is Bn. In certain embodiments, at least one instance of R^J is halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^J is substituted alkenyl. In certain embodiments, at least one instance of R^J is unsubstituted alkenyl. In certain embodiments, at least one instance of R^J is substituted alkynyl. In certain embodiments, at least one instance of R^J is unsubstituted alkynyl. In certain embodiments. at least one instance of R^J is substituted carbocyclyl. In certain embodiments, at least one instance of R^J is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^J is saturated carbocyclyl. In certain embodiments, at least one instance of R^J is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^J is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^J is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^J is substituted heterocyclyl. In certain embodiments, at least one instance of R^J is unsubstituted

heterocyclyl. In certain embodiments, at least one instance of R^J is saturated heterocyclyl. In certain embodiments, at least one instance of R^J is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^J is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^J is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^J is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^J is substituted aryl. In certain embodiments, at least one instance of R^J is unsubstituted aryl. In certain embodiments, at least one instance of R^J is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^J is substituted phenyl. In certain embodiments, at least one instance of R^J is unsubstituted phenyl. In certain embodiments, at least one instance of R^J is substituted heteroaryl. In certain embodiments, at least one instance of R^J is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^J is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^J is monocyclic heteroaryl. In certain embodiments, at least one instance of R^J is 5-membered, monocyclic heteroaryl. In certain embodiments, no instance of R^J is substituted imidazolyl. In certain embodiments, at least one instance of R^J is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^J is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^J is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^J is $-OR^a$. In certain embodiments, at least one instance of R^J is -OH. In certain embodiments, at least one instance of R^J is -0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^J is –OMe. In certain embodiments, at least one instance of R^J is -OEt. In certain embodiments, at least one instance of R^J is –OPr. In certain embodiments, at least one instance of R^J is –OBu. In certain embodiments, at least one instance of R^J is –OBn. In certain embodiments, at least one instance of R^J is –OPh. In certain embodiments, at least one instance of R^J is $-SR^a$. In certain embodiments, at least one instance of R^J is -SH. In certain embodiments, at least one instance of R^J is -SMe. In certain embodiments, at least one instance of R^J is $-N(R^a)_2$. In certain embodiments, at least

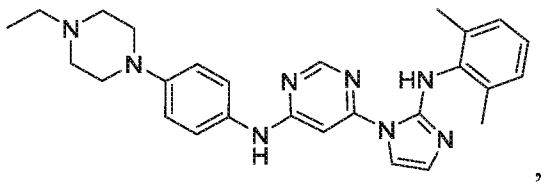
one instance of R^J is -NH_2. In certain embodiments, at least one instance of R^J is -NHMe. In certain embodiments, at least one instance of $\mathbf{R^J}$ is -NMe_2. In certain embodiments, at least one instance of $\mathbf{R^J}$ is -CN. In certain embodiments, at least one instance of $\mathbf{R^J}$ is **-SCN.** In certain embodiments, at least one instance of $\mathbf{R^J}$ is -C(=NR^a)R^a, **-C(=NR^a)OR**\ or **-C(=NR^a)N(R^a)$_2$.** In certain embodiments, at least one instance of $\mathbf{R^J}$ is **-C(=0)R^a** or **- C(=0)OR^a.** In certain embodiments, at least one instance of $\mathbf{R^J}$ is **-C(=0)N(R^a)$_2$.** In certain embodiments, at least one instance of $\mathbf{R^J}$ is -C(=O)NMe_2, **- C(=0)NHMe,** or -C(=O)NH_2. In certain embodiments, at least one instance of $\mathbf{R^J}$ is -$N0_2$. In certain embodiments, at least one instance of R^J is -$NR^aC(=O)R^a$, **-NR^aC(=0)OR^a,** or -$NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of $\mathbf{R^J}$ is **-OC(=0)R^a,** -OC(=0)OR^a, or **-OC(=0)N(R^a)$_2$.**

100258] In certain embodiments, at least one instance of $\mathbf{R^J}$ is halogen or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of $\mathbf{R^J}$ is halogen, unsubstituted C_{1-6} alkyl, or C_{1-6} alkyl substituted with at least one halogen.

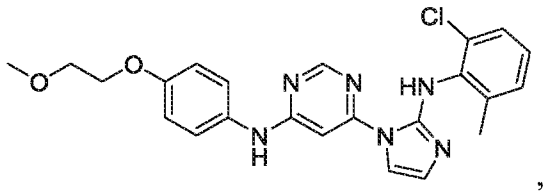
[002591 In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, q is 3. In certain embodiments, q is 4.

100260] In certain embodiments, no instance of $\mathbf{R^J}$ and R^K is substituted or unsubstituted heteroaryl. In certain embodiments, no instance of $\mathbf{R^J}$ and $\mathbf{R^K}$ is substituted or unsubstituted imidazolyl. In certain embodiments, no instance of $\mathbf{R^J}$ and R^K is substituted imidazolyl.

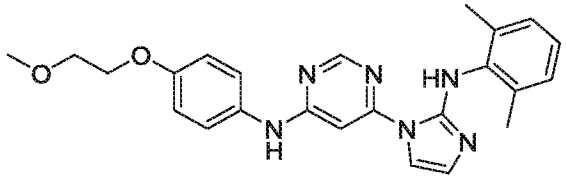
100261 1 In certain embodiments, the compound of Formula (IV) is of the formula:



(IV-1 or HG-10-7-01),



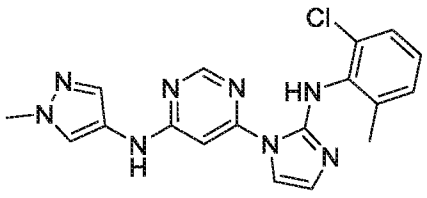
(IV-2),



(IV-3),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

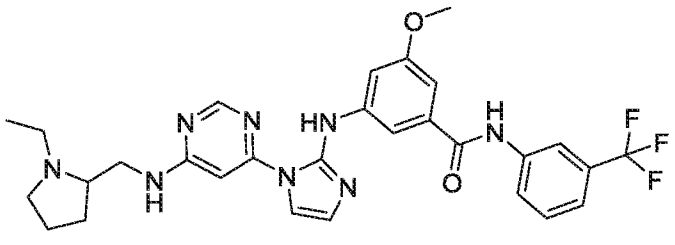
[00262 1 In certain embodiments, the compound of Formula **(IV)** is of the formula:



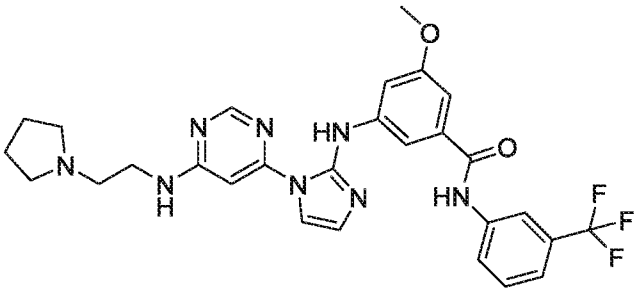
(IV-4),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

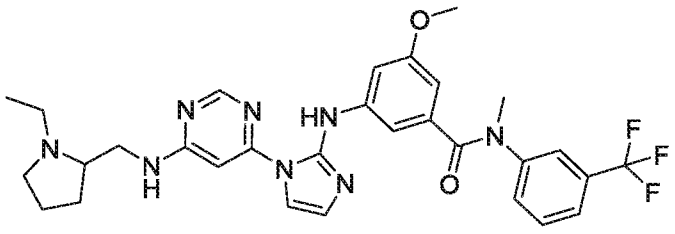
[002631 In certain embodiments, the compound of Formula **(IV)** is of the formula:



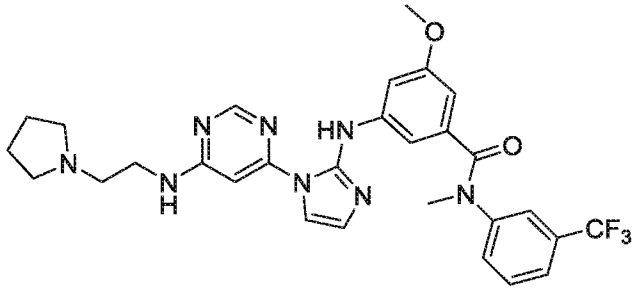
(IV-5),



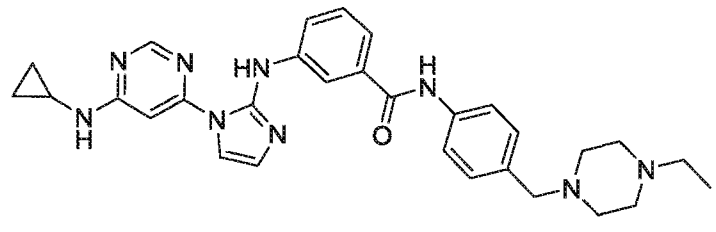
(IV-6),



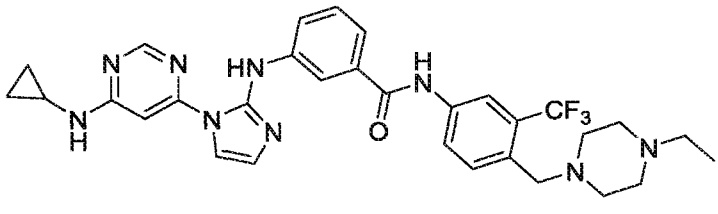
(IV-7),



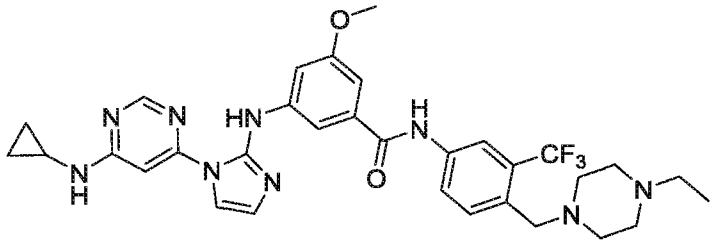
(IV-8),



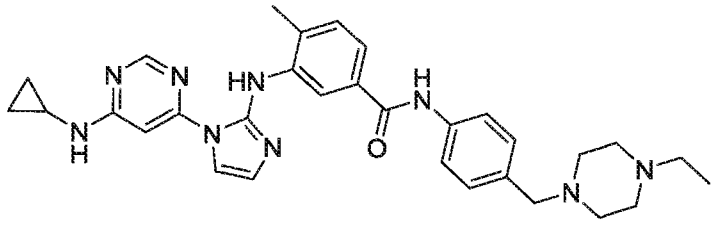
(IV-9),



(IV-10),



(IV-11),

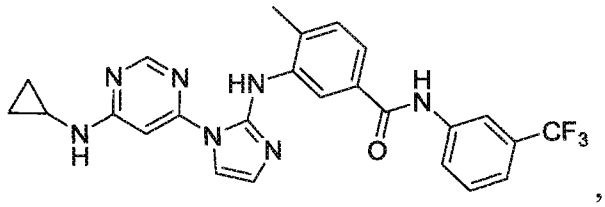


(IV-12),

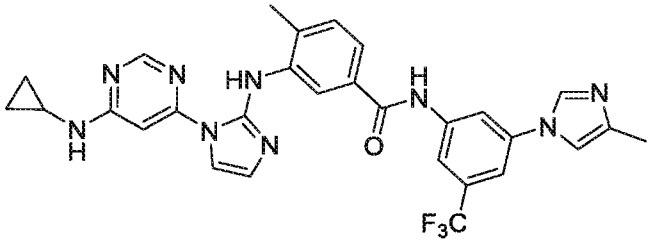
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00264] In certain embodiments, a compound of Formula **(IV)** is HG-10-7-01, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

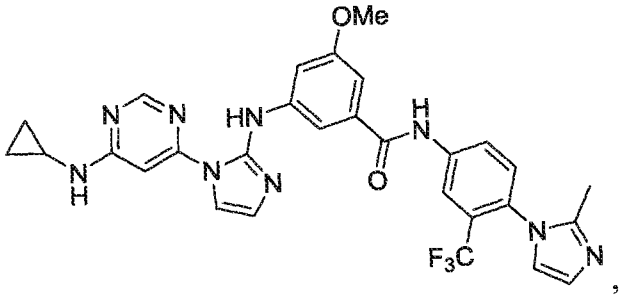
[00265] In certain embodiments, a compound of Formula **(IV)** is not of the formula:

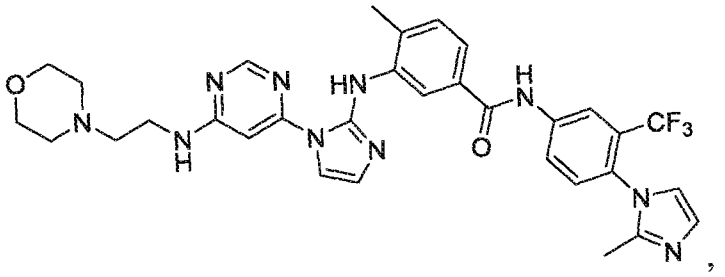


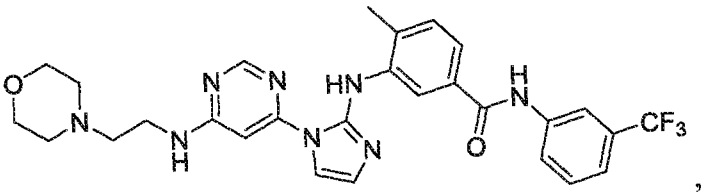
,

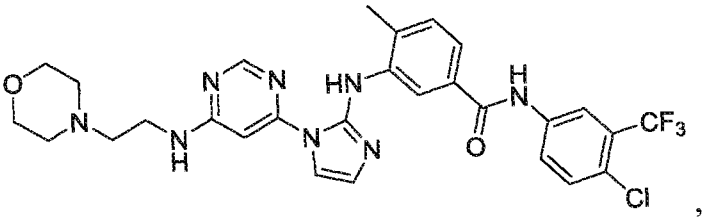


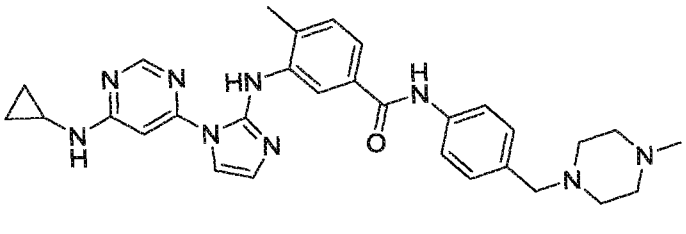
,

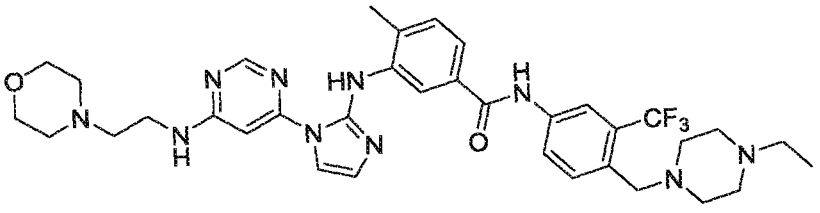


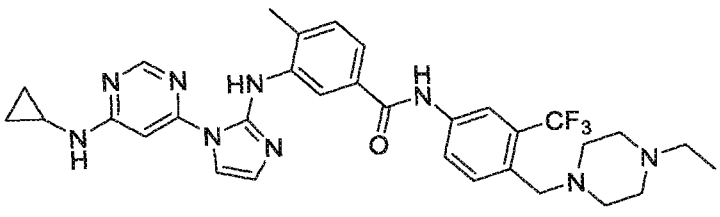








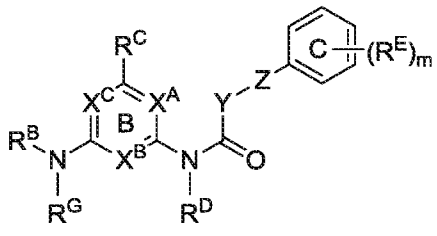




or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, or tautomer thereof.

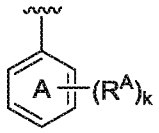
Compounds of **Formula (V)**

[00266] In another aspect, the present disclosure provides urea or carbamate compounds of Formula (V) for use in the present invention:



(V),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

R^G is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aikenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl, or of the formula:  ;

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aikenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^a, -$N(R^a)_2$, -SR^a, -CN, -SCN, -$C(=NR^a)R^a$, -$C(=NR^a)OR^a$, -$C(=NR^a)N(R^a)_2$, –$C(=O)R^a$, –$C(=O)OR^a$, -$C(=O)N(R^a)_2$, –NO_2, –$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)N(R^a)_2$, –$OC(=O)R^a$, -$OC(=O)OR^a$, or -$OC(=O)N(R^a)_2$, or two R^A groups are joined to form a substituted or unsubstituted carbocyclic ring, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted aryl ring, or substituted or unsubstituted heteroaryl ring;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aikenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted

or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^a groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, 4, or 5;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^C is independently N or CR^X, wherein each instance of R^x is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(-O)N(R^a)_2$, $-N0_2$, $-NR^aC(=O)R^a$, $-NR^aC(-O)OR^a$, $-NR^aC(-O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

or: X^B is CR^X, and R^G and R^X of X^B are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

R^C is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)0R^a$, $-C(-O)N(R^a)_2$, $-N0_2$, $-NR^aC(-O)R^a$, $-NR^aC(-O)OR^a$, $-NR^aC(-O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^D is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

Y is –O– or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

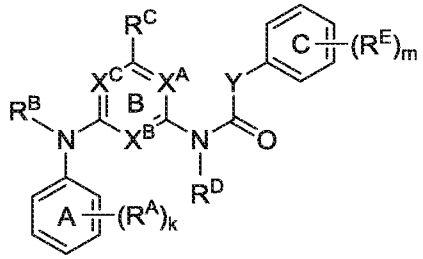
Z is a bond or $-C(R^Z)_2-$, wherein each instance of R^Z is independently hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

each instance of R^E is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-NR^aS(=O)R^a$, $-NR^aS(=O)OR^a$, $-NR^aS(=O)N(R^a)_2$, $-NR^aS(=O)_2R^a$, $-NR^aS(=O)_2OR^a$, $-NR^aS(=O)_2N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

m is 0, 1, 2, 3, 4, or 5.

[002671 Unless expressly provided otherwise, the moieties and variables described in the subsection **Compounds of Formula (V)** apply only to Formula **(V).** The moieties and variables included but not described in detail in the subsection **Compounds of Formula (V)** are as described in detail in other subsections.

[00268] In certain embodiments, a compound of Formula (V) is of Formula **(V-A):**



(V-A),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein:

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)()R^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$:

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted

or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^a groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, 4, or 5;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^C is independently N or CR^X, wherein each instance of R^x is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=0)R^a$, $-C(=0)OR^a$, $-C(-0)N(R^a)_2$, $-N0_2$, $-NR^aC(=0)R^a$, $-NR^aC(0)GR^a$, $-NR^aC(-0)N(R^a)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$;

R^C is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^8$, -CN, $-SCN$, $-C(=NR^a)R^8$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=0)R^a$, $-C(=0)OR^a$, $-C(-0)N(R^a)_2$, $-N0_2$, $-NR^aC(=0)R^a$, $-NR^aC(=<))OR^a$, $-NR^aC(=0)N(R^a)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$;

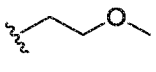
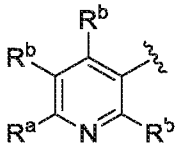
R^D is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

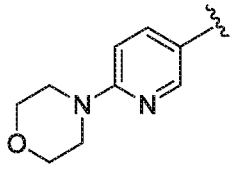
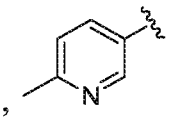
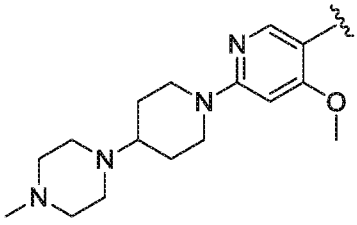
Y is -O- or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{i-6} alkyl, or a nitrogen protecting group;

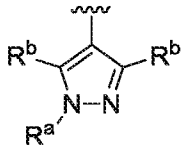
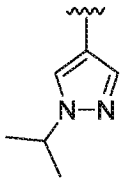
each instance of R^E is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=0)R^a$,

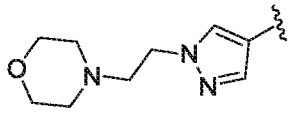
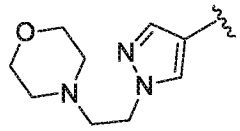
–C(=0)OR^a, -C(=0)N(R^a)$_2$, -N0$_2$, –NR^{a}C(=0)R^a, –NR^{a}C(=O)0 R^a, -NR^{a}C(=0)N(R^a)$_2$, –OC(=0)R^a, –0C(=O)0R^a, or –OC(=0)N(R^a)$_2$; and

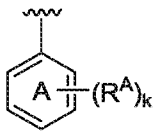
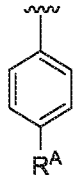
m is 0, 1, 2, 3, 4, or 5.

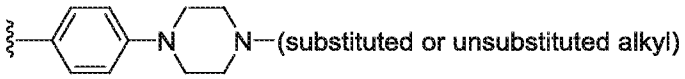
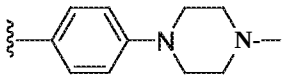
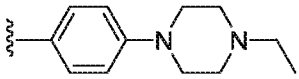
[00269] Formula (V) includes substituent R^G. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is substituted or unsubstituted alkyl. In certain embodiments, R^G is substituted C$_{1-6}$ alkyl (*e.g.*, –CF$_3$, perfluoroethyl, perfluoropropyl, perfluorobutyl, Bn, or C$_{1-6}$ alkyl substituted with at least one instance of halogen and/or –OR^a)). In certain embodiments, R^G is C$_{1-6}$ alkyl substituted with at least one instance of –OR^a, optionally wherein R^a is hydrogen or substituted or unsubstituted, C$_{1-6}$ alkyl. In certain embodiments, R^G is of the formula;  . In certain embodiments, R^G is unsubstituted C$_{1-6}$ alkyl (e.g., Me, Et, Pr, or Bu). In certain embodiments, R^G is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted, C$_{1-6}$ alkenyl). In certain embodiments, R^G is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted, C$_{1-6}$ alkynyl). In certain embodiments, R^G is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^G is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^G is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^G is substituted or unsubstituted 2-pyridyl. In certain embodiments, R^G is substituted or unsubstituted 3-pyridyl. In certain embodiments, R^G is of the formula:  , wherein R^a is hydrogen, halogen, substituted or unsubstituted, C$_{1-6}$ alkyl, –OH, -0(substituted or unsubstituted, C$_{1-6}$ alkyl), or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur; and each instance of R^b is independently hydrogen, halogen, substituted or unsubstituted, C$_{1-6}$ alkyl, –OH, or –0(substituted or unsubstituted, C$_{1-6}$ alkyl). In certain embodiments, R^G is of the formula:

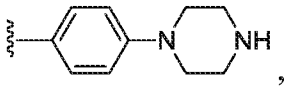
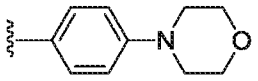
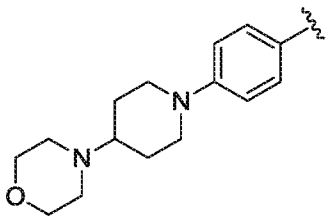
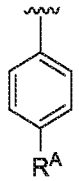
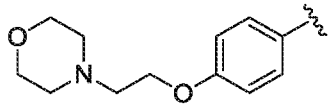
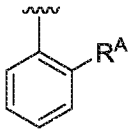
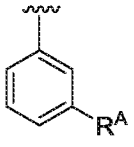

, 
, or 
. In certain embodiments, R^G is substituted or unsubstituted 4-pyridyl. In certain embodiments, R^G is substituted or unsubstituted 1-pyrazolyl. In certain embodiments, R^G is substituted or unsubstituted 3-pyrazolyl. In certain embodiments, R^G is substituted or unsubstituted 4-pyrazolyl. In certain embodiments, R° is of the formula:

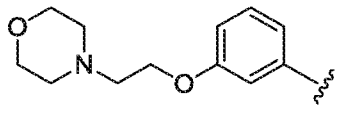
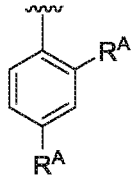
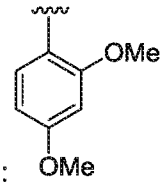
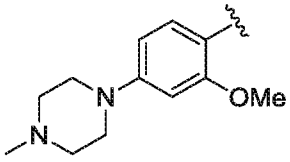
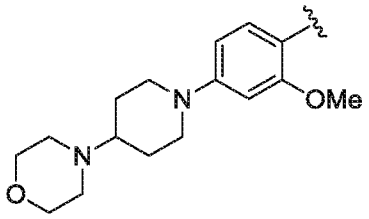
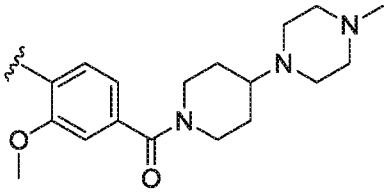
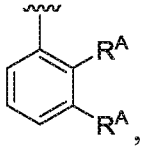
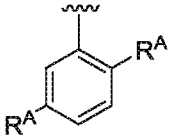
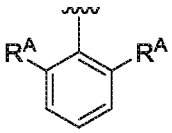
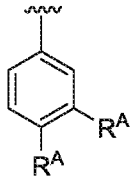
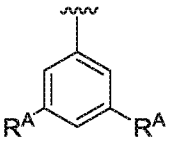
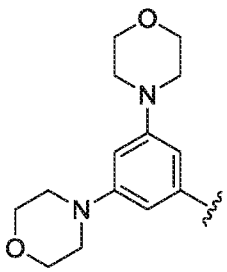

, wherein R^a is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, a nitrogen protecting group, or -(substituted or unsubstituted, C_{1-6} alkylene)-(substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur); and each instance of R^b is independently hydrogen, halogen, substituted or unsubstituted, C_{1-6} alkyl, –OH, or –Ofsubstituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, R^G is of the formula: 
,

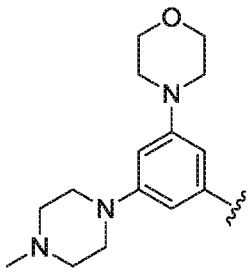
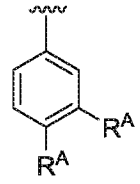
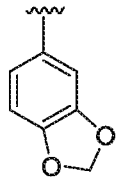
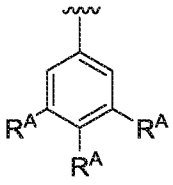
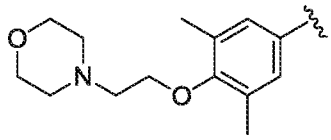
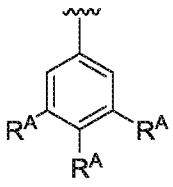

, or 
. In certain embodiments, R^G is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, or substituted or unsubstituted tetrazoly!. In certain embodiments, R^G is substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl. In certain embodiments, R^G is substituted or unsubstituted, bicyclic, 9- to 10-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

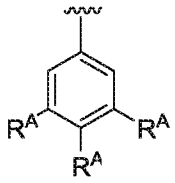
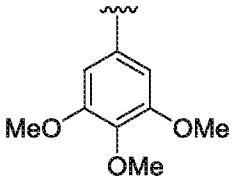
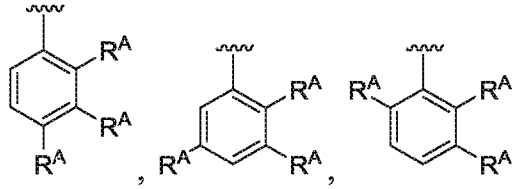
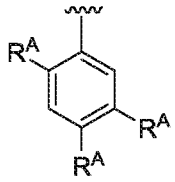
[00270] In certain embodiments, R^G is of the formula:  . Ring A is unsubstituted *(e.g.,* when k is 0) or substituted with one or more substituents R^A *(e.g.,* when k is 1, 2, 3, 4, or 5). In certain embodiments, Ring A is an unsubstituted phenyl ring. In certain embodiments, Ring A is a substituted phenyl ring. In certain embodiments, Ring A is of the formula:  , optionally wherein R^A is substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments. Ring A is of the formula:

 , *e.g.,*  or  . In certain embodiments, Ring A is of the formula:

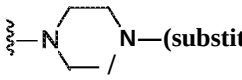
 ,  , or  , In certain embodiments, Ring A is of the formula:  , optionally wherein R^A is halogen, substituted or unsubstituted, C_{1-6} alkyl, or $-OR^a$. In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  , optionally wherein R^A is halogen, substituted or unsubstituted, C_{1-6} alkyl, or –OR". In

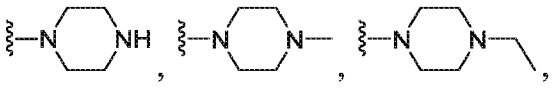
certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  , optionally wherein each instance of R^A is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, -OR\ -C(=0)R[a], -€(=0)OR [a], -C(=0)N(R[a])$_2$, or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is of the formula:  ,  ,  , or  . In certain embodiments, Ring A is of the formula:  ,  ,  , or  . In certain embodiments, Ring A is of the formula:  , optionally wherein each instance of R^A is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, -OR[a], or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is of the formula:  or

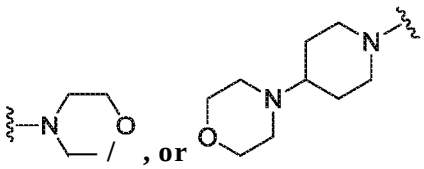

. In certain embodiments, Ring A is of the formula:  ,
wherein the two instances of R^A are joined to form a substituted or unsubstituted carbocyclic ring *(e.g.,* substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclic ring), substituted or unsubstituted heterocyclic ring *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur), substituted or unsubstituted aryl ring *(e.g.,* substituted or unsubstituted phenyl ring), or substituted or unsubstituted heteroaryl ring *(e.g.* , substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  , optionally wherein each instance of R^A is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, $-OR^a$, or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  , wherein each instance of R^A is

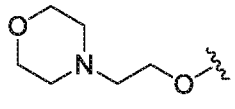
independently -OR[a]. In certain embodiments. Ring A is of the formula:  , wherein each instance of R^A is independently -0(substituted or unsubstituted alkyl). In certain embodiments, Ring A is of the formula:  . In certain embodiments. Ring A is of the formula:  , or  .

|00271| In Formula (V), Ring A may include one or more substituents R^A. In certain embodiments, all instances of R^A are the same. In certain embodiments, at least two instances of R^A are different. In certain embodiments, at least one instance of R^A is halogen *(e.g.,* F, **CI,** Br, or I). In certain embodiments, at least one instance of R^A is substituted or unsubstituted alkyl *(e.g.,* substituted or unsubstituted, **Ci_6** alkyl). In certain embodiments, at least one instance of R^A is **-CH 3.** In certain embodiments, at least one instance of R^A is **-CF 3,** unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn. In certain embodiments, at least one instance of **R^A** is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, **C i-6** alkenyl). In certain embodiments, at least one instance of R^A is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, **Ci-6** alkynyl). In certain embodiments, at least one instance of R^A is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, **3-** to **7-**membered carbocyclyl). In certain embodiments, at least one instance of **R^A** is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, **5-** to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^A is of the formula:

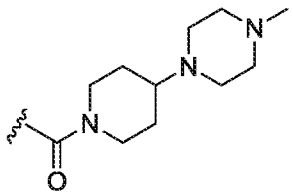


. In certain embodiments, at least one instance of R^A is of the formula: 



. In certain embodiments, at least one instance of R^A is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^A is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^A is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^A is -OR^a. In certain embodiments, at least one instance of R^A is –OH. In certain embodiments, at least one instance of R^A is –0(substituted or unsubstituted alkyl), such as –0(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, –OBn, or 

). In certain embodiments, at least one instance of R^A is –0(substituted or unsubstituted phenyl) (*e.g.*, –QPh)). In certain embodiments, at least one instance of R^A is –SR^a (*e.g.*, –SH, –Sfsubstituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^A is -$N(R^a)_2$ (*e.g.*, -NH_2, -NH(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NHMe), or –N(substituted or unsubstituted, C_{1-6} alkyl)–{substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NMe_2)). In certain embodiments, at least one instance of R^A is -CN, -SCN, or –NO_2. In certain embodiments, at least one instance of R^A is –$C(=NR^a)R^a$, --$C(=NR^a)OR^a$, or –$C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^A is –$C(=O)R^a$ or –$C(=O)OR^a$. In certain embodiments, at least one instance of R^A is --$C(=O)N(R^a)_2$ (*e.g.*, –$C(=O)NH_2$, –C(=0)NHMe, –$C(=O)NMe_2$, or



). In certain embodiments, at least one instance of R^A is –

$NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00272] Each instance of R^A, R^C, R^E, and R^x may independently include one or more substituents R^a. In certain embodiments, all instances of R^a are the same. In certain embodiments, at least two instances of R^a are different. In certain embodiments, at least one instance of R^a is H. In certain embodiments, each instance of R^a is H. In certain embodiments, at least one instance of R^a is substituted or unsubstituted acyl (*e.g.,* acetyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkyl (*e.g.,* substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^a is $-CH_3$. In certain embodiments, at least one instance of R^a is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn. In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkenyl (*e.g.,* substituted or unsubstituted, C_{1-6} alkenyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkynyl (*e.g.,* substituted or unsubstituted, C_{1-6} alkynyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl (*e.g.* , substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl (*e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is substituted or unsubstituted aryl (*e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl (*e.g.* , substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is a nitrogen protecting group (*e.g.,* Bn, Boc, Cbz, Fmoc, trifluoroacetyl, tnphenylmethyl, acetyl, or Ts) when attached to a nitrogen atom. In certain embodiments, at least one instance of R^a is an oxygen protecting group (*e.g.,* silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom. In certain embodiments, at least one instance of R^a is a sulfur protecting group (*e.g.,* acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-

sulfenyl, or triphenylmethyl) when attached to a sulfur atom. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heterocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00273] In certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, k is 3. In certain embodiments, k is 4. In certain embodiments, k is 5.

[00274] Formula (V) includes substituent R^B on the nitrogen atom that connects Rings A and B. In certain embodiments, R^B is hydrogen. In certain embodiments, R^B is substituted or unsubstituted acyl (*e.g.*, acetyl). In certain embodiments, R^B is substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn). In certain embodiments, R^B is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00275] Formula (V) includes a heteroaryl ring as Ring B that includes moieties X^A, X^B, and X^C in the heteroaryl ring system. In certain embodiments, X^A is CR^X, and each of X^B and X^C is N. In certain embodiments, X^A is CH, and each of X^B and X^C is N. In certain embodiments, X^B is CR^X, and each of X^A and X^C is N. In certain embodiments, X^B is CH, and each of X^A and X^C is N. In certain embodiments, X^C is CR^X, and each of X^A and X^B is N. In certain embodiments, X^C is CH, and each of X^A and X^B is N. In certain embodiments, X^A is N, and each of X^B and X^C is independently CR^X. In certain embodiments, X^A is N, and each of X^B and X^C is CH. In certain embodiments, X^B is N, and each of X^A and X^C is independently CR^X. In certain embodiments, X^B is N, and each of X^A and X^C is CH. In certain embodiments, X^C is N, and each of X^A and X^B is independently CR^X. In certain embodiments, X^C is N, and each of X^A and X^B is CH. In certain embodiments, each of X^A, X^B, and X^C is independently CR^X. In certain embodiments, each of X^A, X^B, and X^C is CH.

[00276] In certain embodiments, X^B is CR^X, and R^G and R^X of X^B are joined to form a substituted or unsubstituted heterocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two

atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur, further wherein at least one atom in the heterocyclic ring system is nitrogen). In certain embodiments, $\mathbf{X}^B$ is CR^X, and R^G and R^x of $\mathbf{X}^B$ are joined to form a substituted or unsubstituted heteroaryl ring *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur, further wherein at least one atom in the heteroaryl ring system is nitrogen). In certain embodiments, $\mathbf{X}^B$ is CR^X, and R^G and R^x of $\mathbf{X}^B$ are joined to form substituted or unsubstituted pyrrolyl ring.

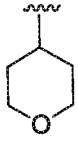
100277] In certain embodiments, all instances of R^X are the same. In certain embodiments, at least two instances of R^X are different. In certain embodiments, at least one instance of R^X is hydrogen. In certain embodiments, at least one instance of R^X is halogen *(e.g.,* **F, Cl,** Br, or **I). In** certain embodiments, at least one instance of R^X is substituted or unsubstituted alkyl *(e.g.,* substituted or unsubstituted, $\mathbf{C}_{1-6}$ alkyl). In certain embodiments, at least one instance of R^x is -C¾. In certain embodiments, at least one instance of R^X is **-CF** $_3$**,** unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn. In certain embodiments, at least one instance of R^x is substituted or unsubstituted alkenyl *(e.g.,* substituted or unsubstituted, C_{1-6} alkenyl). In certain embodiments, at least one instance of R^X is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, $\mathbf{C}_{1-6}$ alkynyl). In certain embodiments, at least one instance of R^X is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^x is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^X is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^X is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^X is substituted or unsubstituted heteroaryl *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^X is $-OR^a$ *(e.g.,* —OH, —Ofsubstituted or unsubstituted, C_{1-6} alkyl) *(e.g.,* —OMe, —OEt, -OPr,

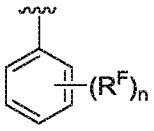
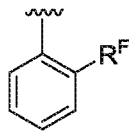
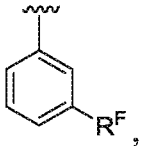
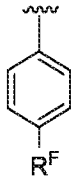
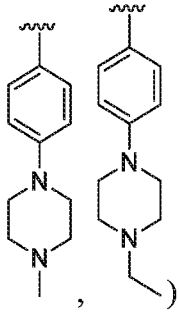
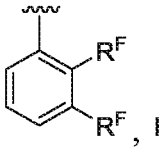
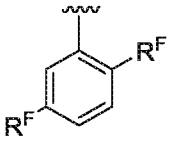
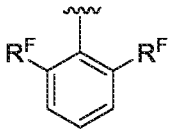
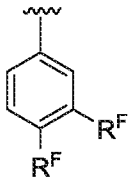
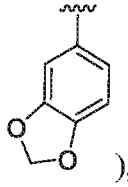
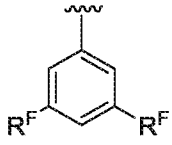
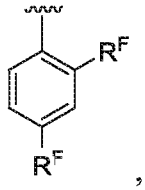
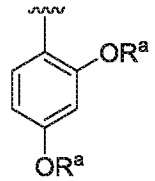
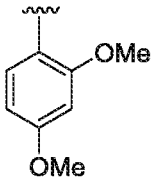
–OBu, or –OBn), or –0(substituted or unsubstituted phenyl) (*e.g.*, -GPh)). In certain embodiments, at least one instance of R^x is -SR^a (*e.g.*, –SH, -S(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -SMe, -SEt, -SPr, -SBu, or-SBn), or -S(substituted or unsubstituted phenyl) (*e.g.*, -SPh)). In certain embodiments, at least one instance of R^x is -$N(R^a)_2$ (*e.g.*, -NH_2, -NH(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NHMe), or –N(substituted or unsubstituted, C_{1-6} alkyl)–{substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NMe_2)). In certain embodiments, at least one instance of R^x is –CN, -SCN, or -NO_2. In certain embodiments, at least one instance of R^x is –$C(=NR^a)R^a$, -$C(=NR^a)OR^a$, or –$C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^x is -$C(=O)R^a$, -$C(=O)OR^a$, or-$C(=O)N(R^a)_2$ (*e.g.*, -$C(=O)NH_2$, -C(=O)NHMe, or-C(=())NMe_2). In certain embodiments, at least one instance of R^X is -$NR^aC(=O)R^a$, –$NR^aC(=O)OR^a$, or –$NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^x is -$OC(=O)R^a$, -$OC(=O)OR^a$, or -$OC(=O)N(R^a)_2$.

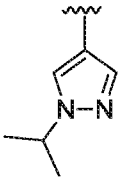
100278 1 Formula (V) includes substituent R^c on Ring B. In certain embodiments, R^c is hydrogen. In certain embodiments, R^c is halogen (*e.g.*, F, CI, Br, or I). In certain embodiments, R^C is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, R^C is -CH_3. In certain embodiments, R^c is -CF_3, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn. In certain embodiments, R^C is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkenyl). In certain embodiments, R^C is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkynyl). In certain embodiments, R^C is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^C is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^c is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^C is substituted or unsubstituted phenyl. In certain embodiments, R^c is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^c is -OR^a (*e.g.*, -OH, -0(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –

0(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, R^C is -SR^a (*e.g.*, –SH, –Sfsubstituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or -SBn), or -Sisubstituted or unsubstituted phenyl) (*e.g.*, -SPh)). In certain embodiments, R^C is -$N(R^a)_2$ (*e.g.*, –NH_2, -NH(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NHMe), or -N(substituted or unsubstituted, C_{1-6} alkyl)-(substituted or unsubstituted, C_{1-6} alkyl) (*e.g.*, -NMe_2)). In certain embodiments, R^c is -CN, --SCN, or –NO_2. In certain embodiments, R^C is –$C(=NR^a)R^a$, –$C(=NR^a)OR^a$, or -$C(=NR^a)N(R^a)_2$. In certain embodiments, R^c is -$C(=O)R^a$, –$C(=O)OR^a$, or –$C(=O)N(R^a)_2$ (*e.g.*, -$C(=O)NH_2$,-C(=O)NHMe, or -$C(=O)NMe_2$). In certain embodiments, R^C is -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, or -$NR^aC(=O)N(R^a)_2$. In certain embodiments, R^C is –$OC(=O)R^a$, –$OC(=O)OR^a$, or –$OC(=O)N(R^a)_2$.

100279] Formula (V) includes substituent R^D on a nitrogen atom of the urea or carbamate moiety. In certain embodiments, R^D is hydrogen. In certain embodiments, R^D is substituted or unsubstituted alkyl, such as substituted or unsubstituted, C_{1-6} alkyl (*e.g.*, -CH_3, –CF_3, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn). In certain embodiments, R^D is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkenyl). In certain embodiments, R^D is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkynyl). In certain embodiments, R^D is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^D is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^D is substituted or unsubstituted oxetanyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted tetrahydro furanyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted pyrrol idinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted morpholinyl.

In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^D is substituted or unsubstituted phenyl. In certain

embodiments, R^D is of the formula:  , wherein each instance of R^F is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and n is 0, 1, 2, 3, 4, or 5. In certain embodiments, R^D is of the formula:  ,  , or  (*e.g.*, ). In certain embodiments, R^D is of the formula:  ,  ,  ,  (*e.g.*, ), or  . In certain embodiments, R^D is of the formula:  ,  (*e.g.*, ). In certain embodiments, R^D is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^D is substituted or unsubstituted 1-pyrazolyl, substituted or unsubstituted 3-pyrazolyl, or

substituted or unsubstituted 4-pyrazolyl *(e.g.,* 

). In certain embodiments, R^D is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazo!yl, substituted or unsubstituted isothiazolyl, or substituted or unsubstituted tetrazolyl. In certain embodiments, R^D is substituted or unsubstituted pyridyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

100280] In certain embodiments, R^D is a nitrogen protecting group *(e.g.,* Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

100281 1 Formula (V) includes divalent moiety Y. In certain embodiments, Y is -0-. In certain embodiments, Y is $-NR^Y-$. In certain embodiments, Y is -NH-.

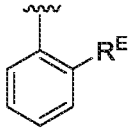
100282] In certain embodiments, R^Y is hydrogen. In certain embodiments, R^Y is substituted or unsubstituted acyl *(e.g.,* acetyl). In certain embodiments, R^Y is substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn). In certain embodiments, R^Y is a nitrogen protecting group *(e.g.,* Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

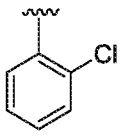
100283 1 Formula (V) includes divalent moiety Z. In certain embodiments, Z is a bond. In certain embodiments, Z is $-C(R^Z)_2-$. In certain embodiments, Z is $-CH_2-$. In certain embodiments, Z is –CHF– or $-CF_2-$.

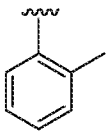
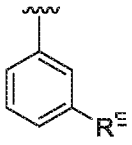
100284] In certain embodiments, the two instances of R^Z are the same. In certain embodiments, the two instances of R^Z are not the same. In certain embodiments, at least one instance of R^Z is hydrogen. In certain embodiments, each instance of R^Z is hydrogen. In certain embodiments, at least one instance of R^Z is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one instance of R^Z is substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* $–CH_3$, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn).

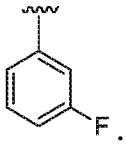
100285] In certain embodiments, -Y-Z- is $-N(R^Y)-$. In certain embodiments, -Y–Z– is –NH-. In certain embodiments, -Y-Z- is -N(Me)-. In certain embodiments,

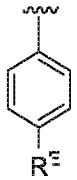
–Y–Z– is -O—. In certain embodiments, –Y–Z– is –N(R^Y)-C(R^Z)$_2$– *(e.g.,* –N(R^Y)--CH_2-). In certain embodiments, –Y–Z– is ---NH--CH_2---. In certain embodiments, --Y--Z- is -N(Me)-CH_2-. In certain embodiments, -Y-Z- is -0-C(R^Z)$_2$- *(e.g.,* -0-CH_2-).

[00286] Formula (V) includes a phenyl ring as Ring C, which is unsubstituted *(e.g.,* when m is 0) or substituted with one or more substituents R^E *(e.g.,* when m is 1, 2, 3, 4, or 5). In certain embodiments, Ring C is an unsubstituted phenyl ring. In certain embodiments, Ring C is a substituted phenyl ring. In certain embodiments, Ring C is of the formula: 

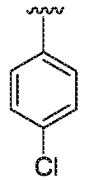
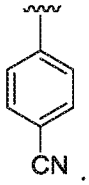
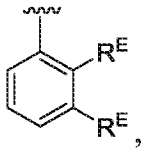
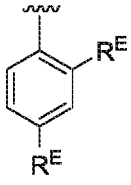
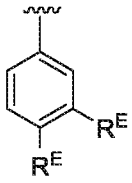
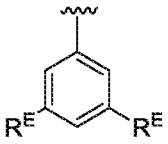
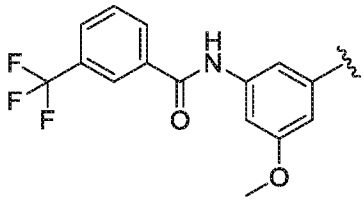
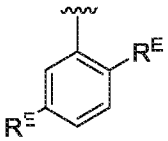
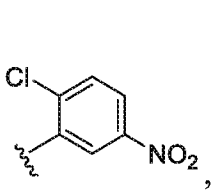
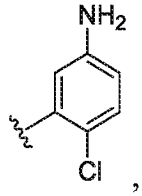
, optionally wherein R^E is halogen, substituted or unsubstituted, C_{1-6} alkyl, -OR^a, -N(R^a)$_2$, -C(=0)R^a, -C(=0)OR^a, -C(=0)N(R^a)$_2$, -NR^{a}C(=0)R^a, –NR^{a}C(==0)OR^a, --NR^{a}C(=0)N(R^a)$_2$, -NR^{a}S(=0)R^a, –NR^{a}S(=0)OR^a, -NR^{a}S(=0)N(R^a)$_2$, -NR^{a}S(=0)$_2$R^a, -NR^{a}S(=0)$_2$OR^a, -NR^{a}S(=0)$_2$N(R^a)$_2$, -OC(=0)R^a, –OC(=0)OR^a, –OC(=0)N(R^a)$_2$, -CN, -SCN, or –N0$_2$. In certain embodiments, Ring C is of the formula: 

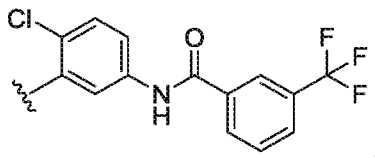
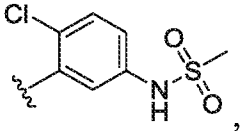
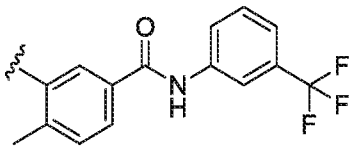
or 
. In certain embodiments, Ring C is **of** the formula: 

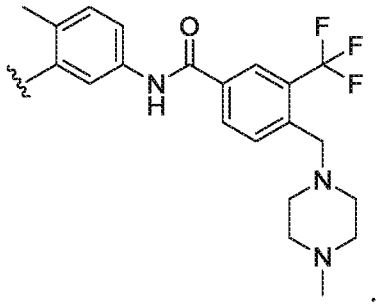
, optionally wherein R^E is halogen, substituted or unsubstituted, C_{1-6} alkyl, –OR^a, –N(R^a)$_2$, –C(=0)R^a, –C(=0)OR^a, –C(=0)N(R^a)$_2$, –NR^{a}C(=0)R^a, -NR^{a}C(-0)OR^a, -NR^{a}C(-0)N(R^a)$_2$, -NR^{a}S(-0)R^a, –NR^{a}S(-0)OR^a, -NR^{a}S(=0)N(R^a)$_2$, –NR^{a}S(=0)$_2$R^a, –NR^{a}S(=O)$_2$0 R^a, –NR^{a}S(=0)$_2$N(R^a)$_2$, –OC(=0)R^a, –OC(=0)OR^a, –OC(=0)N(R^a)$_2$, -CN, -SCN, or –N0$_2$. In certain embodiments, Ring C is of the formula: 

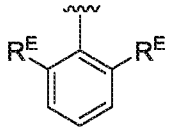
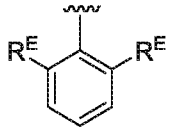
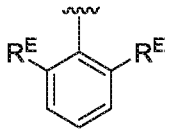
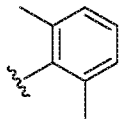
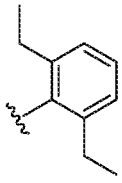
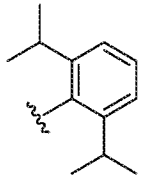
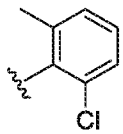
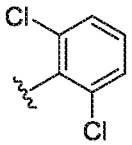
. In certain embodiments, Ring C is **of** the formula: 

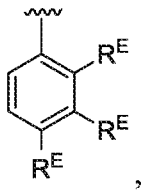
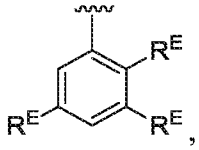
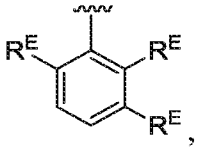
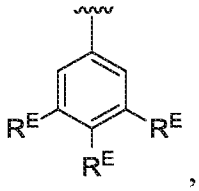
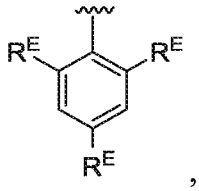
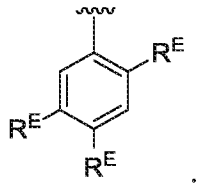
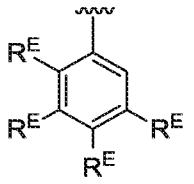
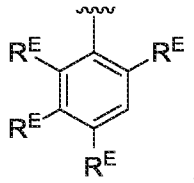
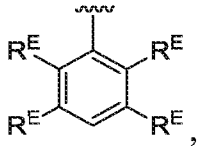
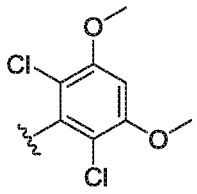
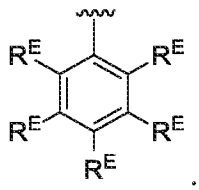
, optionally wherein R^E is halogen, substituted or unsubstituted, C_{1-6} alkyl, –OR^a, -N(R^a)$_2$, –C(=0)R^a, –€(=0)OR^a, –C(=0)N(R^a)$_2$, –NR^{a}C(=0)R^a, –NR^{a}C(=O)0R^a, -NR^{a}C(-0)N(R^a)$_2$, –NR^{a}S(=0)R^a, –NR^{a}S(=0)OR^a, -NR^{a}S(-0)N(R^a)$_2$, -NR^{a}S(-0)$_2$R^a, –NR^{a}S(=0)$_2$OR^a, –NR^{a}S(=0)$_2$N(R^a)$_2$, –OC(=0)R^a, -OC(=0)OR^a, –OC(=0)N(R^a)$_2$, --

CN, –SCN, or –NO_2. In certain embodiments, Ring C is of the formula:  or  . In certain embodiments, Ring C is of the formula:  ,  , or  . In certain embodiments, Ring C is of the formula:  , optionally wherein each instance of R^E is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, -OR^a, -$N(R^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)N(R^a)_2$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)N(R^a)_2$, -$NR^aS(=O)R^a$, –$NR^aS(=O)_2R^a$, -$NR^aS(=O)_2N(R^a)_2$, –$OC(=O)R^a$, –$OC(=O)OR^a$, –$OC(=O)N(R^a)_2$, -CN, -SCN, or -NO_2. In certain embodiments, Ring C is of the formula:  . In certain embodiments. Ring C is of the formula:  , optionally wherein each instance of R^E is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, –OR^a, -$N(R^a)_2$, –$C(=O)R^a$, -$C(=O)OR^a$, –$C(=O)N(R^a)_2$, –$NR^aC(=O)R^a$, –$NR^aC(=O)OR^a$, –$NR^aC(=O)N(R^a)_2$, -$NR^aS(=O)R^a$, –$NR^aS(=O)OR^a$, –$NR^aS(=O)N(R^a)_2$, -$NR^aS(=O)_2R^a$, –$NR^aS(=O)_2OR^a$, –$NR^aS(=O)_2N(R^a)_2$, –$OC(=O)R^a$, **-$OC(=O)OR^a$, -$OC(=O)N(R^a)_2$, -CN,** -SCN, or-**NO_2.** In certain embodiments, Ring C is of the formula:  ,  ,




, or

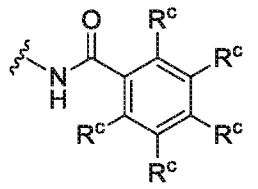

. In certain embodiments, Ring C is of the formula:


. In certain embodiments, Ring C is of the formula:  ,
wherein each instance of R^E is independently substituted or unsubstituted alkyl. In certain embodiments, Ring C is of the formula:  , wherein each instance of R^E is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-NR^aS(=O)R^a$, $-NR^aS(=O)OR^a$, $-NR^aS(=O)N(R^a)_2$, $-NR^aS(=G)_2R^a$, $-NR^aS(=O)_2OR^a$, $-NR^aS(=O)_2N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)N(R^a)_2$, $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  or  . In certain embodiments, Ring C is of the formula:  In certain embodiments, Ring C is of the formula:  In certain embodiments, Ring C is of the formula:






, or  . In certain embodiments, Ring C is of the formula:  or  . In certain embodiments, Ring C is of the formula:  , optionally wherein each instance of R^E is independently halogen, substituted or unsubstituted, C_{1-6} alkyl, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-NR^aS(=O)R^a$, $-NR^aS(=O)OR^a$, $-NR^aS(=O)N(R^a)_2$, $-NR^aS(=O)_2R^a$, $-NR^aS(=O)_2OR^a$, $-NR^aS(=O)_2N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)N(R^a)_2$, $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  .

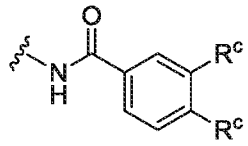
[00287] In Formula (V), Ring C may include one or more substituents R^E. In certain embodiments, all instances of R^E are the same. In certain embodiments, at least two instances of R^E are different. In certain embodiments, at least one instance of R^E is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^E is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^E is $-CH_3$. In certain embodiments, at least one instance of R^E is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, perfluorobutyl, or Bn. In certain embodiments, at least one instance of R^E is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted, C_{1-6} alkenyl). In certain embodiments, at least one

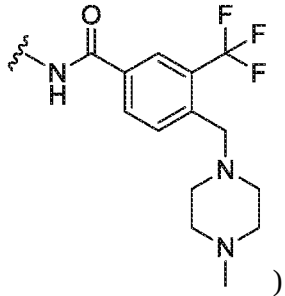
instance of R^E is substituted or unsubstituted alkynyl *(e.g.,* substituted or unsubstituted, C_{i-6} alkynyl). In certain embodiments, at least one instance of R^E is substituted or unsubstituted carbocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^E is substituted or unsubstituted heterocyclyl *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^E is substituted or unsubstituted aryl *(e.g.,* substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^E is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^E is substituted or unsubstituted heteroaryl *(e.g.,* substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^E is -OR^a *(e.g.,* -OH, –<)(substituted or unsubstituted, C_{1-6} alkyl) *(e.g.,* -QMe, –OEt, –OPr, –OBu, or –OBn), or –<)(substituted or unsubstituted phenyl) *(e.g.,* –OPh)). In certain embodiments, at least one instance of R^E is -SR^a *(e.g.,* -SH, -S(substituted or unsubstituted, C_{1-6} alkyl) *(e.g.,* -SMe, -SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) *(e.g.,* -SPh)). In certain embodiments, at least one instance of R^E is -$N(R^a)_2$ *(e.g.,* -NH_2, –NHfsubstituted or unsubstituted, C_{1-6} alkyl) *(e.g.,* -NHMe), or –N(substituted or unsubstituted, C_{1-6} alkyl)–{substituted or unsubstituted, C_{1-6} alkyl) *(e.g.,* -NMe_2)). In certain embodiments, at least one instance of R^E is -CN, –SCN, or –NO_2. In certain embodiments, at least one instance of R^E is –$C(=NR^a)R^a$, –$C(=NR^a)OR^a$, or -$C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^E is -$C(=O)R^a$, -$C(=O)OR^a$, or -$C(=O)N(R^a)_2$ *(e.g.,* -C(=O)NH_2, -C(=O)NHMe, or -C(=O)NMe_2). In certain embodiments, at least one instance of R^E is -$NR^aC(=O)R^a$, optionally wherein each instance of R^a is independently H, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted phenyl, or a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^E is –$NHC(=O)R^a$, wherein R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^E is of the formula:



,

optionally wherein each instance of R^c is independently H, halogen, substituted or unsubstituted, C_{i-6} alkyl, --OH, or --O(substituted or unsubstituted, Ci-6 alkyl). In certain embodiments, at least one instance of R^E is of the formula:

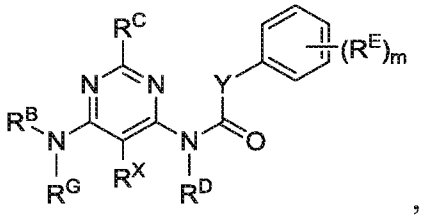




(e.g.,). In certain embodiments, at least one instance of R^E is $-NR^aC(=O)OR^a$ or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^E is $-OC(=O)R^a$, $-OC(=O)OR^a$ or $-OC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^E is $-NR^aS(=O)R^a$, $-NR^aS(=O)OR^a$, or $-NR^aS(=O)N(R^a)_2$, optionally wherein each instance of R^a is independently H, substituted or unsubstituted, C_{i-6} alkyl, nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom. In certain embodiments, at least one instance of R^E is $-NR^aS(=O)_2R^a$, $-NR^aS(=O)_2OR^a$, or $-NR^aS(=O)_2N(R^a)_2$, optionally wherein each instance of R^a is independently H, substituted or unsubstituted, C_{1-6} alkyl, nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom. In certain embodiments, at least one instance of R^E is $-NHS(=O)_2R^a$, optionally wherein R^a is substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is $-NHS(=O)_2Me$.

100288] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.

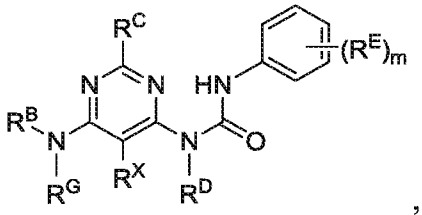
[00289] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

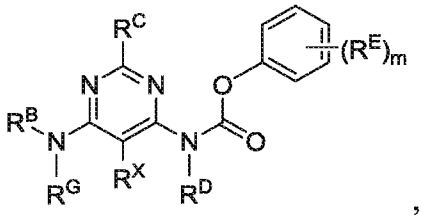
[00290] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

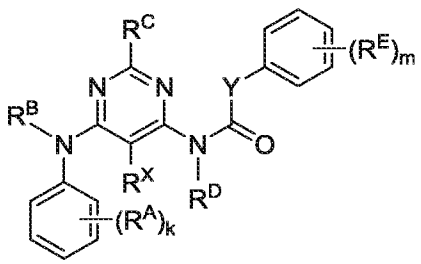
[00291] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

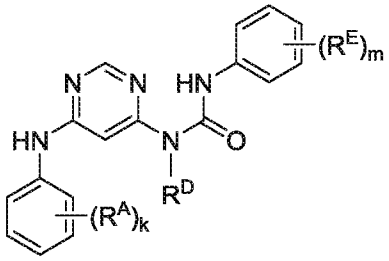
[00292] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

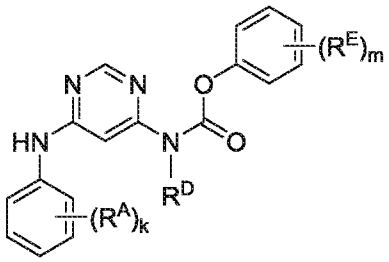
[00293] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

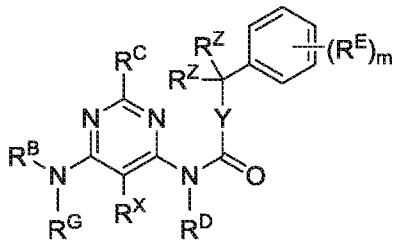
[00294] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

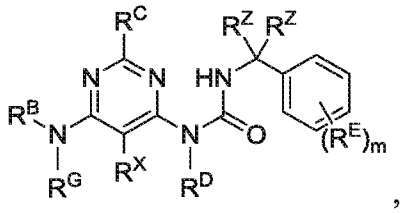
[00295] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

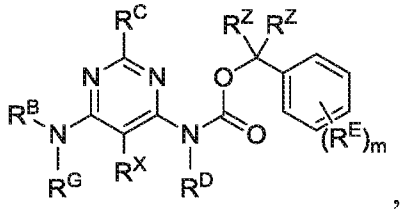
[00296] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

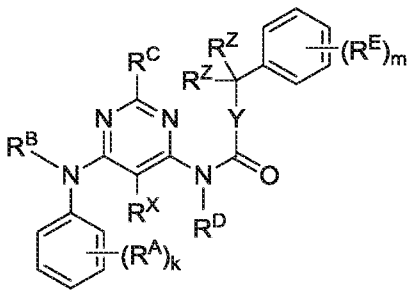
[00297] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

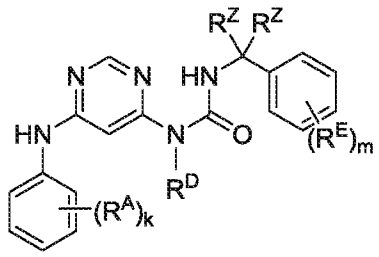
[00298] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

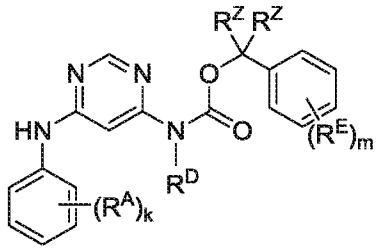
[00299] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

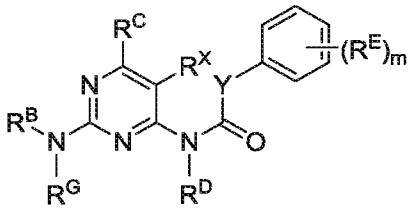
[003001 In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

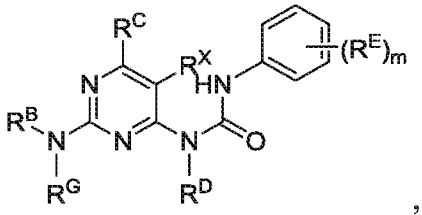
[00301 1 In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crysta!, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

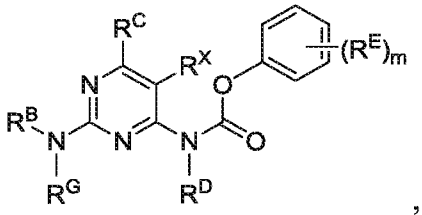
[00302] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

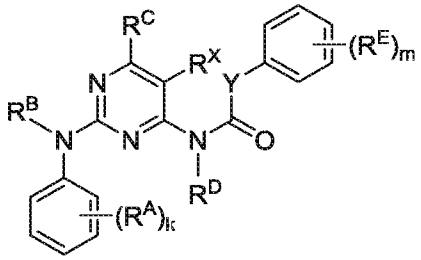
[003031 In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

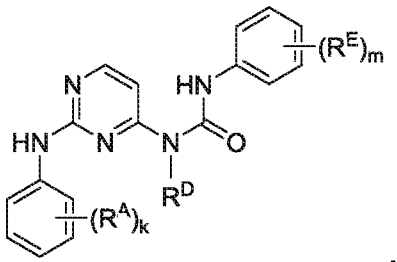
[00304| In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

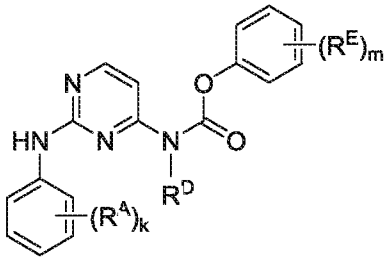
[003051 In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

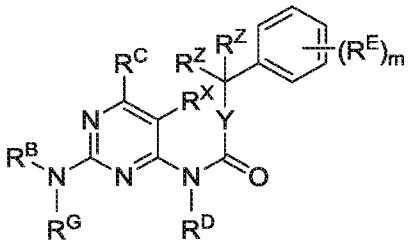
[00306] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

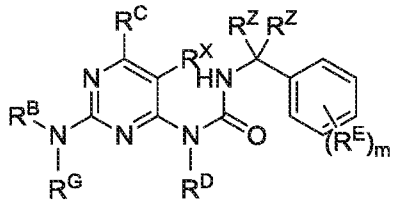
[003071 In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

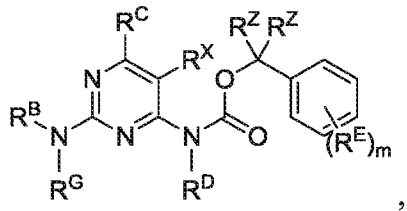
[00308] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

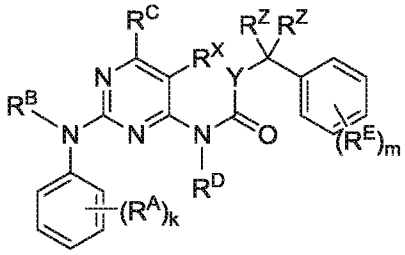
[00309] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

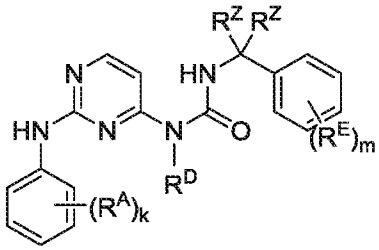
[00310] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

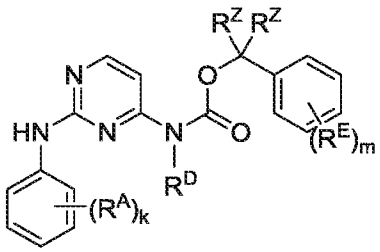
[00311] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

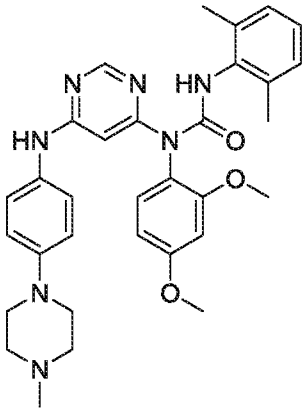
[00312] In certain embodiments, the compound of Formula (V) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

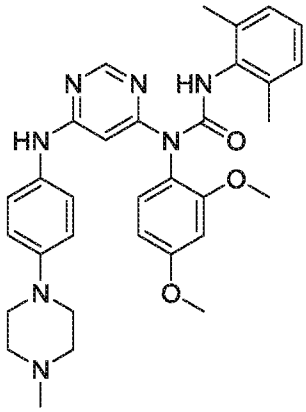
1003131 In certain embodiments, the compound of Formula (V) is not of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

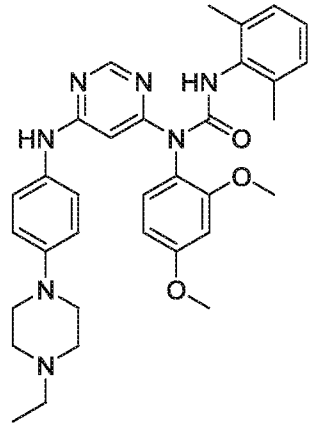
[00314| In certain embodiments, the compound of Formula (V) is of the formula:



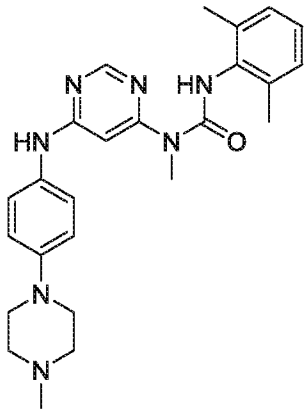
(V-1 or HG-9-91-01),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

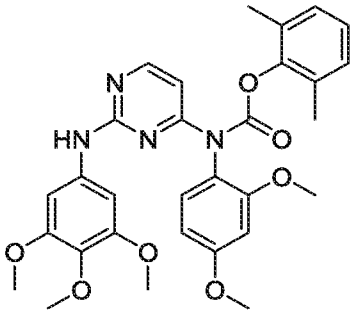
[00315] In certain embodiments, the compound of Formula (V) is of the formula:



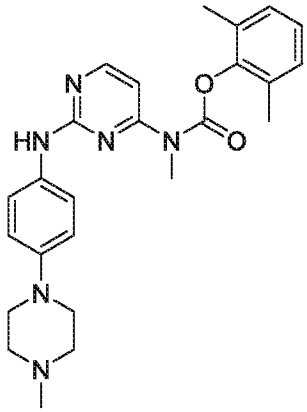
(**V-2** or HG-10-11-01),



(**V-3** or HG-9-148-01),



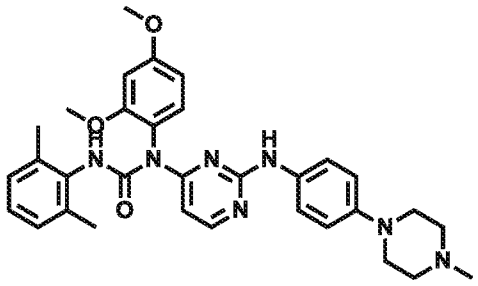
(V-4 or HG-9-88-01),



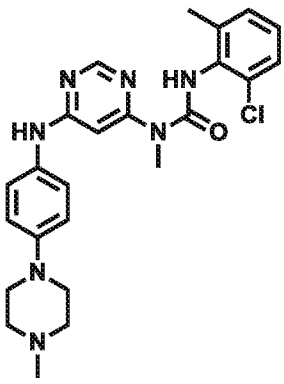
(V-5 or HG-9-150-01),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

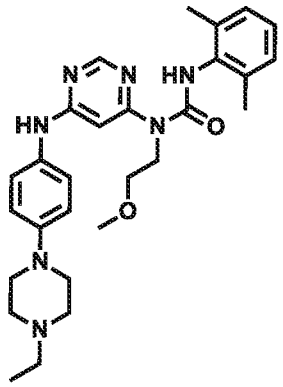
[0031 6] In certain embodiments, the compound of Formula (V) is of the formula:



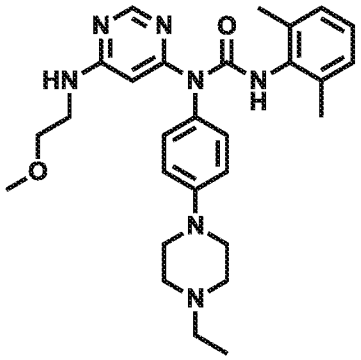
(HG-9-96-01),



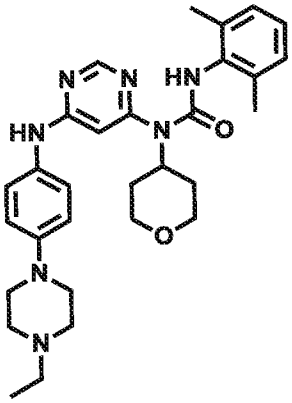
(HG-9- 148-02),



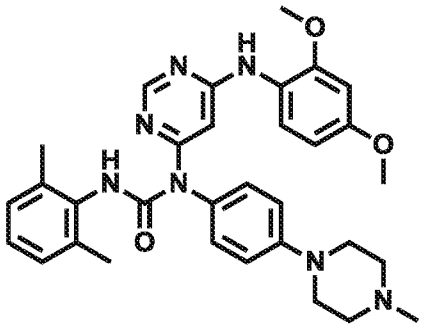
(HG-10-8-01),



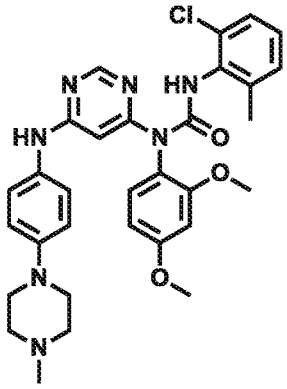
(HG-10-8-02),



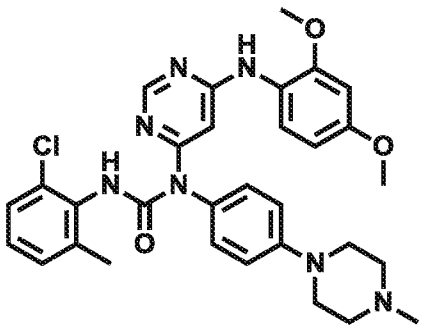
(HG-10-9-01),



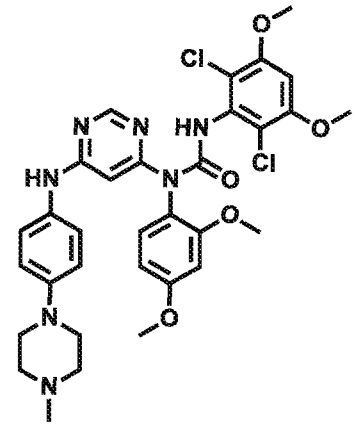
(HG-10-15-02),



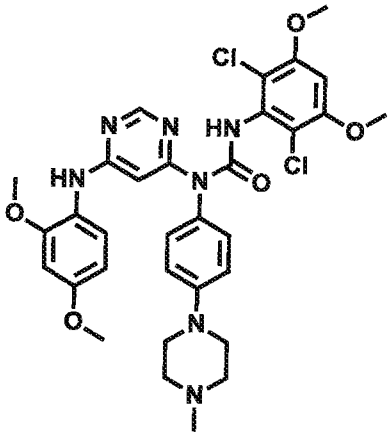
(HG-1 0-1 5-03),



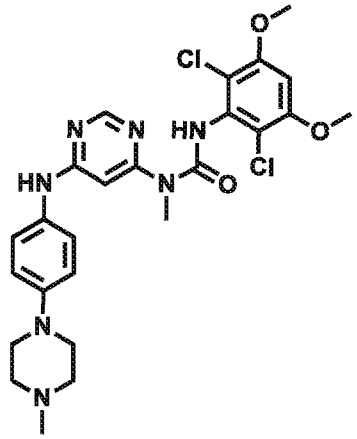
(HG-1 0-1 5-04),



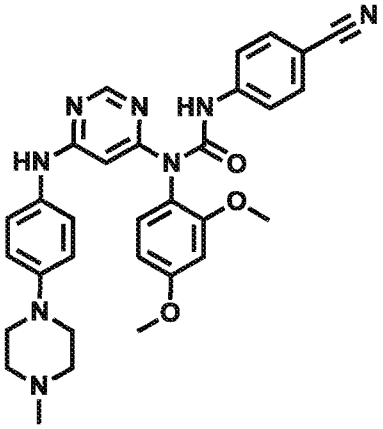
(HG-10-27-01),



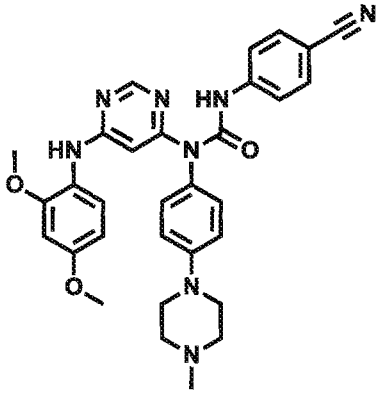
(HG-10-27-02),



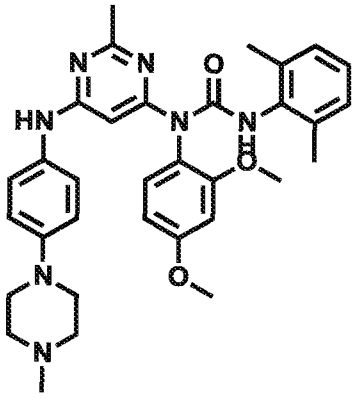
(HG-10-28-01),



(HG-10-31-01),



(HG-1 0-3 1-02),



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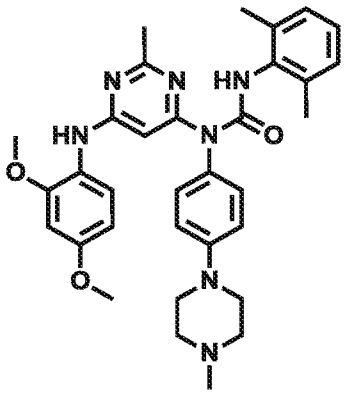

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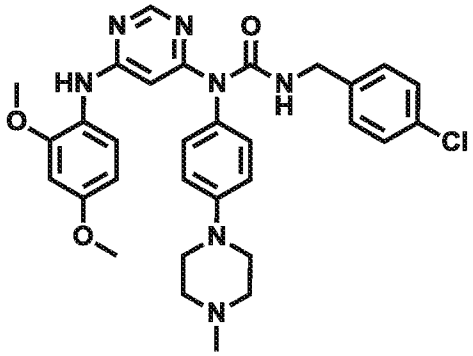
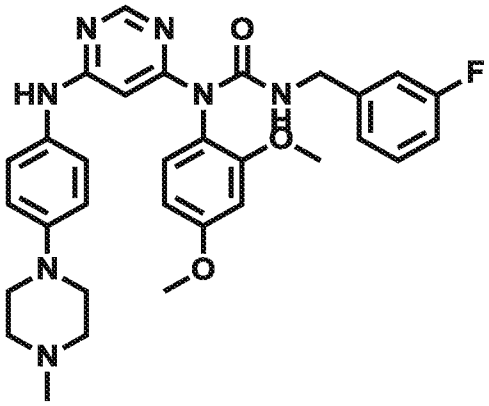
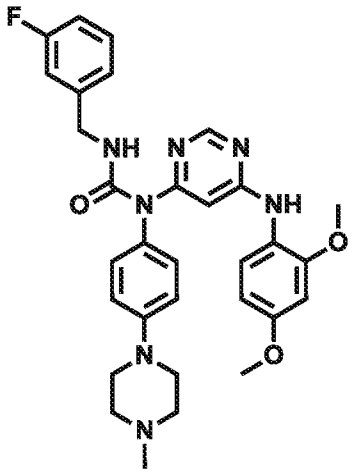


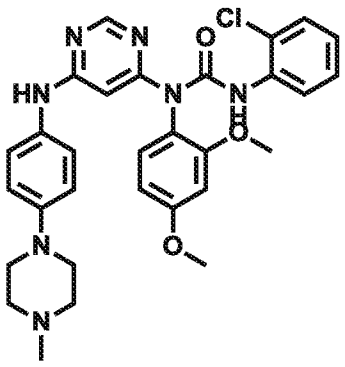
(HG 10-59-02),



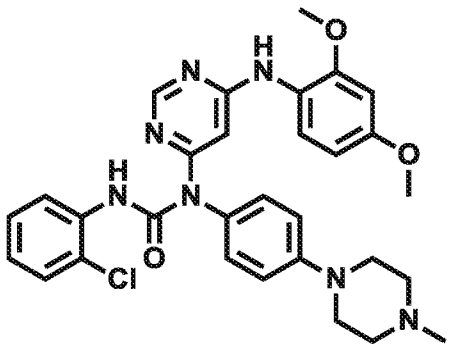
(HG 10-60-01 or HG-10-60-01),



(HG 10-60-02),



(HG 10-61-01 or HG-10-61-01),



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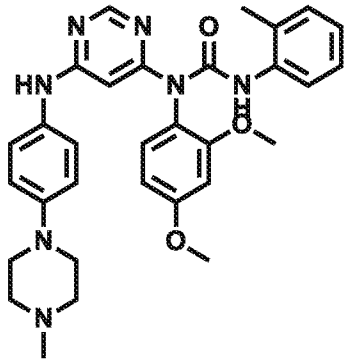
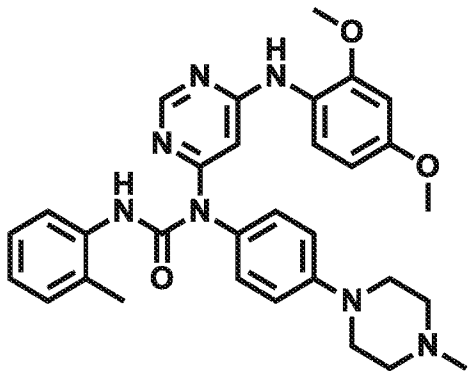
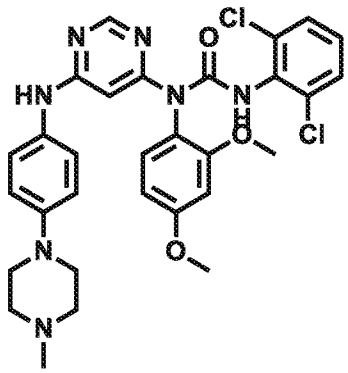


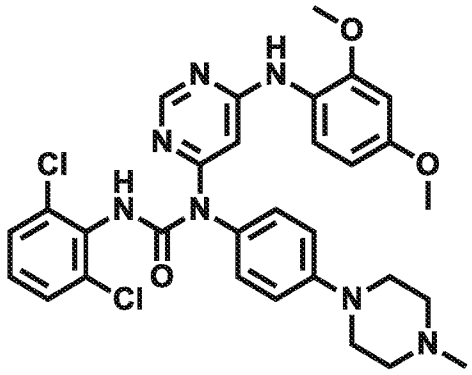
(HG 10-62-01 or HG- 10-62-01),



(HG 10-62-02 or HG- 10-62-02),



(HG 10-63-01 or HG-10-63-01),



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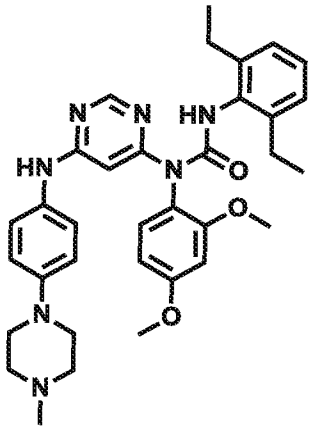
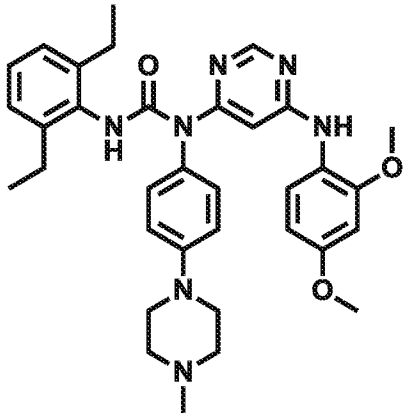
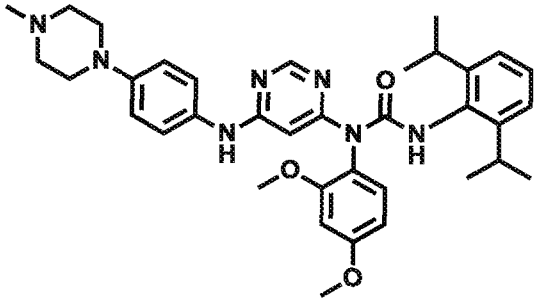


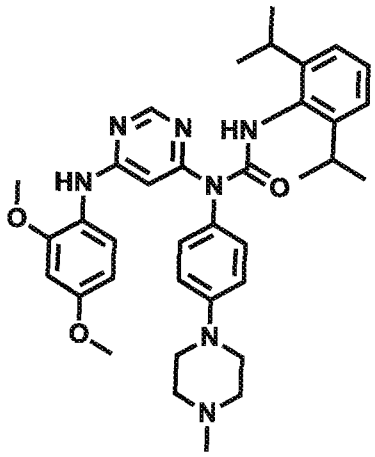
(HG 10-64-01 or HG- 10-64-01),



(HG 10-64-02 or HG- 10-64-02),



(HG 10-65-01),



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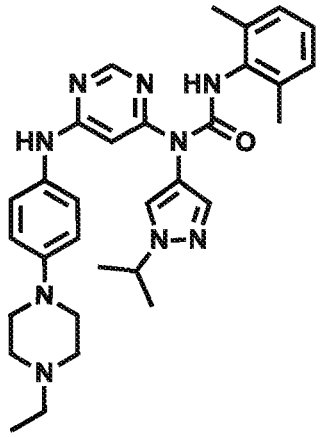

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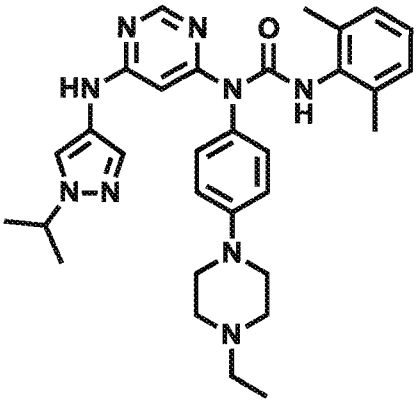

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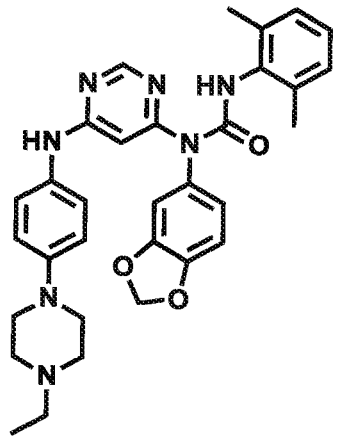

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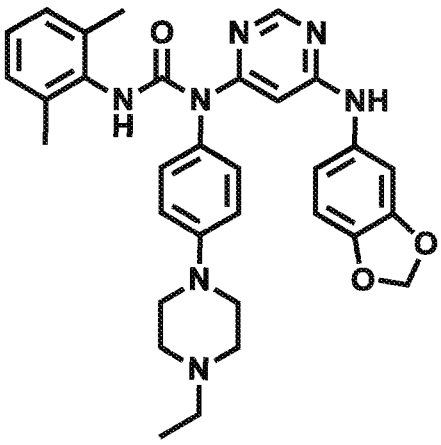

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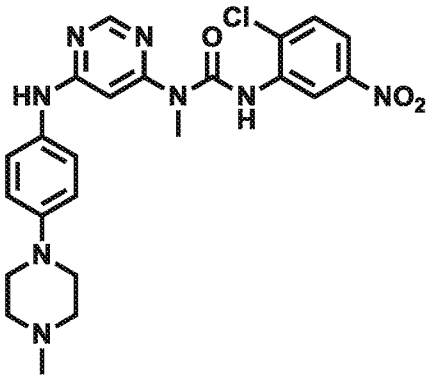

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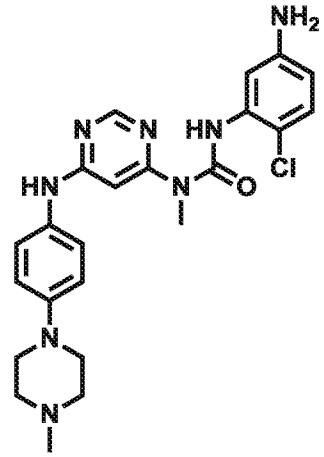

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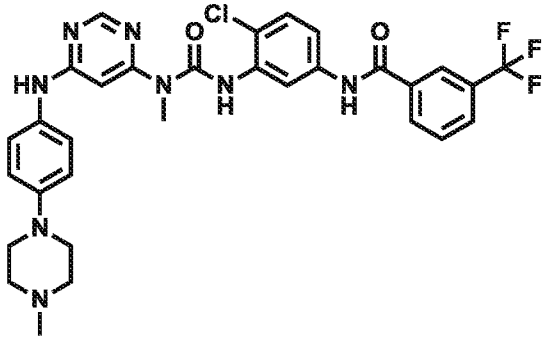

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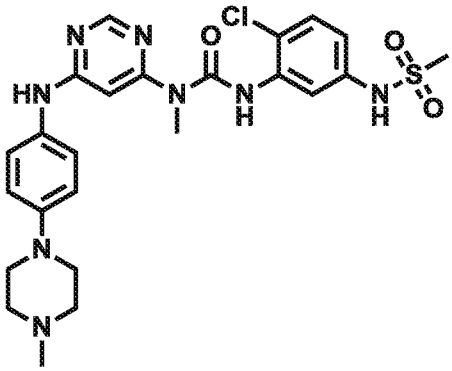
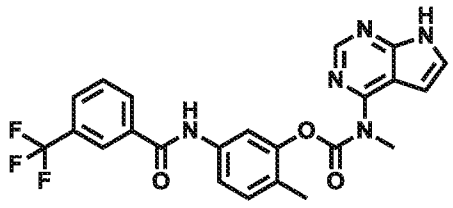


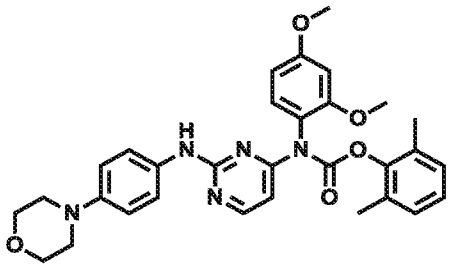
(HG-1 1-22-01),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

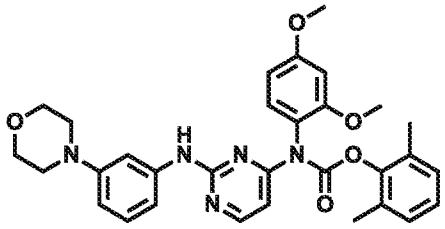
[003 17 1 In certain embodiments, the compound of Formula (V) is of the formula:



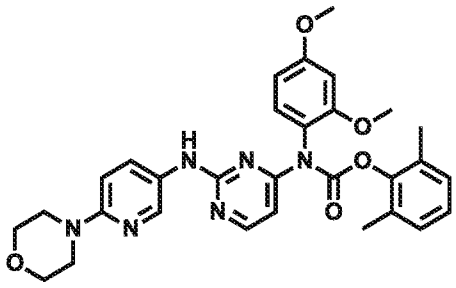
(HG-3-09-01),



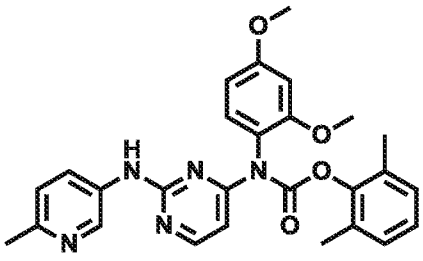
(HG--9-87-02),



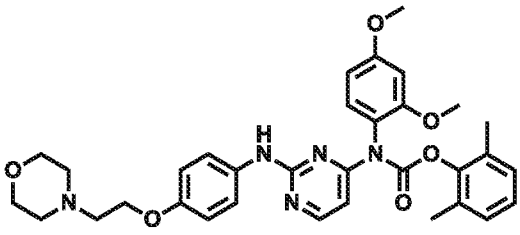
(HG-9-87-03),



(HG-9-87-04),



(HG-9-88-02),



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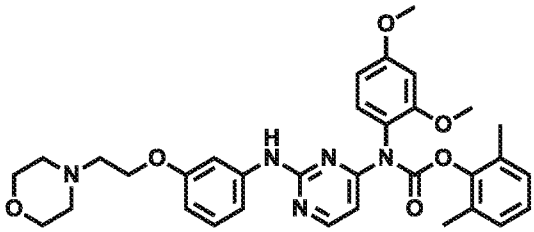

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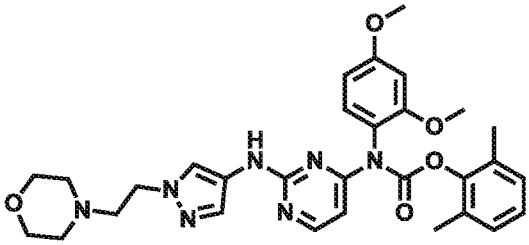
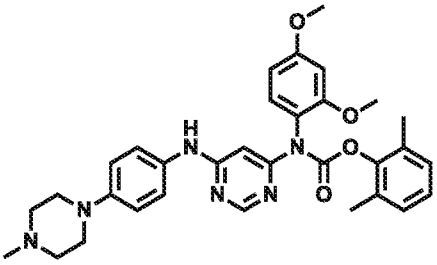
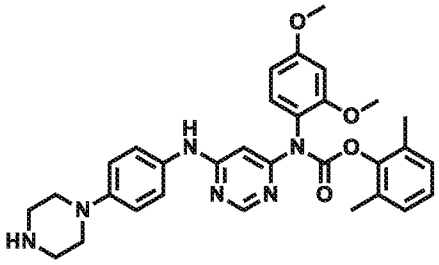


(HG-9-88-05),



(HG-9-90-01),



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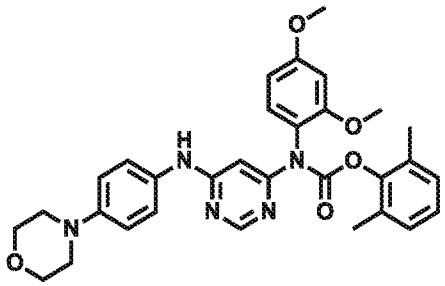

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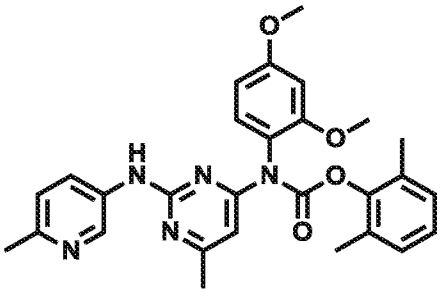
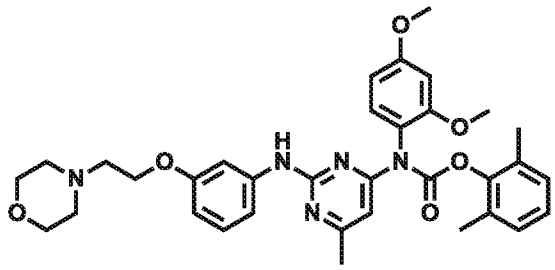


(HG-9-139-02),



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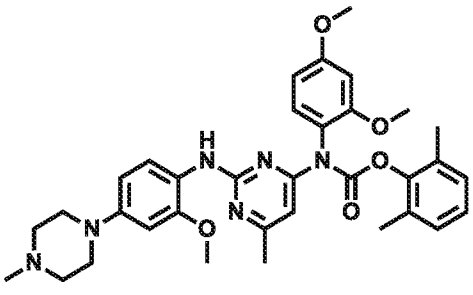

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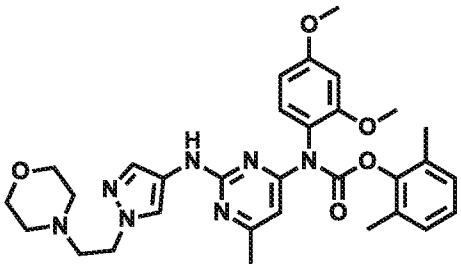
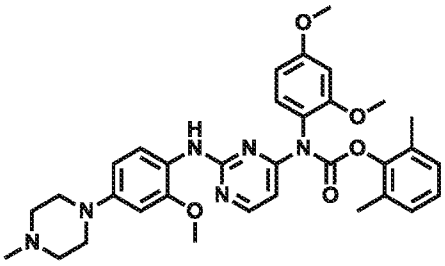


(HG-9-139-05),



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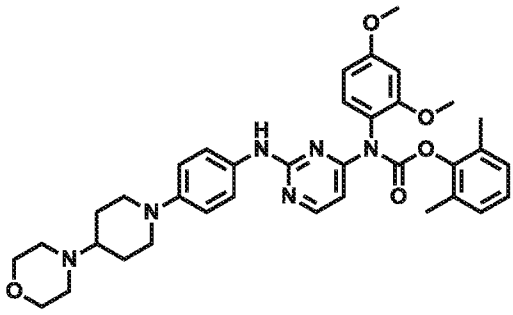

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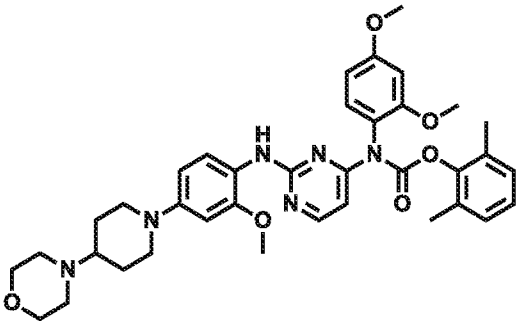

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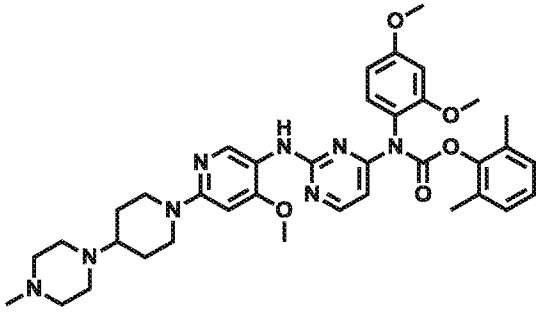
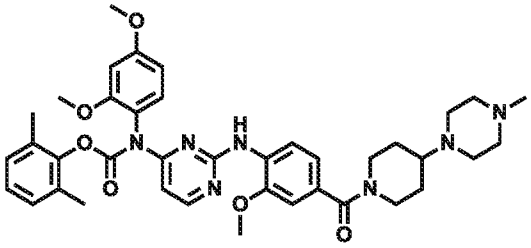


(HG-9-144-03),



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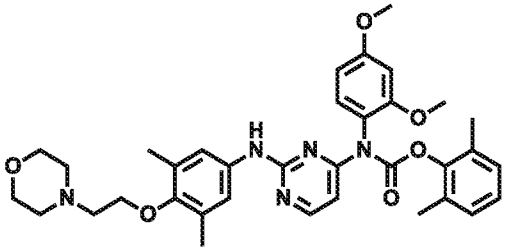
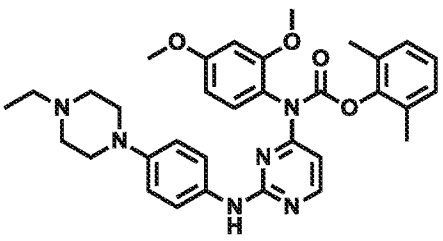


(HG-9-144-05),



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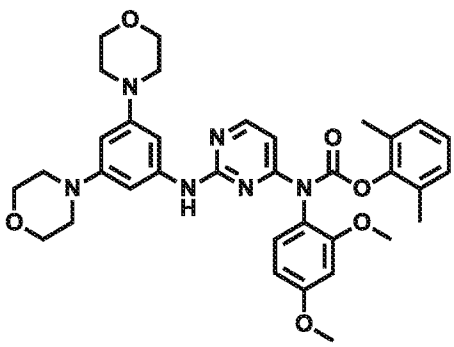
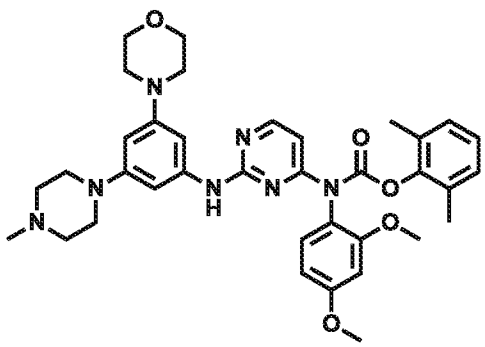
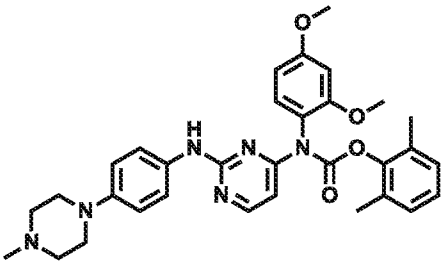


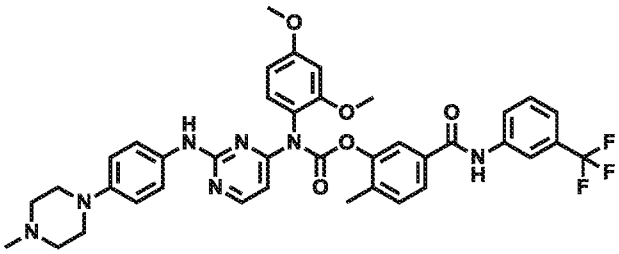
(HG-11-6-01),



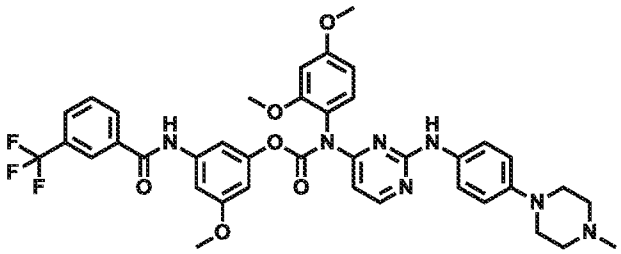
(HG-11-6-02),



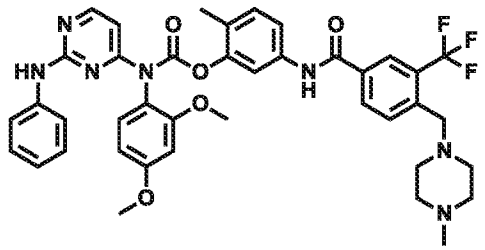
(WH-4-023),



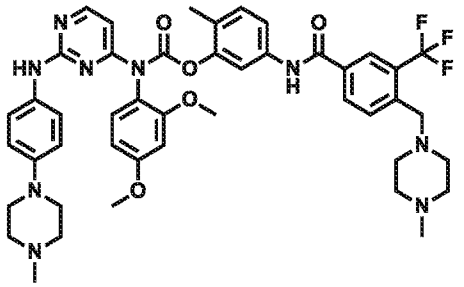
(WH-4-025),



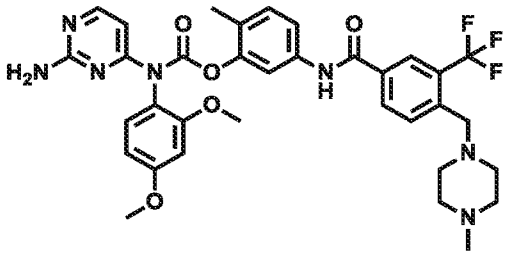
(WH4-113),



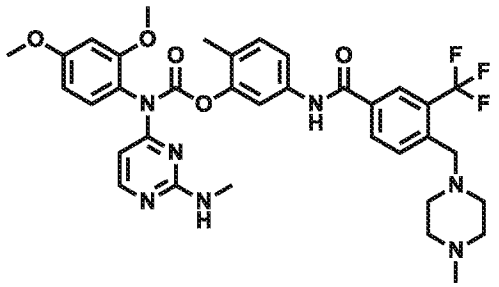
(WH4-124-1),



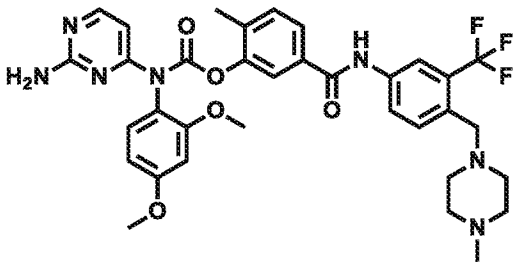
(WH4-124-2),



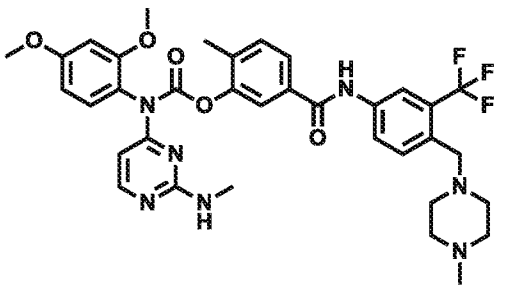
(WH4-199-1),



(WH4-199-2),



(WH4-200-1),

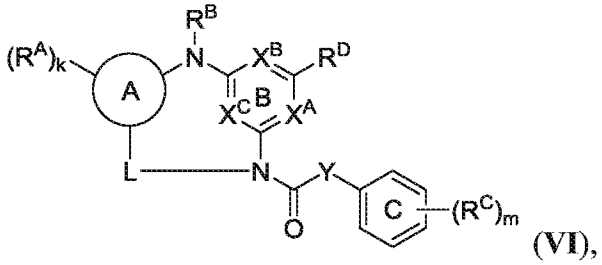


(WH4-200-2),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

Compounds of Formula (VI)

[003181 In one aspect, the present disclosure provides macrocyclic compounds of Formula **(VI)** for use in the present invention:



(VI),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein:

Ring A is a substituted or unsubstituted phenyl ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur;

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^a groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, or 4;

L is a substituted or unsubstituted, saturated or unsaturated C_{3-10} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -0-, -S-, $-NR^N-$, -N=, or =N-, wherein each instance of R^N is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^C is independently N or CR^X, wherein R^X is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=0)R^a$, $-C(=0)OR^a$, $-C(=0)N(R^a)_2$, $-N0_2$, $-NR^aC(=0)R^a$, $-NR^aC(=0)OR^a$, $-NR^aC(=0)N(R^a)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$;

Y is -O- or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

or when Y is $-NR^Y-$ and X^A is CR^X, R^Y and R^X of X^A are joined to form a substituted or unsubstituted, monocyclic, 5- to 7-membered heterocyclic ring that is fused with Ring B;

each instance of R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=0)R^a$,

- C(=0)OR^a, - C(=0)N(R^a)$_2$, -N0 $_2$, –NR^{a}C(=0)R ^{a}, -NR ^{a}C(O)0R ^{a}, - NR^{a}C(=0)N(R ^{a})$_2$, –OC(=0)R ^{a}, –OC(=0)OR ^{a}, or –OC(=0)N(R ^{a})$_2$;

m is 0, 1, 2, 3, 4, or 5; and

R^D is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, –OR^a, -N(R ^{a})$_2$, –SR^a, –CN, -SCN, –C(=NR^a)R^a, –C(=NR^a)OR^a, –C(=NR^a)N(R^a)$_2$, - C(=0)R^a, –C(=O)0R ^{a}, - C(=0)N(R ^{a})$_2$, -NO $_2$, –NR^{a}C(=0)R ^{a}, –NR^{a}C(=0)OR ^{a}, –NR^{a}C(=0)N(R ^{a})$_2$, - OC(=0)R ^{a}, -OC(=0)OR ^{a}, or-OC(=0)N(R ^{a})$_2$.

[00319] In certain embodiments. Ring A is a substituted or unsubstituted phenyl ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur;

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, –OR^a, –N(R^a)$_2$, -SR\ -CN, -SCN, -C(=NR ^{a})R^a, -C(=NR ^{a})OR^a, -C(=NR ^{a})N(R^a)$_2$, -C(=0)R ^{a}, –C(=0)OR ^{a}, - C(=0)N(R^a)$_2$, -NO $_2$, –NR^{a}C(=0)R ^{a}, –NR^{a}C(=0)OR ^{a}, - NR^{a}C(=0)N(R ^{a})$_2$, -OC (=0)R^a, –OC(=0)OR ^{a}, or –OC(=0)N(R ^{a})$_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^a groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, or 4;

L is a substituted or unsubstituted, saturated or unsaturated C_{3-10} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -0-, –S–, -NR ^{N}- , -N=, or =N-, wherein each instance

of R^N is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^C is independently N or CR^X, wherein R^X is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

Y is –O– or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

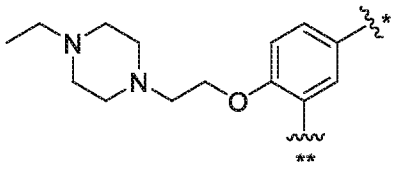
each instance of R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, -SR\ -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

m is 0, 1, 2, 3, 4, or 5; and

R^D is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(-0)OR^a$, or-$OC(-0)N(R^a)_2$.

100320] Unless expressly provided otherwise, the moieties and variables described in the subsection Compounds of Formula **(VI)** apply only to Formula (VI). The moieties and variables included but not described in detail in the subsection **Compounds of Formula** (VI) are as described in detail in other subsections.

[00321] Formula (VI) includes Ring A that is unsubstituted *(e.g.,* when k is 0) or substituted with one or more substituents R^A *(e.g.,* when k is 1, 2, 3, or 4). In certain embodiments, Ring A is an unsubstituted phenyl ring. In certain embodiments, Ring A is a substituted phenyl ring. In certain embodiments, Ring A is a substituted or unsubstituted, monocyclic, 5-membered heteroaryl ring *(e.g.* , furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, or isothiazolyl ring), wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is a substituted or unsubstituted, monocyclic, 6-membered heteroaryl ring *(e.g.,* a pyridyl, pyrazinyl, pyrimidinyl, or pyridazinyl ring), wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is of the formula: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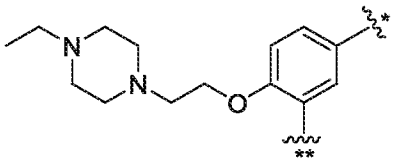
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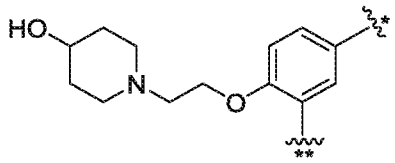
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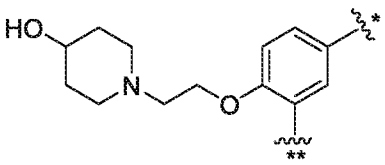
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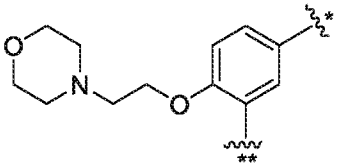
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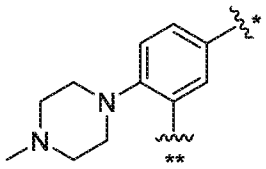
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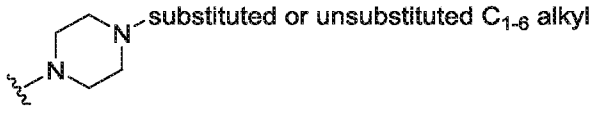
wherein the radical marked with "*" is directly attached to $N(R^B)$, and the radical marked with "**" is directly attached to L.

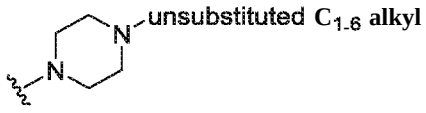
[00322] In Formula **(VI),** Ring A may include one or more substituents R^A. In certain embodiments, at least two instances of R^A are different. In certain embodiments, all instances of R^A are the same. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instaiace of R^A is Cl. In certain embodiments, at least one instance of R^A is Br. In certain embodiments, at least one instance of R^A is I (iodine). In certain embodiments, at least one instance of R^A is substituted alkyl. In certain embodiments, at least one instance of R^A is unsubstituted alkyl. In certain

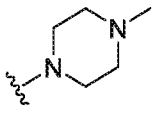
embodiments, at least one instance of R^A is unsubstituted C_{1-6} alky]. In certain embodiments, all instances of R^A are unsubstituted Ci_{-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^A is -CH_3. In certain embodiments, all instances of R^A are –CH_3. In certain embodiments, at least one instance of R^A is substituted methyl. In certain embodiments, at least one instance of R^A is –CH_2F. In certain embodiments, at least one instance of R^A is -CHF_2. In certain embodiments, at least one instance of R^A is –CF_3. In certain embodiments, at least one instance of R^A is ethyl. In certain embodiments, at least one instance of R^A is propyl. In certain embodiments, at least one instance of R^A is butyl. In certain embodiments, at least one instance of R^A is pentyl. In certain embodiments, at least one instance of R^A is hexyl. In certain embodiments, at least one instance of R^A is Bn. In certain embodiments, at least one instance of R^A is substituted alkenyl. In certain embodiments, at least one instance of R^A is unsubstituted alkenyl. In certain embodiments, at least one instance of R^A is substituted alkynyl. In certain embodiments, at least one instance of R^A is unsubstituted alkynyl. In certain embodiments, at least one instance of R^A is substituted carbocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted carbocyclyl. In certain embodiments, at least one instaiice of R^A is saturated carbocyclyl. In certain embodiments, at least one instance of R^A is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^A is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is substituted heterocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^A is saturated heterocyclyl. In certain embodiments, at least one instance of R^A is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^A is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^A is substituted or unsubstituted, monocyclic, 3- to 7-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group

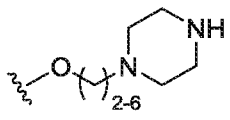
consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl. In certain embodiments, at least one instance of R^A is of the formula:



, such as



(e.g., ). In certain embodiments, at least one instance of R^A is substituted aryl. In certain embodiments, at least one instance of R^A is unsubstituted aryl. In certain embodiments, at least one instance of R^A is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^A is substituted phenyl. In certain embodiments, at least one instance of R^A is unsubstituted phenyl. In certain embodiments, at least one instance of R^A is substituted heteroaryl. In certain embodiments, at least one instance of R^A is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^A is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^A is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^A is $-OR^a$. In certain embodiments, at least one instance of R^A is -OH. In certain embodiments, at least one instance of R^A is –()(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^A is –OMe. In certain embodiments, at least one instance of R^A is –OEt. In certain embodiments, at least one instance of R^A is –OPr. In certain embodiments, at least one instance of R^A is –OBu. In certain embodiments, at least one instance of R^A is -OBn. In certain embodiments, at least one instance of R^A is -OPh. In certain embodiments, at least one instance of R^A is of the formula:



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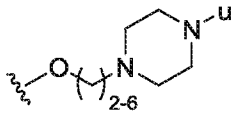

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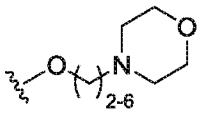

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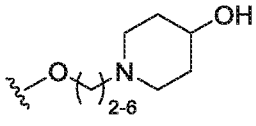

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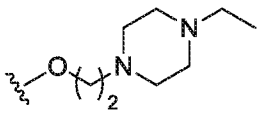
In certain embodiments, at least one instance of R^A is of the formula:



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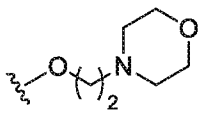

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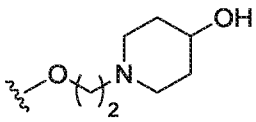
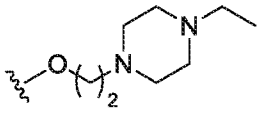


. In certain embodiments, k is 1; and R^A is of the formula:



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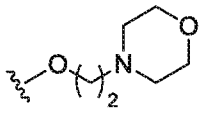

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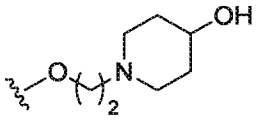


. In certain embodiments, at least one instance of R^A is $-SR^a$. In certain embodiments, at least one instance of R^A is –SH. In certain embodiments, at least one instance of R^A is –SMe. In certain embodiments, at least one instance of R^A is $-N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-NH_2$. In certain embodiments, at least one instance of R^A is - NHMe. In certain embodiments, at least one instance of R^A is $-NMe_2$. In certain embodiments, at least one instance of R^A is --CN. In certain embodiments, at least one instance of R^A is - SCN. In certain embodiments, at least one instance of R^A is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(-NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-C(=O)R^a$ or $-C(=O)OR^a$. In certain embodiments, at least one instance of R^A is $-C(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-C(=O)NMe_2$, –C(=O)NHMe, or $-C(=O)NH_2$. In certain embodiments, at least one instance of R^A is $-NG_2$. In certain embodiments, at least one instance of R^A is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^A is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

100323 1 Each instance of R^A, R^c, R^D, and R^X may independently include one or more substituents R^a. In certain embodiments, all instances of R^a are the same. In certain embodiments, at least two instances of R^a are different. In certain embodiments, at least one instance of R^a is H. In certain embodiments, each instance of R^a is H. In certain embodiments, at least one instance of R^a is substituted acyl. In certain embodiments, at least one instance of R^a is unsubstituted acyl. In certain embodiments, at least one instance of R^a is acetyl. In certain embodiments, at least

one instance of R^a is substituted alkyl. In certain embodiments, at least one instance of R^a is unsubstituted alkyl. In certain embodiments, at least one instance of R^a is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^a is methyl. In certain embodiments, at least one instance of R^a is ethyl. In certain embodiments, at least one instance of R^a is propyl. In certain embodiments, at least one instance of R^a is butyl. In certain embodiments, at least one instance of R^a is pentyl. In certain embodiments, at least one instance of R^a is hexyl. In certain embodiments, at least one instance of R^a is Bn. In certain embodiments, at least one instance of R^a is substituted alkenyl. In certain embodiments, at least one instance of R^a is unsubstituted alkenyl. In certain embodiments, at least one instance of R^a is substituted alkynyl. In certain embodiments, at least one instance of R^a is unsubstituted alkynyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^a is saturated carbocyclyl. In certain embodiments, at least one instance of R^a is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^a is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^a is saturated heterocyclyl. In certain embodiments, at least one instance of R^a is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^a is heterocyclyl, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^a is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^a is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^a is monocyclic aryl. In certain embodiments, at least one instance of R^a is substituted phenyl. In certain embodiments, at least one instance of R^a is unsubstituted phenyl. In certain embodiments, at least one instance of R^a is bicyclic aryl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^a is heteroaryl, wherein one, two, three, or four atoms of the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^a is monocyclic heteroaryl. In certain embodiments, at least one instance of R^a is 5- or 6-membered, monocyclic heteroaryl. In certain embodiments, at least

one instance of R^a is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^a is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^a is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^a is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^a is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, TUP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^a is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^a is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a heterocyclic ring, wherein one, two, or three atoms of the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^a are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms of the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

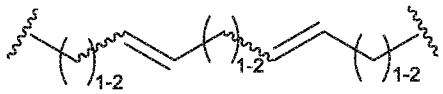
[00324] In certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, k is 3. In certain embodiments, k is 4.

[00325] In certain embodiments, k is 1; and R^A is $-OR^a$. In certain embodiments, k is 1; and R^A is -0(substituted or unsubstituted, C_{1-6} alkyl).

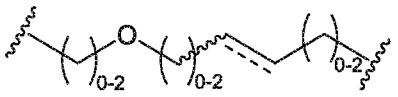
[00326] Formula **(VI)** includes divalent linker L. L consists of a chain, and optionally one or more hydrogen atoms and/or one or more substituents *(e.g.,* =0) on the chain, where any two substituents may optionally be joined to form a ring. In certain embodiments, the molecular weight of L is not more than about 300 g/mol, not more than about 200 g/mol, not more than about 150 g/mol, not more than about 100 g/mol, or not more than 80 g/mol. In certain embodiments, the molecular weight of L

is between 50 and 150 g/mol, inclusive. In certain embodiments, L consists of not more than about 70 atoms, not more than about 50 atoms, not more than about 30 atoms, not more than about 20 atoms, or not more than 15 atoms. In certain embodiments, L consists of between 10 and 30 atoms, inclusive. In certain embodiments, L does not include unsaturated bonds in the chain. In certain embodiments, L consists of one unsaturated bond in the chain. In certain embodiments, L consists of 2, 3, or 4 unsaturated bonds in the chain. In certain embodiments, L is a substituted or unsubstituted, saturated or unsaturated C_{3-10} hydrocarbon chain (*e.g.*, a C_{5-6} hydrocarbon chain). In certain embodiments, L is a substituted or unsubstituted, saturated or unsaturated C_{3-10} hydrocarbon chain (*e.g.*, a C_{5-6} hydrocarbon chain), wherein one chain atom of the hydrocarbon chain is replaced with –O–, -S-, -NR^N-, -N=, or =N-. In certain embodiments, L is a substituted or unsubstituted, saturated or unsaturated, C_{3-10} hydrocarbon chain (*e.g.*, a C_{5-6} hydrocarbon chain), wherein 2, 3, 4, or 5 chain atoms of the hydrocarbon chain are independently replaced with -0-, -S-, –NR^N-, -N=, or =N-. In certain embodiments, L is a substituted or unsubstituted, saturated or unsaturated C_{5-6} hydrocarbon chain, wherein one or two chain atoms of the hydrocarbon chain are independently replaced with –O–, –S–, or --NR^N-. In certain embodiments, L is of the formula:

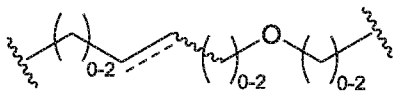
. In certain embodiments, L is of the formula:



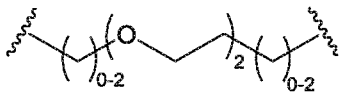
. In certain embodiments, L is of the formula:



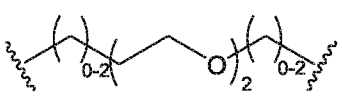
,



,

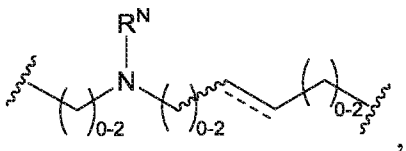


, or

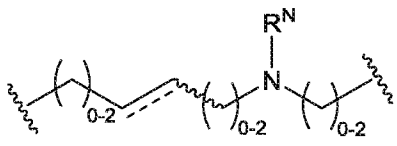


.

In certain embodiments, L is of the formula:



,



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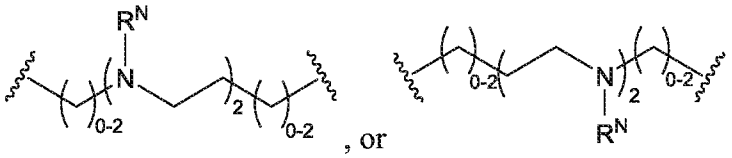
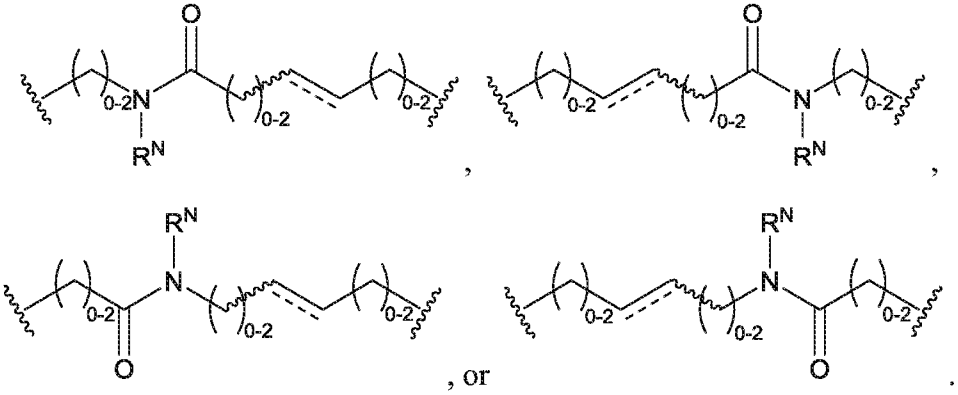
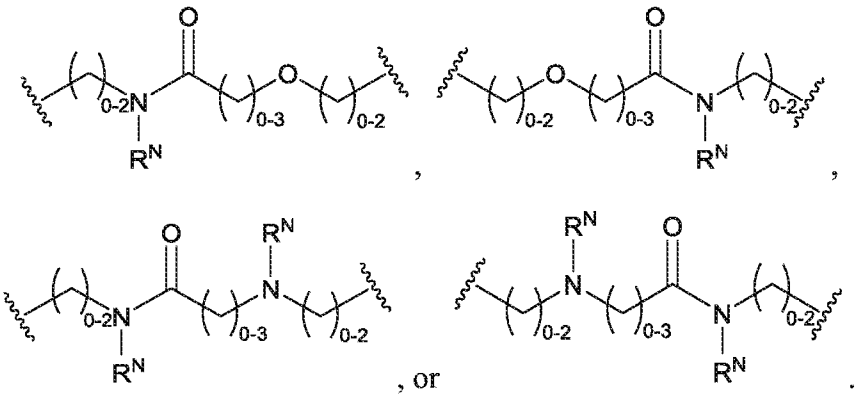


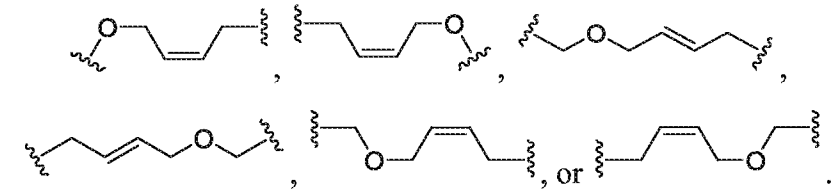
In certain embodiments, L is of the formula:

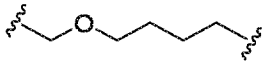


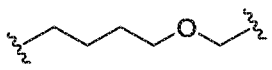
In certain embodiments, L is of the formula:

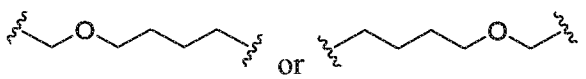


In certain embodiments, L is of the formula:



In certain embodiments, L is of the formula:  or

 . In certain embodiments, L is of the formula:

 .

[00327] In certain embodiments, at least two instances of R^N are different. In certain embodiments, all instances of R^N are the same. In certain embodiments, at least one instance of R^N is H. In certain embodiments, each instance of R^N is H. In certain embodiments, at least one instance of R^N is substituted acyl. In certain

embodiments, at least one instance of R^N is unsubstituted acyl. In certain embodiments, at least one instance of R^N is acetyl. In certain embodiments, at least one instance of R^N is unsubstituted C_{1-6} alkyl. In certain embodiments, each instance of R^N is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^N is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^N is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^N is unsubstituted methyl. In certain embodiments, at least one instance of R^N is substituted methyl. In certain embodiments, at least one instance of R^N is $-CH_2F$. In certain embodiments, at least one instance of R^N is $-CHF_2$. In certain embodiments, at least one instance of R^N is $-CF_3$. In certain embodiments, at least one instance of R^N is ethyl. In certain embodiments, at least one instance of R^N is propyl. In certain embodiments, at least one instance of R^N is butyl. In certain embodiments, at least one instance of R^N is pentyl. In certain embodiments, at least one instance of R^N is hexyl. In certain embodiments, at least one instance of R^N is Bn. In certain embodiments, at least one instance of R^N is a nitrogen protecting group. In certain embodiments, at least one instance of R^N is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00328] Formula (VI) includes substituent R^B on a nitrogen atom. In certain embodiments, R^B is H. In certain embodiments, R^B is substituted acyl. In certain embodiments, R^B is unsubstituted acyl. In certain embodiments, R^B is acetyl. In certain embodiments, R^B is unsubstituted C_{1-6} alkyl. In certain embodiments, R^B is substituted C_{1-6} alkyl. In certain embodiments, R^B is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^B is unsubstituted methyl. In certain embodiments, R^B is substituted methyl. In certain embodiments, R^B is $-CH_2F$. In certain embodiments, R^B is $-CHF_2$. In certain embodiments, R^B is $-CF_3$. In certain embodiments, R^B is ethyl. In certain embodiments, R^B is propyl. In certain embodiments, R^B is butyl. In certain embodiments, R^B is pentyl. In certain embodiments, R^B is hexyl. In certain embodiments, R^B is Bn. In certain embodiments, R^B is a nitrogen protecting group. In certain embodiments, R^B is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00329] Formula (VI) includes Ring B that includes moieties X^A, X^B, and X^C in the ring system. In certain embodiments, X^A is CR^X, and each of X^B and X^C is N. In certain embodiments, X^A is CH, and each of X^B and X^C is N. In certain embodiments, X^B is CR^X, and each of X^A and X^C is N. In certain embodiments, X^B is CH, and each

of X^A and X^C is N. In certain embodiments, X^C is CR^X, and each of X^A and X^B is N. In certain embodiments, X^C is CH, and each of X^A and X^B is N. In certain embodiments, X^A is N, and each of X^B and X^C is independently CR^X. In certain embodiments, X^A is N, and each of X^B and X^C is CH. In certain embodiments, X^B is N, and each of X^A and X^C is independently CR^X. In certain embodiments, X^B is N, and each of X^A and X^C is CH. In certain embodiments, X^C is N, and each of X^A and X^B is independently CR^X. In certain embodiments, X^C is N, and each of X^A and X^B is CH. In certain embodiments, each of X^A, X^B, and X^C is independently CR^X. In certain embodiments, each of X^A, X^B, and X^C is CH.

100330] In certain embodiments, when X^A, X^B, or X^C is CR^X, R^X is H. In certain embodiments, R^X is halogen. In certain embodiments, R^X is F. In certain embodiments, R^X is CI. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is substituted alkyl. In certain embodiments, R^X is unsubstituted alkyl. In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted Ci_{-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is substituted methyl. In certain embodiments, R^X is $-CH_2F$. In certain embodiments, R^X is $-CHF_2$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, R^X is ethyl. In certain embodiments, R^X is propyl. In certain embodiments, R^X is butyl. In certain embodiments, R^X is pentyl. In certain embodiments, R^X is hexyl. In certain embodiments, R^X is Bn. In certain embodiments, R^X is substituted alkenyl. In certain embodiments, R^X is unsubstituted alkenyl. In certain embodiments, R^X is substituted alkynyl. In certain embodiments, R^X is unsubstituted alkynyl. In certain embodiments, R^X is substituted carbocyclyl. In certain embodiments, R^X is unsubstituted carbocyclyl. In certain embodiments, R^X is saturated carbocyclyl. In certain embodiments, R^X is unsaturated carbocyclyl. In certain embodiments, R^X is monocyclic carbocyclyl. In certain embodiments, R^X is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^X is substituted heterocyclyl. In certain embodiments, R^X is unsubstituted heterocyclyl. In certain embodiments, R^X is saturated heterocyclyl. In certain embodiments, R^X is unsaturated heterocyclyl. In certain embodiments, R^X is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^X is monocyclic heterocyclyl. In certain embodiments, R^X is 3- to 7-membered, monocyclic

heterocyclyl. In certain embodiments, R^X is substituted aryl. In certain embodiments, R^X is unsubstituted aryl. In certain embodiments, R^X is 6- to 10-membered aryl. In certain embodiments, R^X is substituted phenyl. In certain embodiments, R^X is unsubstituted phenyl. In certain embodiments, R^X is substituted heteroaryl. In certain embodiments, R^X is unsubstituted heteroaryl. In certain embodiments, R^X is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^X is monocyclic heteroaryl. In certain embodiments, R^X is 5-membered, monocyclic heteroaryl. In certain embodiments, R^X is 6-membered, monocyclic heteroaryl. In certain embodiments, R^X is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^X is $-OR^a$. In certain embodiments, R^X is -OH. In certain embodiments, R^X is –0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, R^X is –OMe. In certain embodiments, R^X is –OEt. In certain embodiments, R^X is –OPr. In certain embodiments, R^X is –OBu. In certain embodiments, R^X is –OBn. In certain embodiments, R^X is –OPh. In certain embodiments, R^X is $-SR^a$. In certain embodiments, R^X is -SH. In certain embodiments, R^X is -SMe. In certain embodiments, R^X is $-N(R^a)_2$. In certain embodiments, R^X is $-NH_2$. In certain embodiments, R^X is -NHMe. In certain embodiments, R^X is $-NMe_2$. In certain embodiments, R^X is --CN. In certain embodiments, R^X is –SCN. In certain embodiments, R^X is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(-NR^a)N(R^a)_2$. In certain embodiments, R^X is $-C(=0)R^a$ or $-C(=0)OR^a$. In certain embodiments, R^X is $-C(=0)N(R^a)_2$. In certain embodiments, R^X is $-C(=0)NMe_2$, $-C(=0)NHMe$, or $-C(=0)NH_2$. In certain embodiments, R^X is $-NQ_2$. In certain embodiments, R^X is $-NR^aC(=0)R^a$, $-NR^aC(=0)OR^a$, or $-NR^aC(=())N(R^a)_2$. In certain embodiments, R^X is $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$.

100331 Formula (VI) includes divalent moiety Y. In certain embodiments, Y is -0-. In certain embodiments, Y is $-NR^Y-$. In certain embodiments, Y is -Nil-. In certain embodiments, Y is $-NR^Y-$; X^A is CR^X; and R^Y and R^X of X^A are joined to form a substituted or unsubstituted, monocyclic, 5- to 7-membered heterocyclic ring that is fused with Ring B, optionally wherein there are 2 or 3 nitrogen atoms, 0 or 1 oxygen atom, and 0 or 1 sulfur atom, in the monocyclic heterocyclic ring system. The monocyclic heterocyclic ring formed by joining R^Y and R^X of X^A is fused with Ring B to form a substituted or unsubstituted, bicyclic, 9- to 11-membered ring. In certain

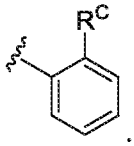
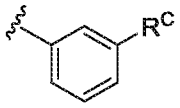
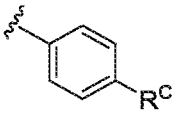
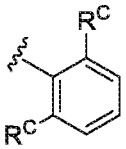
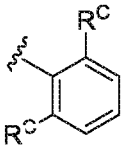
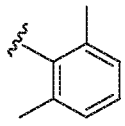
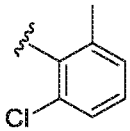
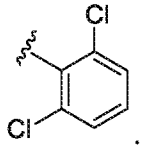
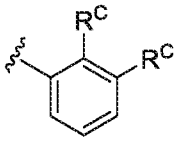
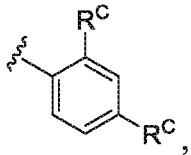
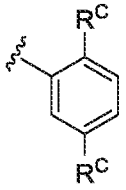
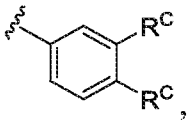
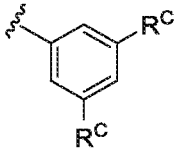
embodiments, Y is –NR¾- ; X^A is CR^X; and R^Y and R^x of X^A are joined to form a substituted or unsubstituted, monocyclic, 6-membered heterocyclic ring that is fused with Ring B.

[00332] In certain embodiments, when Y is -NR^Y--, R^Y is H. In certain embodiments, R^Y is substituted acyl. In certain embodiments, R^Y is unsubstituted acyl. In certain embodiments, R^Y is acetyl. In certain embodiments, R^Y is unsubstituted C_{1-6} alkyl. In certain embodiments, R^Y is substituted C_{1-6} alkyl. In certain embodiments, R^Y is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^Y is unsubstituted methyl. In certain embodiments, R^Y is substituted methyl. In certain embodiments, R^Y is -CH_2F. In certain embodiments, R^Y is -CHF_2. In certain embodiments, R^Y is –CF_3. In certain embodiments, R^Y is ethyl. In certain embodiments, R^Y is propyl. In certain embodiments, R^Y is butyl. In certain embodiments, R^Y is pentyl. In certain embodiments, R^Y is hexyl. In certain embodiments, R^Y is Bn. In certain embodiments, R^Y is a nitrogen protecting group. In certain embodiments, R^Y is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00333] In Formula **(VI),** Ring B includes substituent R^D. In certain embodiments, R^D is II. In certain embodiments, R^D is halogen. In certain embodiments, R^D is F. In certain embodiments, R^D is Cl. In certain embodiments, R^D is Br. In certain embodiments, R^D is I (iodine). In certain embodiments, R^D is substituted alkyl. In certain embodiments, R^D is unsubstituted alkyl. In certain embodiments, R^D is unsubstituted C_{1-6} alkyl. In certain embodiments, R^D is substituted Ci_{-6} alkyl. In certain embodiments, R^D is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^D is -CH_3. In certain embodiments, R^D is substituted methyl. In certain embodiments, R^D is –CH_2F. In certain embodiments, R^D is -CHF_2. In certain embodiments, R^D is -CF_3. In certain embodiments, R^D is ethyl. In certain embodiments, R^D is propyl. In certain embodiments, R^D is butyl. In certain embodiments, R^D is pentyl. In certain embodiments, R^D is hexyl. In certain embodiments, R^D is Bn. In certain embodiments, R^D is substituted alkenyl. In certain embodiments, R^D is unsubstituted alkenyl. In certain embodiments, R^D is substituted alkynyl. In certain embodiments, R^D is unsubstituted alkynyl. In certain embodiments, R^D is substituted carbocyclyl. In certain embodiments, R^D is unsubstituted carbocyclyl. In certain embodiments, R^D is saturated carbocyclyl. In certain embodiments, R^D is unsaturated carbocyclyl. In certain embodiments, R^D is

monocyclic carbocyclyl. In certain embodiments, R^D is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^D is substituted heterocyclyl. In certain embodiments, R^D is unsubstituted heterocyclyl. In certain embodiments, R^D is saturated heterocyclyl. In certain embodiments, R^D is unsaturated heterocyclyl. In certain embodiments, R^D is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^D is monocyclic heterocyclyl. In certain embodiments, R^D is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^D is substituted aryl. In certain embodiments, R^D is unsubstituted aryl. In certain embodiments, R^D is 6- to 10-membered aryl. In certain embodiments, R^D is substituted phenyl. In certain embodiments, R^D is unsubstituted phenyl. In certain embodiments, R^D is substituted heteroaryl. In certain embodiments, R^D is unsubstituted heteroaryl. In certain embodiments, R^D is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^D is monocyclic heteroaryl. In certain embodiments, R^D is 5-membered, monocyclic heteroaryl. In certain embodiments, R^D is 6-membered, monocyclic heteroaryl. In certain embodiments, R^D is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^D is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, R^D is $-OR^a$. In certain embodiments, R^D is –OH. In certain embodiments, R^D is –0(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, R^D is –OMe. In certain embodiments, R^D is –OEt. In certain embodiments, R^D is –OPr. In certain embodiments, R^D is –OBu. In certain embodiments, R^D is –OBn. In certain embodiments, R^D is –OPh. In certain embodiments, R^D is $-SR^a$. In certain embodiments, R^D is -SH. In certain embodiments, R^D is -SMe. In certain embodiments, R^D is $-N(R^a)_2$. In certain embodiments, R^D is $-NH_2$. In certain embodiments, R^D is -NHMe. In certain embodiments, R^D is $-NMe_2$. In certain embodiments, R^D is –CN. In certain embodiments, R^D is –SCN. In certain embodiments, R^D is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^D is $-C(=0)R^a$ or $-C(=0)OR^a$. In certain embodiments, R^D is $-C(=0)N(R^a)_2$. In certain embodiments, R^D is $-C(=0)NMe_2$, –C(=O)NHMe, or -C(=0)NH_2. In certain embodiments, R^D is -N0 $_2$. In certain embodiments, R^D is -

$NR^aC(==0)R^a$, $-NR^aC(=0)OR^a$, or $-NR^aC(-0)N(R^a)_2$. In certain embodiments, R^D is $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^a)_2$.

1003341 Formula **(VI)** includes Ring C that is unsubstituted *(e.g.*, when m is 0) or substituted with one or more substituents R^C *(e.g.*, when m is 1, 2, 3, 4, or 5). In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  , wherein each instance of R^C is independently substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  ,  ,  ,  , or  . In certain embodiments, at least two instances of R^C are different. In certain embodiments, all instances of R^C are the same. In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, at least one instance of R^C is CI. In certain embodiments, at least one instance of R^C is Br. In

certain embodiments, at least one instance of R^C is I (iodine). In certain embodiments, at least one instance of R^C is substituted alkyl. In certain embodiments, at least one instance of R^C is unsubstituted alkyl. In certain embodiments, at least one instance of R^C is unsubstituted C_{1-6} alkyl. In certain embodiments, all instances of R^C are unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^C is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^C is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, at least one instance of R^C is $-CH_3$. In certain embodiments, all instances of R^C are $-CH_3$. In certain embodiments, at least one instance of R^C is substituted methyl. In certain embodiments, at least one instance of R^C is $-CH_2F$. In certain embodiments, at least one instance of R^C is $-CHF_2$. In certain embodiments, at least one instance of R^C is $-CF_3$. In certain embodiments, at least one instance of R^C is ethyl. In certain embodiments, at least one instance of R^C is propyl. In certain embodiments, at least one instance of R^C is butyl. In certain embodiments, at least one instance of R^C is pentyl. In certain embodiments, at least one instance of R^C is hexyl. In certain embodiments, at least one instance of R^C is Bn. In certain embodiments, each instance of R^C is independently halogen *(e.g.,* CI) or substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* unsubstituted C_{1-6} alkyl *(e.g..* Me)). In certain embodiments, at least one instance of R^C is substituted alkenyl. In certain embodiments, at least one instance of R^C is unsubstituted alkenyl. In certain embodiments, at least one instance of R^C is substituted alkynyl. In certain embodiments, at least one instance of R^C is unsubstituted alkynyl. In certain embodiments, at least one instance of R^C is substituted carbocyclyl. In certain embodiments, at least one instance of R^C is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^C is saturated carbocyclyl. In certain embodiments, at least one instance of R^C is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^C is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^C is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^C is substituted heterocyclyl. In certain embodiments, at least one instance of R^C is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^C is saturated heterocyclyl. In certain embodiments, at least one instance of R^C is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^C is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In

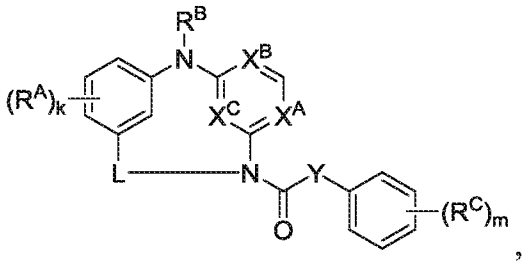
certain embodiments, at least one instance of R^C is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^C is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^C is substituted aryl. In certain embodiments, at least one instance of R^C is unsubstituted aryl. In certain embodiments, at least one instance of R^C is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^C is substituted phenyl. In certain embodiments, at least one instance of R^C is unsubstituted phenyl. In certain embodiments, at least one instance of R^C is substituted heteroaryl. In certain embodiments, at least one instance of R^C is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^C is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^C is monocyclic heteroaryl. In certain embodiments, at least one instance of R^C is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^C is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^C is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^C is 9- or 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^C is $-OR^a$. In certain embodiments, at least one instance of R^C is -OH. In certain embodiments, at least one instance of R^C is -©(substituted or unsubstituted, C_{1-6} alkyl). In certain embodiments, at least one instance of R^C is -OMe. In certain embodiments, at least one instance of R^C is -OEt. In certain embodiments, at least one instance of R^C is -OPr. In certain embodiments, at least one instance of R^C is -OBu. In certain embodiments, at least one instance of R^C is -OBn. In certain embodiments, at least one instance of R^C is –OPh. In certain embodiments, at least one instance of R^C is $-SR^a$. In certain embodiments, at least one instance of R^C is -SH. In certain embodiments, at least one instance of R^C is -SMe. In certain embodiments, at least one instance of R^C is $-N(R^a)_2$. In certain embodiments, at least one instance of R^C is $-NH_2$. In certain embodiments, at least one instance of R^C is –NHMe. In certain embodiments, at least one instance of R^C is $-NMe_2$. In certain embodiments, at least one instance of R^C is -CN. In certain embodiments, at least one instance of R^C is –SCN. In certain embodiments, at least one instance of R^C is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^C is $-C(=O)R^a$ or $-C(=O)OR^a$. In certain embodiments, at least one

instance of R^C is -C(=0)N(R^a)$_2$. In certain embodiments, at least one instance of R^C is -C(=0)NMe$_2$, -C(=0)NHMe, or -C(=0)NH$_2$. In certain embodiments, at least one instance of R^C is -NO$_2$. In certain embodiments, at least one instance of R^C is -$NR^aC(=0)R^a$, -$NR^aC(=0)OR^a$, or -$NR^aC(=0)N(R^a)_2$. In certain embodiments, at least one instance of R^C is -$OC(=0)R^a$, -$OC(=0)OR^a$, or -$OC(=0)N(R^a)_2$.

[00335] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.

[00336] In certain embodiments, m is 2; and each instance of R^C is halogen *(e.g.,* CI). In certain embodiments, m is 2; and each instance of R^C is substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, m is 2; and each instance of R^C is methyl. In certain embodiments, m is 2; and each instance of R^C is independently halogen *(e.g.,* Cl) or substituted or unsubstituted, C_{1-6} alkyl *(e.g.,* unsubstituted C_{1-6} alkyl (e.g., Me)).

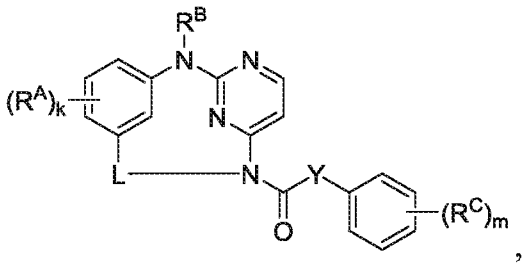
[00337] In certain embodiments, the compound of Formula (VI) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

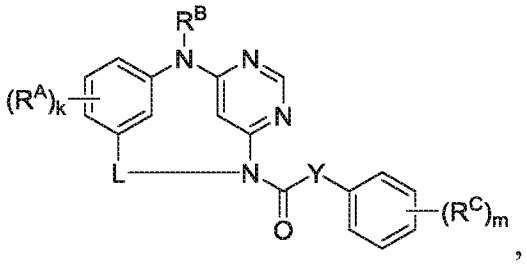
[003381 In certain embodiments, the compound of Formula (VI) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

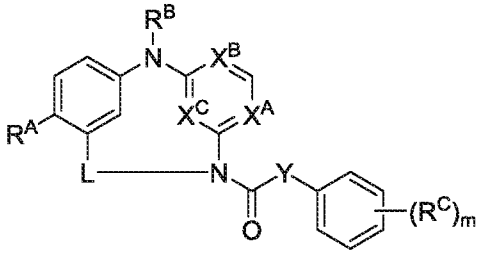
[00339] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

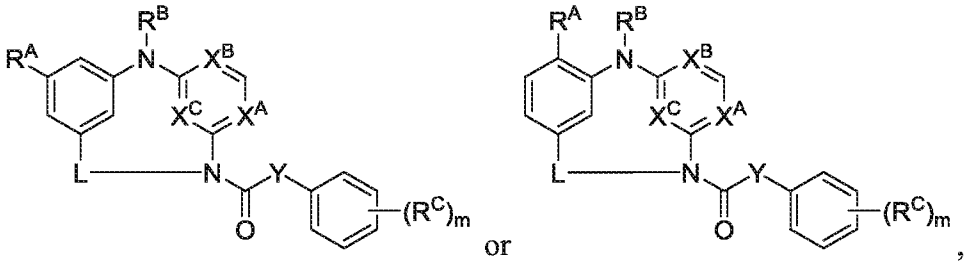
[00340] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00341] In certain embodiments, the compound of Formula **(VI)** is of the formula:

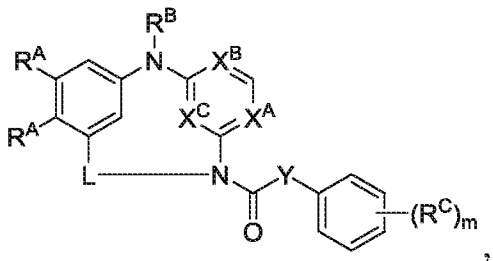


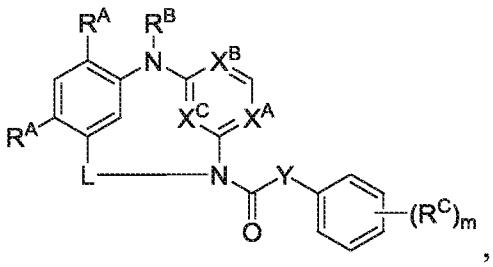
or

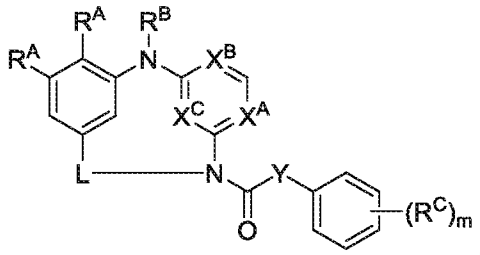
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00342] In certain embodiments, the compound of Formula **(VI)** is of the formula:

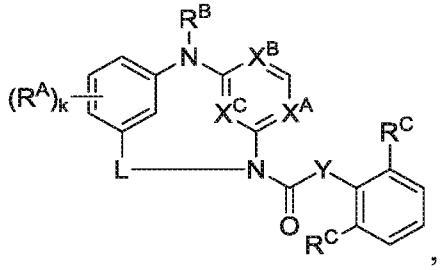

,


,


,

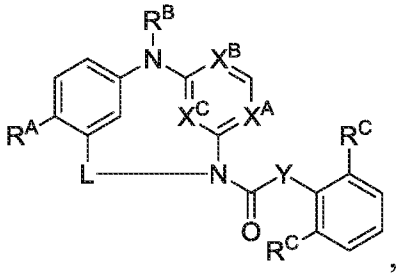
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00343] In certain embodiments, the compound of Formula **(VI)** is of the formula:


,

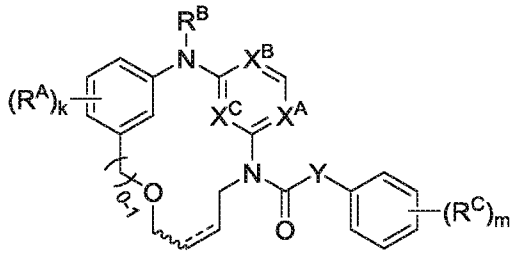
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00344] In certain embodiments, the compound of Formula **(VI)** is of the formula:


,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

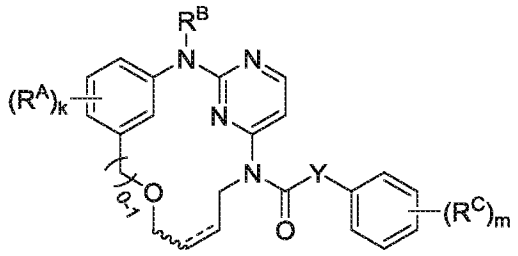
[00345] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

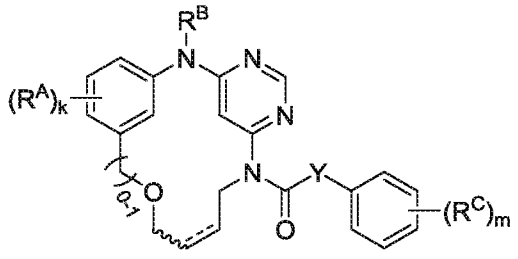
[00346] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

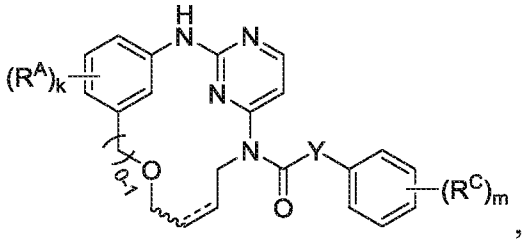
[003471 In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

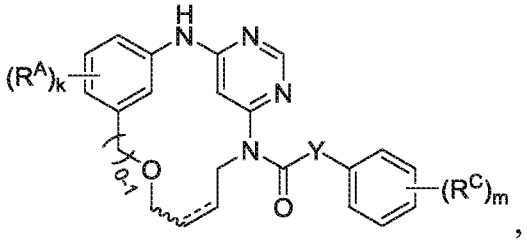
[00348] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

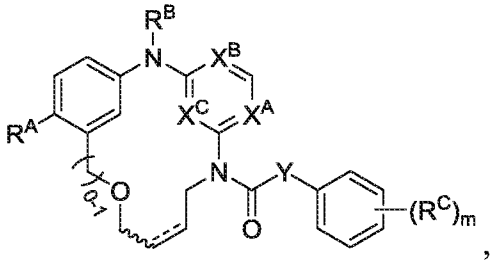
[00349] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

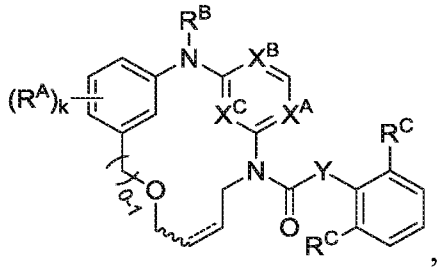
[00350] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

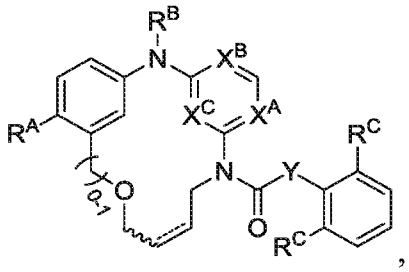
[00351] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

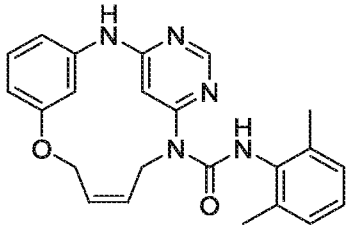
1003521 In certain embodiments, the compound of Formula **(VI)** is of the formula:



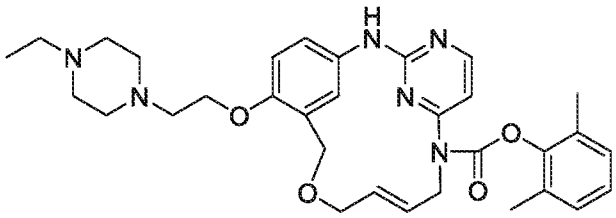
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

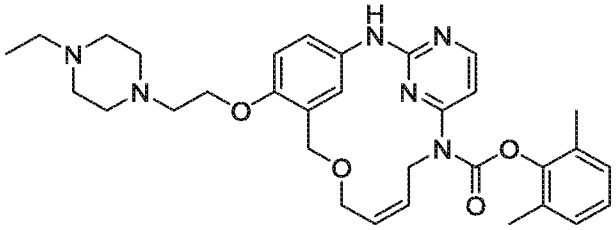
1003531 In certain embodiments, the compound of Formula **(VI)** is of the formula:



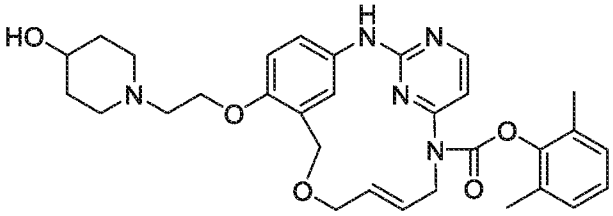
(**VI-1** or HG-10-32-01),



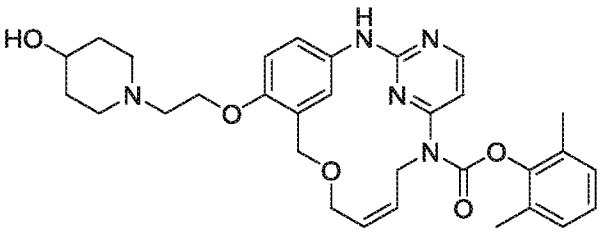
(**VI-2** or HG-10-86-01),



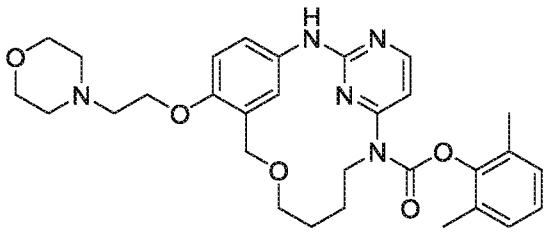
(VI-3 or HG-10-86-02),



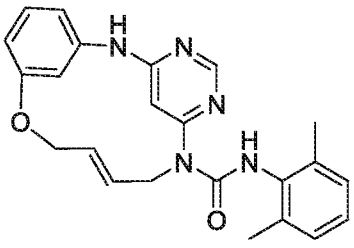
(VI-4 or HG-10-88-01),



(**VI-5** or HG-10-88-02),



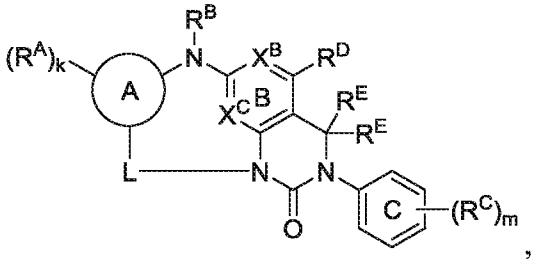
(**VI-6** or HG-10-93-01),



(**VI-7**),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

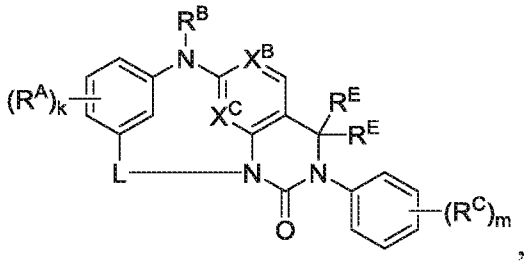
[00354 1 In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein each instance of R^E is independently hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, the two instances of R^E are the same. In certain embodiments, the two instances of R^E are not the same. In certain embodiments, at least one instance of R^E is hydrogen. In certain embodiments, each instance of R^E is hydrogen. In certain embodiments, at least one instance of R^E is halogen *(e.g.,* F, CI, Br, or I). In certain embodiments, at least one instance of R^E is substituted or unsubstituted, C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is Me. In certain embodiments, at least one instance of R^E is substituted methyl *(e.g.,* $-CF_3$ or Bn), Et, substituted ethyl *(e.g.,* perfluoroethyl), Pr, substituted propyl *(e.g.,* perfluoropropyl), Bu, or substituted butyl *(e.g.,* perfluorobutyl).

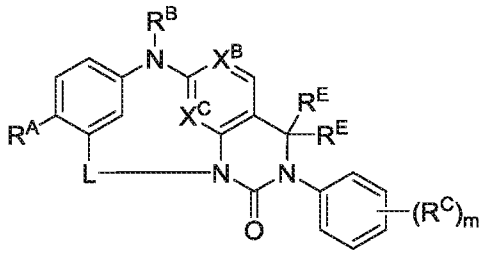
[00355] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

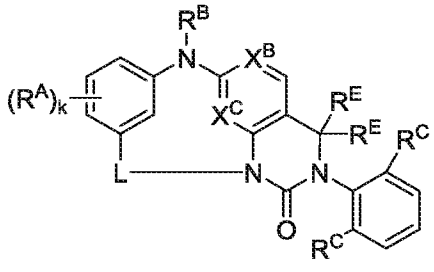
[00356] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

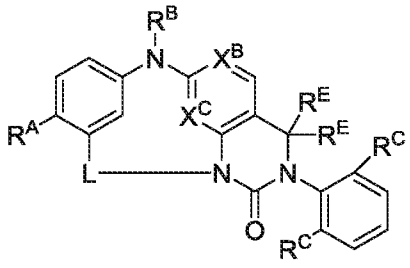
[003571 In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

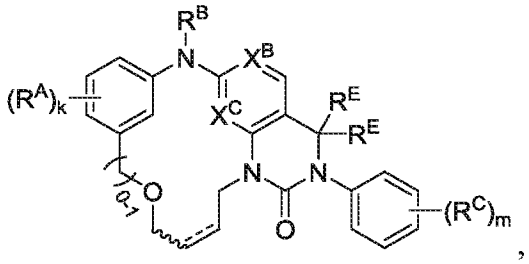
[00358] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

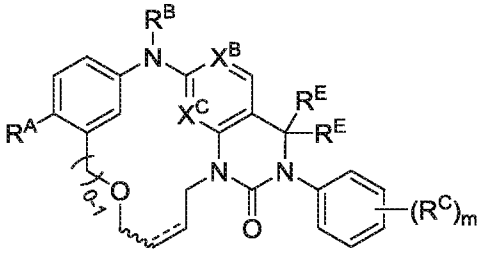
[00359] In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

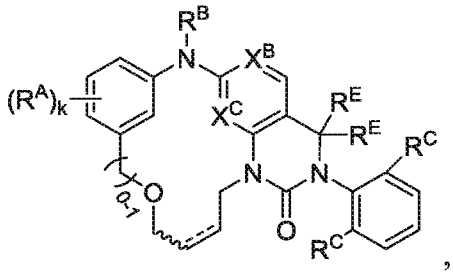
[003601 In certain embodiments, the compound of Formula **(VI)** is of the formula:



,

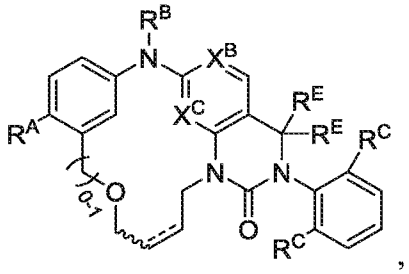
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00361] In certain embodiments, the compound of Formula (VI) is of the formula:



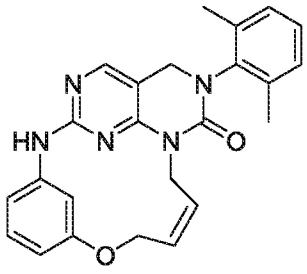
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00362] In certain embodiments, the compound of Formula (VI) is of the formula:

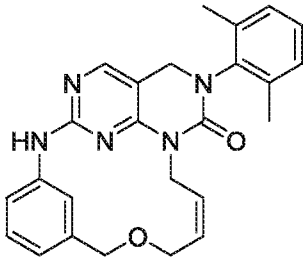


or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

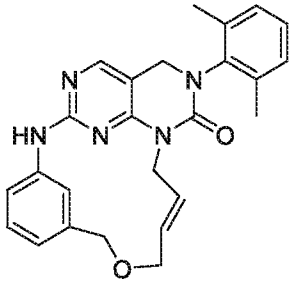
[00363] In certain embodiments, the compound of Formula (VI) is of the formula:



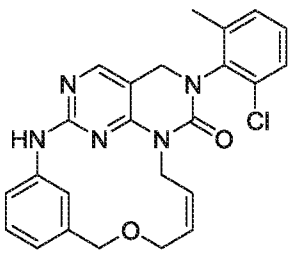
(YKL-05-120)



(YKL-05-200-1)



(YKL-05--200-2)



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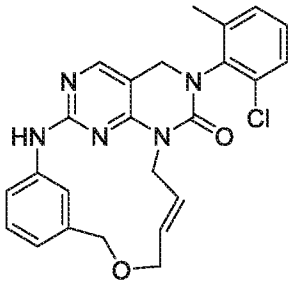
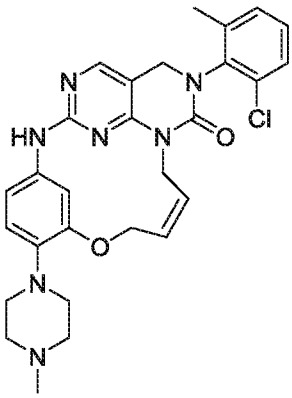
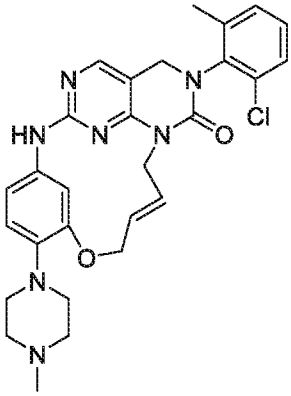


(YKL-05-201-2)



(YKL-05-202-1)



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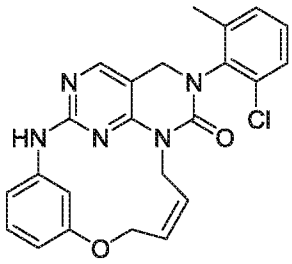
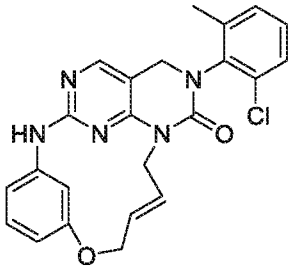
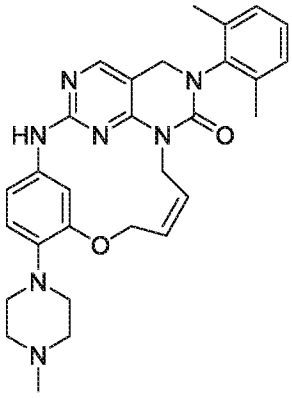


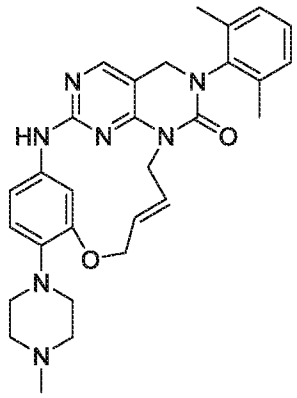
(YKL-05-203-1)



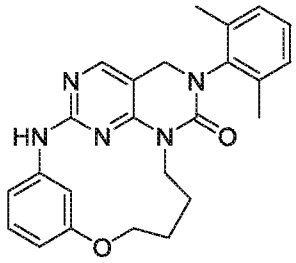
(YKL-05-203-2)



(YKL-05-204-1)



(YKL-05-204-2)



(YKL-05-205)

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00364] In certain embodiments, the compound of Formula **(VI)** is YKL-05-205, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00365] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula **(I),** or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof (e.g., a pharmaceutically acceptable salt thereof).

[00366] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula **(II),** or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof (e.g., a pharmaceutically acceptable salt thereof).

[00367] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula **(III),** or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof *(e.g.* , a pharmaceutically acceptable salt thereof).

[00368] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula **(IV),** or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof *(e.g.* , a pharmaceutically acceptable salt thereof).

[00369] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula **(V),** or a pharmaceutically acceptable salt,

solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof (*e.g.,* a pharmaceutically acceptable salt thereof).

[00370] In certain embodiments, a SIK inhibitor for use in the invention described herein is a compound of Formula (VI), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof (*e.g.,* a pharmaceutically acceptable salt thereof).

100371 1 The SIK inhibitors described herein may be able to bind a SIK. In certain embodiments, the SIK inhibitor covalently binds to a SIK. In certain embodiments, the SIK inhibitor non-covalently binds to a SIK. In certain embodiments, the SIK inhibitor reversibly binds to a SIK. In certain embodiments, the SIK inhibitor non-reversibly binds to the SIK. In certain embodiments, the SIK inhibitor modulates (*e.g.,* inhibit) the activity (*e.g.* , aberrant activity, such as increased activity) of a SIK. In certain embodiments, the SIK inhibitor inhibits the activity of a SIK. The inhibition of SIK may be in the context of a disease associated with aberrant or increased SIK activity.

100372] The binding affinity of a SIK inhibitor described herein to a SIK may be measured by the dissociation constant (A¾ value of an adduct of the SIK inhibitor and the SIK using methods known in the art (*e.g.* , isothermal titration calorimetry (ITC)). In certain embodiments, the adduct comprises the SIK inhibitor and the SIK, which are bound (*e.g.,* non-covalently bound) to each other. In certain embodiments, the K_d value of the adduct is not more than about 100 μM, not more than about 10 μM, not more than about 1 μM, not more than about 100 nM, not more than about 10 nM, or not more than about 1 nM. In certain embodiments, the K_d value of the adduct is at least about 1 nM, at least about 10 nM, at least about 100 nM, at least about 1 μM, at least about 10 uM, or at least about 100 μM. Combinations of the above-referenced ranges are also within the scope of the disclosure.

[00373] In certain embodiments, the activity of a SIK is inhibited by a SIK inhibitor described herein. The inhibition of the activity of a SIK by a SIK inhibitor described herein may be measured by the half maximal inhibitory concentration (IC_{50}) value of the SIK inhibitor when the SIK inhibitor, or a pharmaceutical composition thereof, is contacted with the SIK. The IC_{50} values may be obtained using methods known in the art (*e.g.,* by a competition binding assay). In certain embodiments, the IC_{50} value of a SIK inhibitor described herein is not more than about 1 mM, not more

than about 100 μM, not more than about 10 μM, not more than about 1 μM, not more than about 100 nM, not more than about 10 nM, or not more than about 1 nM. In certain embodiments, the IC50 value of a SIK inhibitor described herein is at least about 1 nM, at least about 10 nM, at least about 100 nM, at least about 1 uM, at least about 10 μM, at least about 100 μM, or at least about 1 niM. Combinations of the above-referenced ranges are also within the scope of the disclosure.

100374 1 The SIK inhibitors described herein may selectively modulate the activity of a SIK. In certain embodiments, the SIK inhibitors selectively inhibit the activity of a SIK, compared to a different SIK or a protein kinase that is not a SIK.

[00375 J The selectivity of a SIK inhibitor described herein in inhibiting the activity of a first SIK over a second SIK or a protein kinase that is not a SIK may be measured by the quotient of the IC_{50} value of the SIK inhibitor in inhibiting the activity of the second SIK or the protein kinase that is not a SIK over the IC_{50} value of the SIK inhibitor in inhibiting the activity of the first SIK. The selectivity of a SIK inhibitor described herein in modulating the activity of a first SIK over a second SIK or a protein kinase that is not a SIK may also be measured by the quotient of the K_d value of an adduct of the SIK inhibitor and the second SIK or the protein kinase that is not a SIK over the K_d value of an adduct of the SIK inhibitor and the first SIK. In certain embodiments, the selectivity is at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 30-fold, at least about 100-fold, at least about 300-fold, at least about 1,000-fold, at least about 3,000-fold, at least about 10,000-fold, at least about 30,000-fold, or at least about 100,000-fold. In certain embodiments, the SIK inhibitors are selective for SIK2 over SIK 1 and SIK3. In certain embodiments, the SIK inhibitors are selective for SIK3 over SIK1 and SIK2. In certain embodiments, the SIK inhibitors are selective for SIK2 and SIK3 over SIK 1.

Pharmaceutical Compositions, Kits, and Administration

[003761 The present disclosure provides pharmaceutical compositions comprising a SIK inhibitor, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. The pharmaceutical compositions may be useful for treating osteoporosis, preventing osteoporosis, increasing the function of osteocytes, increasing the number of osteoblasts, increasing the activity of osteoblasts, inhibiting the resorption of a bone, decreasing the number of osteoclasts,

inhibiting the activity of osteoclasts, increasing the mass of a bone, down-regulating the expression of the gene SOST, inhibiting the activity of sclerostin, and/or reducing the production of sclerostin in a subject in need thereof.

[00377] In certain embodiments, the subject is an animal. The subject may be of either sex and may be at any stage of development. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal.

[00378] In certain embodiments, the osteocyte is *in vitro*. In certain embodiments, the osteocyte is *ex vivo*. In certain embodiments, the osteocyte is *in vivo*.

[00379] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the SIK inhibitor described herein *(i.e.*, the "active ingredient") into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[00380] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[00381] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00382] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating

agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00383] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00384] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked polyfvinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00385] Exemplary surface active agents and/or emulsifiers include natural emulsifiers *(e.g.,* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays *(e.g.,* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols *(e.g.,* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers *(e.g.,* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives *(e.g.,* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters *(e.g.,* polyoxyethylene sorbitan monolaurate (Tween® 20), polyoxyethylene sorbitan (Tween® 60), polyoxyethylene sorbitan monooleate (Tween® 80), sorbitan monopalmitate (Span® 40), sorbitan monostearate (Span* 60), sorbitan tristearate (Span* 65), glyceryl monooleate, sorbitan monooleate (Span* 80), polyoxyethylene esters *(e.g.,* polyoxyethylene monostearate (Myrj® 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil,

polyoxymethylene stearate, and Solutol®), sucrose fatty acid esters, polyethylene glycol fatty acid esters *(e.g.,* Cremophor®), polyoxyethylene ethers, *(e.g.,* polyoxyethylene lauryl ether (Brij® 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic® F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00386] Exemplary binding agents include starch *(e.g.,* cornstarch and starch paste), gelatin, sugars *(e.g.,* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.),* natural and synthetic gums *(e.g.,* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00387] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[003881 Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00389] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof *(e.g.,* sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof *(e.g.,* citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride,

chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00390] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00391] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00392] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00393] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BUT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® 11, Neolone®, Kathon®, and Euxyl*.

[00394] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00395] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00396] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, camauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, com, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[003971 Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsitiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils *(e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates described herein are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

100398] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00399] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00400] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

[00401] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00402] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[00403] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00404] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.,* tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

[00405] Dosage forms for topical and/or transdermal administration of a SIK inhibitor described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by

dissolving and'or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and'Or gel.

|00406| Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid formulations to the dermis *via* a liquid jet injector and/or *via* a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the **SIK** inhibitor in powder form through the outer layers of the skin to the dermis are suitable.

[004071 Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and'or water-in-oil emulsions such as creams, ointments, and'or pastes, and/or solutions and/or suspensions. Topically administrate formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

100408 1 A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration *via* the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and'or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1

nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00409] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00410] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methyl hydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00411] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00412] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an

orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00413] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1-1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this disclosure.

[00414] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00415] SIK inhibitors provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of

the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00416] The SIK inhibitors and compositions provided herein can be administered by any route, including enteral *(e.g.* , oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration *(e.g.,* systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent *(e.g.,* its stability in the environment of the gastrointestinal tract), and/or the condition of the subject *(e.g.,* whether the subject is able to tolerate oral administration). In certain embodiments, the **SIK** inhibitor or pharmaceutical composition described herein is suitable for topical administration to the eye of a subject.

[00417] In certain embodiments, the **SIK** inhibitor described herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, a therapeutically effective amount is an amount effective for treating osteoporosis. In certain embodiments, a therapeutically effective amount is an amount effective for both treating osteoporosis and inhibiting SIK *(e.g.* , inhibiting the activity of SIK and/or reducing the production of SIK). In certain embodiments, a therapeutically effective amount is an amount effective for increasing the formation of a bone *(e.g.* , increasing the mass of the bone), or inhibiting the resorption of the bone, or both. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a SIK by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a SIK by not more than 10%, not more than 20%, not more than 30%, not more than

40%, not more than 50%, not more than 60%, not more than 70%, not more than 80%, not more than 90%, not more than 95%, or not more than 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a SIK by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00418] When a property *(e.g.*, the activity of a SIK, activity of osteoclasts, activity of sclerostin, or resorption of a bone) is inhibited, the property is inhibited by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 98%.

100419] When a production *(e.g.*, the production of SIK or sclerostin) is reduced, the production is reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 98%.

100420 1 The exact amount of a SIK inhibitor required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular SIK inhibitor, mode of administration, and the like. An effective amount may be included in a single dose *(e.g.*, single oral dose) or multiple doses *(e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, any two doses of the multiple doses include different or substantially the same amounts of a compound described herein. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses a day, two doses a day, one dose a day, one dose every other day, one dose every third day, one dose every week, one dose every two weeks, one dose every three weeks, or one dose every four weeks. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is one dose per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is two doses per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses per day. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the duration between the first dose and last dose of the multiple doses is one

day, two days, four days, one week, two weeks, three weeks, one month, two months, three months, four months, six months, nine months, one year, two years, three years, four years, five years, seven years, ten years, fifteen years, twenty years, or the lifetime of the subject, tissue, or cell. In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject, tissue, or cell. In certain embodiments, a dose *(e.g.,* a single dose, or any dose of multiple doses) described herein includes independently between 0.1 μg and 1 μg, between 0.001 mg and 0.01 mg, between 0.01 mg and 0.1 mg, between 0.1 mg and 1 mg, between 1 mg and 3 mg, between 3 mg and 10 mg, between 10 mg and 30 mg, between 30 mg and 100 mg, between 100 mg and 300 mg, between 300 mg and 1,000 mg, or between 1 g and 10 g, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 1 mg and 3 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 3 mg and 10 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 10 mg and 30 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 30 mg and 100 mg, inclusive, of a compound described herein.

[00421] Dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult. In certain embodiments, a dose described herein is a dose to an adult human whose body weight is 70 kg.

[00422] A SIK inhibitor or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents *(e.g.,* therapeutically and/or prophylactically active agents that are different from the SIK inhibors described herein) useful in treating and/or preventing osteoporosis. The SIK inhibitors or compositions can be administered in combination with additional pharmaceutical agents. In certain embodiments, the additional pharmaceutical agents improve the activity of the SIK inhibitor *(e.g.* , potency and/or efficacy in treating osteoporosis, preventing osteoporosis, increasing the function of osteocytes,

increasing the number of osteoblasts, increasing the activity of osteoblasts, inhibiting the resorption of a bone, decreasing the number of osteoclasts, inhibiting the activity of osteoclasts, increasing the mass of a bone, down-regulating the expression of the gene SOST, inhibiting the activity of sclerostin, reducing the production of sclerostin, down-regulating the expression of the gene TNFSF11, inhibiting the activity of receptor activator of nuclear factor kappa-B ligand (RANKL), inhibiting the activity of SIK, inhibiting the activity of Src, and/or inhibiting the activity of CSF1R, in a subject in need thereof). In certain embodiments, the additional pharmaceutical agents improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution of the SIK inhibitor in a subject in need thereof. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a SIK inhibitor described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the SIK inhibitor and the additional pharmaceutical agent, but not both.

100423] The SIK inhibitor or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies in treating osteoporosis. Pharmaceutical agents include small organic molecules such as drug compounds *(e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing osteoporosis. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent approved by a regulatory agency *(e.g.*, the US FDA) for treating and/or preventing osteoporosis. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in

different doses. The particular combination to employ in a regimen will take into account compatibility of the SIK inhibitor described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00424] In certain embodiments, the additional pharmaceutical agent is a binder or inhibitor of SIK. In certain embodiments, the additional pharmaceutical agent is a Src inhibitor *(e.g.*, KX2-391, bosutinib, saracatinib, PP1, PP2, quercetin, dasatinib, NVP-BHG712, SU6656, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof; or a combination thereof). In certain embodiments, the additional pharmaceutical agent is a CSFIR inhibitor *(e.g.*, GW2580, BLZ945, pexidartinib (PLX3397), linifanib (ABT-869), OSI-930, CEP-32496, AZD6495, JNJ-28312141, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof; or a combination thereof. Furhter examples of the additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-angiogenesis agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, and anti-allergic agents. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of epigenetic or transcriptional modulators *(e.g.*, DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimitotic drugs *(e.g.*, taxanes and vinca alkaloids), hormone receptor modulators *(e.g.*, estrogen receptor modulators and androgen receptor modulators), cell signaling pathway inhibitors *(e.g.*, tyrosine SIK inhibitors), modulators of protein stability *(e.g.*, proteasome inhibitors), Hsp90 inhibitors, glucocorticoids, *all-trans* retinoic acids, and other agents that promote differentiation. In certain embodiments, the SIK inhibitors described herein or pharmaceutical compositions can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, and chemotherapy.

[00425] Also encompassed by the disclosure are kits *(e.g.*, pharmaceutical packs). In certain embodiments, the kit comprises a pharmaceutical composition or compound *(e.g.*, a SIK inhibitor; a SIK inhibitor and a Src inhibitor; or a SIK inhibitor

and a CSFIR inhibitor) described herein, and instructions for using the pharmaceutical composition or compound. In certain embodiments, the kit further comprises a first container *(e.g.,* a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In certain embodiments, the first container comprises the pharmaceutical composition or compound. In some embodiments, the kit further comprises a second container *(e.g.,* a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In certain embodiments, the second container comprises a pharmaceutical excipient. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

100426] A kit described herein further includes instructions for using the compound or pharmaceutical composition. The kit may also include information as required by a regulatory agency, such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of treatment of osteoporosis. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of prevention of osteoporosis. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of increasing the function of osteocytes. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of increasing the number of osteoblasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of increasing the activity of osteoblasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of inhibiting the resorption of a bone. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of decreasing the number of osteoclasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of inhibiting the activity of osteoclasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of increasing the mass of a bone. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of down-regulating the expression of the gene SOST. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in

need of inhibiting the activity of sclerostin. In certain embodiments, the instructions include instructions for administering the SIK inhibitor to a subject in need of reducing the production of sclerostin. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of treatment of osteoporosis. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSF1R inhibitor, or the pharmceutial composition to a subject in need of prevention of osteoporosis. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFI R inhibitor, or the pharmceutial composition to a subject in need of increasing the function of osteocytes. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSF1R inhibitor, or the pharmceutial composition to a subject in need of increasing the number of osteoblasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of increasing the activity of osteoblasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFI R inhibitor, or the pharmceutial composition to a subject in need of inhibiting the resorption of a bone. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of decreasing the number of osteoclasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of inhibiting the activity of osteoclasts. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFl R inhibitor, or the pharmceutial composition to a subject in need of increasing the mass of a bone. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of down-regulating the expression of the gene SOST. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK

inhibitor and CSF1R inhibitor, or the pharmceutial composition to a subject in need of inhibiting the activity of sclerostin. In certain embodiments, the instructions include instructions for administering the SIK inhibitor and Src inhibitor, the SIK inhibitor and CSFIR inhibitor, or the pharmceutial composition to a subject in need of reducing the production of sclerostin. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment and Uses

[004271 The present disclosure further provides methods of using SIK inhibitors and pharmaceutical compositions for, for example., treating and/or preventing osteoporosis.

100428 1 A role for the class Ila histone deacetylase HDAC5 as a negative regulator of MEF2C-driven SOST expression has been described both *in vitro* in Ocy454 osteocytic cells (17) and *in vivo* (18). Class IIa HDACs are uniquely endowed with N-terminal extensions that allow them to sense and transduce signaling information (19). When phosphorylated, class IIa HDACs are sequestered in the cytoplasm via binding to 14-3-3 proteins. When de-phosphorylated, they are able to translocate to the nucleus to inhibit MEF2-driven gene expression (20). PTH signaling in osteocytes may use both HDAC5 and the closely related family member HDAC4 to block MEF2C-driven SOST expression.

100429 1 Like class Ila HDACs, cAMP-regulated transcriptional coactivators (CRTC) proteins shuttle from the cytoplasm to the nucleus where they function as CREB coactivators (21). Here, it is also shown that PTH-stimulated RANKL expression may require CRTC2. Both HDAC4/5 and CRTC2 are known substrates of SIK (21-24), and SIK3 deficiency in growth plate chondrocytes may increase nuclear HDAC4 and delays MEF2-driven chondrocyte hypertrophy (23). PTH signaling, via cAMP, may inhibit SIK2 cellular activity in osteocytes. SIK inhibition, both *in vitro* and *in vivo,* achieved via YKL-05-093, is sufficient to mimic many of the effects of PTH: HDAC4/5/CRTC2 dephosphorylation, SOST inhibition, and/or RANKL stimulation. A major arm of PTH signaling in osteocytes may involve SIK inhibition, as revealed by RNA-seq analysis of PTH- versus YKL-05-093-treated osteocytes. YKL-05-099 (25), an analog of YKL-05-093 more suitable to long-tenn *in vivo* use, was shown to boost osteoblast numbers, bone formation, and bone mass in mice. A

novel PTH receptor/cAMP/SIK/class IIa HDAC/CRTC axis may play a crucial role in osteocyte biology.

[00430] In one aspect, the present disclosure provides methods of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a SIK inhibitor.

[00431] In one aspect, the present disclosure provides methods of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a SIK inhibitor and Src inhibitor.

100432 1 In one aspect, the present disclosure provides methods of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a SIK inhibitor and CSF1R inhibitor.

[00433 1 In one aspect, the present disclosure provides methods of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a pharmaceutical composition described herein.

[00434] In another aspect, the present disclosure provides methods of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of a SIK inhibitor.

[004351 In another aspect, the present disclosure provides methods of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of a SIK inhibitor and Src inhibitor.

[00436) In another aspect, the present disclosure provides methods of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of a SIK inhibitor and CSFIR inhibitor.

[00437] In another aspect, the present disclosure provides methods of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of a pharmaceutical composition described herein.

[004381 In another aspect, the present disclosure provides methods of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00439] In another aspect, the present disclosure provides methods of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

100440] In another aspect, the present disclosure provides methods of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

100441 1 In another aspect, the present disclosure provides methods of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

100442 1 In another aspect, the present disclosure provides methods of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

100443 j In another aspect, the present disclosure provides methods of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00444] In another aspect, the present disclosure provides methods of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSF1R inhibitor.

[00445) In another aspect, the present disclosure provides methods of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

[00446] In another aspect, the present disclosure provides methods of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00447 1 In another aspect, the present disclosure provides methods of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00448] In another aspect, the present disclosure provides methods of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

100449] In another aspect, the present disclosure provides methods of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

[00450] In another aspect, the present disclosure provides methods of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00451] In another aspect, the present disclosure provides methods of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00452) In another aspect, the present disclosure provides methods of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

[00453 1 In another aspect, the present disclosure provides methods of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

100454 1 In another aspect, the present disclosure provides methods of decreasing the number of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00455J In another aspect, the present disclosure provides methods of decreasing the number of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00456] In another aspect, the present disclosure provides methods of decreasing the number of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSF1R inhibitor.

100457] In another aspect, the present disclosure provides methods of decreasing the number of osteoclasts in a subject in need thereof comprising

administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

[00458] In another aspect, the present disclosure provides methods of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

100459] In another aspect, the present disclosure provides methods of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

100460 1 In another aspect, the present disclosure provides methods of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

100461] In another aspect, the present disclosure provides methods of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

100462] In another aspect, the present disclosure provides methods of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

100463] In another aspect, the present disclosure provides methods of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

100464 1 In another aspect, the present disclosure provides methods of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

100465] In another aspect, the present disclosure provides methods of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

100466] In another aspect, the present disclosure provides methods of down-regulating the expression of the gene SOST in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

100467] In another aspect, the present disclosure provides methods of dovvn-regulating the expression of the gene SOST in a subject in need thereof comprising

administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00468] In another aspect, the present disclosure provides methods of down-regulating the expression of the gene SOST in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

[00469] In another aspect, the present disclosure provides methods of down-regulating the expression of the gene SOST in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

[00470] In another aspect, the present disclosure provides methods of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00471] In another aspect, the present disclosure provides methods of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00472] In another aspect, the present disclosure provides methods of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

[00473] In another aspect, the present disclosure provides methods of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

[00474] In another aspect, the present disclosure provides methods of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor.

[00475] In another aspect, the present disclosure provides methods of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and Src inhibitor.

[00476] In another aspect, the present disclosure provides methods of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a SIK inhibitor and CSFIR inhibitor.

[00477] In another aspect, the present disclosure provides methods of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition described herein.

100478] In another aspect, the present disclosure provides uses of SIK inhibitors in a method described herein.

[00479] In another aspect, the present disclosure provides uses of SIK inhibitors and Src inhibitors in a method described herein.

[00480] In another aspect, the present disclosure provides uses of SIK inhibitors and CSFIR inhibitors in a method described herein.

[00481] In another aspect, the present disclosure provides uses of a pharmaceutical composition described herein in a method described herein.

EXAMPLES

100482] In order that the disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the SIK inhibitors, pharmaceutical compositions, uses, and methods provided herein and are not to be construed in any way as limiting their scope.

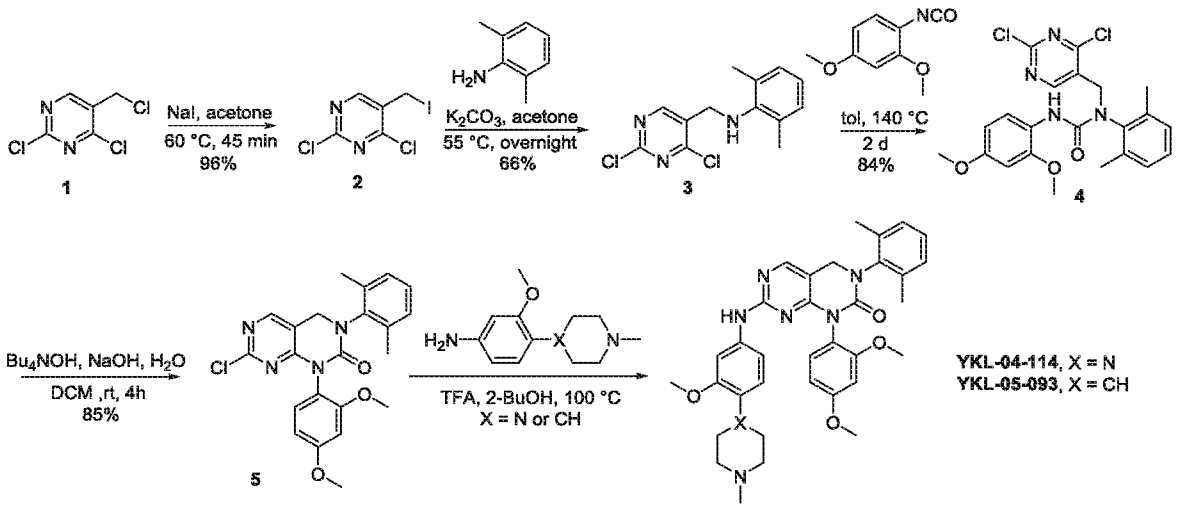
Example 1. Preparation of the SIK inhibitors

100483 1 The SIK inhibitors described herein can be prepared according to the methods known in the art. For example, the SIK inhibitors can be prepared according to the methods described in U.S. provisional application, U.S.S.N. 62/358,524, filed July 5, 2016, and international PCT application publications, WO 2016/014551, WO 2016/014542, and WO 2016/023014; the entire contents of each of which are incorporated herein by reference.

(00484) An exemplary synthesis of YKL-04-1 14 and YKL-05-093 is shown below. Commercially available trichloropyrimidine **1** was activated with sodium iodide to give iodomethyl pyrimidine **2,** which was reacted with 2,6-dimethylaniline to give compound **3.** Coupling of **3** with isocyanate provided compound **4** in good yield. Ring-closing reaction using tetrabutylammonium hydroxide afforded common intermediate 5 in good yield. By varying anilines and isocyanates used in the procedure described above, various analogues of 5 could be synthesized in multigram

scale, which enables the generation of a focused library of inhibitors for structure-activity relationship study. Finally, acid assisted coupling of intermediate 5 with respective aniline tail gave rise to YKL-04-114 and YKL-05-093 in good yields. For ***in vitro*** studies, compounds were dissolved in DMSO at 10 mM stocks. For ***in vivo*** studies, YKL-05-093 was dissolved in PBS plus 25 mM HCl, and solvent was used as vehicle control.

[00485] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on Bruker AVANCE spectrometer at 400 MHz for proton. Spectra are given in ppm (δ) and coupling constants, ***J***, are reported in Hertz. The solvent peak was used as the reference peak for proton spectra. LC-MS spectra were obtained on Agilent 1100 HPLC LC-MS ion trap electrospray ionization (ESI) mass spectrometer.



2,4-dichloro-5-(iodomethyl)pyrimidine ***(2)***

100486] A mixture of 2,4-dichloro-5-(chloromethyl)pyrimidine (15.0 g, 76.0 mmol), NaI (13.7 g, 91.4 mmol) in acetone was stirred at 60 °C for 45 min. The resulting precipitate (NaCl) was removed by filtration and washed with acetone. The combined filtrate was concentrated to give light yellow solid, which was purified by column chromatography on silica gel (eluting with DCM) to obtain 2,4-dichloro-5-(iodomethyl)pyrimidine **2** as a light yellow solid (30.8 g, yield 96%). LCMS (m/z): 289.3 $[M + H]^+$.

N-((2,4-dichloropyrimidin-5-yl)methyl)-2,6-dimethylaniline (3)

[00487] A mixture of 2,4-dichloro-5-(iodomethyl)pyrimidine **2** (7.0 g, 24.2 mmol), 2,6-dimethylaniline (3.8 g, 31.4 mmol), K_2C0_3 (5.0 g, 36.2 mmol) in acetone (60 mL) was stirred at 55 °C overnight. The solvent was removed and the residue was extracted with EtOAc (150 mL x 3). The combined organic phase was washed with brine (80 mL x 3), dried with Na_2S0_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether / EtOAc = 8/1, 4/1, 1/1) to get ,\'-((2,4-dich]oropyrimidin-5- yl)methyl)-2,6-dimethyl aniline **3** as a light brown solid (4.5 g, yield 66%). LCMS (m/z): 282.3 **[M + H]$^+$.**

I-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-l-(2,6-dimethylphenyl)urea (4)

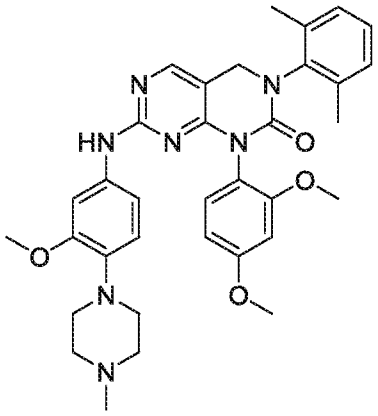
[00488] A round bottomed flask with a Dean-Stark apparatus was charged with *N*-((2,4-dichloropyrimidin-5-yl)methyl) -2,6-dimethylaniline **3** (3.0 g, 10.6 mmol), 1-isocyanato-2,4-dimethoxybenzene (2.5 g, 14.0 mmol), toluene (3 mL). The mixture was stirred at 130 °C for 2 d, cooled to rt, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether / EtOAc = 4/1, 2/1, 1/1, EA) to get l-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-l-(2,6-dimethylphenyl)urea **4** as a light brown solid (4.1 g, yield 84%). LCMS (m/z): 461.4 [M + H]$^+$.

7-chloro-I-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5-dfpyrimidin-2(lH)-one (5)

[00489] To the solution of l-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)- 1-(2,6-dimethylphenyl) urea **4** (3.1 g, 6.7 mmol) in DCM (20 mL) was added BU_4NOH (174 mg, 0.67 mmol), NaOH (474 mg, in 2 mL H_20 , 11.8 mmol). The mixture was stirred at rt for 4 h. The final mixture was diluted with H_20 (20 mL), extracted with DCM (80 mL x 3). The combined organic phase was washed with brine (50 mL × 2), dried with Na_2S0_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluting with DCM/MeOH = 20/1) to give 7-chloro- 1-(2,4-dimethoxyphenyl)- 3-(2,6-dimethylphenyl)- 3,4-dihydropyrimido[4,5-d]pyrimidin-2(1*H*)-one 5 as an off-white solid (2.4 g, yield 85%). ^{1}H NMR (DMSO-J_6, 400 MHz): δ 8.37 (s, 1H), 7.16-7.19 (m, 411), 6.68 (d, *J* =

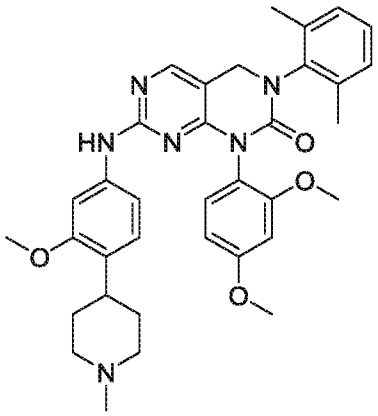
2.4 Hz, IH), 6.58 (dd, ***J*** = 8.8, 2.4 Hz, IH), 4.74 (dd, ***J*** = 5.5, 1.6 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H); LCMS (m/z): 425.4 $[M + H]^+$.

YKL-04-114



[00490] A mixture of 7-chloro- 1-(2,4-dimethoxyphenyl)- 3-(2,6-dimethylphenyl)- 3,4-dihydropyrimido[4,5- d]pyrimidin-2(l ***H***)-one 5 (10 mg, 0.024 mmol), 3-methoxy-4-(4-methylpiperazin- 1-yl)aniline (7.8 mg, 0.035 mmol), and TFA (5.5 mg, 0.048 mmol) in 2-BuOIl (0.5 mL) was stirred at 100 °C overnight. The reaction was cooled and concentrated. The residue was purified by prep-ll PLC (MeOH/lbO 5:95 - 100:0), followed by column chromatography on silica gel (0-10% MeOH in DCM) to afford YKL-04-1 14 as a white solid (8.0 mg, 56%). ^{1}H NMR (DMSO-J $_6$, 400 MHz): δ 9.21 (s, I H), 8.20 (s, I H), 7.25-7.22 (m, 4H), 7.03 (d, ***J*** = 8.4 Hz, IH), 6.98 (s, IH), 6.77 (d, ***J*** = 2.8 Hz, IH), 6.68 (dd, ***J*** - 8.8, 2.8 Hz, IH), 6.51 (d, ***J*** = 8.4 Hz, I H), 4.73 (**d, *J*** = 14.4 Hz, I H), 4.59 (d, ***J*** = 14.4 Hz, I H), 3.91 (s, 3H), 3.73 (s, 311), 3.68 (s, 311), 2.94 (m, 411), 2.58 (m, 411), 2.34 (s, 311), 2.32 (s, 311), 2.29 (s, 3H); LCMS (m/z): 610.7 $[M + H]^+$.

YKL-05-093



[00491] A mixture of 7-chloro- 1-(2,4-dimethoxyphenyl)- 3-(2,6-dimethylphenyl)- 3,4-dihydropyrimido[4,5- d]pyrimidin-2(l *H*)-one **5** (100 mg, 0.24 mmol), 3-methoxy-4-(l-methylpiperidin-4-yl)aniline (78 mg, 0.35 mmol), and TFA (55 mg, 0.48 mmol) in 2-BuOH (5 mL) was stirred at 100 °C overnight. The reaction was cooled and concentrated. The residue was purified by prep-HPLC (MeOH/$H_2$0 5:95 - 100:0), followed by column chromatography on silica gel (0-10% MeOH in DCM) to afford **YKL-05-093** as a white solid (127 mg, 89%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.16 (s, 1H), 8.09 (s, 1H), 7.12-7.09 (m, 4H), 6.95 (d, *J* - 8.0 Hz, 1H), 6.86 (s, 1H), 6.65-6.62 (m, 2H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.47 (d, *J* = 14.8 Hz, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 2.81 (m, 2H), 2.66-2.57 (m, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 1.95-1.90 (m, 2H), 1.56-1.46 (m, 4H); LCMS (m/z): 609.7 $[M + H]^+$.

Example 2. Biological assays

SIK controls osteocyte responses to parathyroid hormone Class IIa HDACs control bone mass through SOST

100492] Having previously demonstrated that HDAC5 blocks MEF2C -driven SOST expression in osteocytes (18), it was sought to determine whether HDAC5 and SOST interact *in vivo* to control bone mass. Two complementary approaches demonstrated that this was the case. First, compound heterozygosity of HDAC5 and SOST rescued the cortical and trabecular high bone mass phenotype of SOST+/- mice (Figures 10A to 10C). Second, anti-sclerostin antibody treatment rescued the trabecular osteopenia present in HDAC5-/- animals (Figure 10D), which have high levels of SOST expression (18).

100493] With evidence that HDAC5 control of SOST is physiologically important, it came into question if other class IIa HDACs function in osteocytes. It has previously been reported that HDAC5-/- mice display mild trabecular osteopenia (18) and (26). For these studies, analyses were extended to include the closely related family member HDAC4 for two reasons. First, endogenous MEF2C immunoprecipitates from Ocy454 cells contained HDAC4 in addition to HDAC5 (Figure 1A and (18)). Second, while no obvious skeletal phenotype was observed when HDAC4 was deleted from osteocytes using DMP1-Cre (27), compound deletion of both HDAC4 and HDAC5 led to a skeletal phenotype not observed in either single mutant strain, characterized by severe trabecular osteopenia *(Table 1* and Figure 10F

for results of static and dynamic histomorphometry results), increased osteocyte density (Figures 1B and 1C), disorganized, "woven" cortical bone (Figure ID), failure to respond to sclerostin antibody (Figure 1OD), and reduced endocortical bone formation (Figure 10E). As previously reported, mice lacking HDAC5 alone show mild cancellous osteopenia and reduced markers of bone formation by histomorphometry (18).

[00494] *Table 1.* Tibial histomorphometry results for 8 week old female mice of the indicated genotype.

	WT (n=8)		HDAC5-/- (n=9)		HDAC4f/f;DMP1-Cre (n=8)		DKO (n=9)	
	value	s.e.m.	value	s.e.m.	value	s.e.m.	value	s.e.m.
BV/TV (%)	8.12	0.880	5.84	0.447	6.72	0.717	**3.45**	0.707
Tb.Th (µm)	34	1.152	**28.9**	1.567	30.1	1.240	***20.5***	0.993
Tb.N (/mm)	2.36	0.201	2.01	0.093	2.2	0.201	1.6	0.263
Tb.Sp (µm)	414	40.636	487	24.333	464	65.724	**804**	166.333
MAR (µm/day)	1.96	0.085	**1.25**	0.087	1.74	0.159	**0.96**	0.010
MS/BS (%)	50.3	1.177	41.6	2.567	42.8	2.915	**35.4**	0.590
BFR/BV (%/year)	2257	56.890	**1462**	102.667	1848	203.534	**1293**	66.000
BFR/BS (µm3/µm2/year)	361	21.201	**193**	23.667	273	30.035	**125**	2.467
N.Ob/B.Pm (/mm)	13.6	0.763	**10.4**	0.887	14.1	0.512	11.9	0.813
Ob.S/B.Pm (%)	21.1	1.389	**14.2**	0.900	19.6	0.710	**14.9**	1.063
OS/BS (%)	14.2	2.039	**7.34**	0.840	14.1	1.852	**3.92**	0.623
O.Th (µm)	4.04	0.198	3.4	0.173	3.92	0.230	**2.94**	0.190
N.OC/B/Pm (N.Oc/B.Pm.) (/mm)	4.35	0.360	4.87	0.413	5.51	0.332	**6.57**	0.790
Oc.S/B.Pm (%)	13.2	0.866	14.2	1.070	15.1	0.965	18	2.017
ES/BS (%)	3.3	0.442	2.99	0.217	4.26	0.431	3.54	0.650

For each parameter, the value is shown followed by s.e.m.
Statistical analysis was performed by one-way ANOVA followed by Tukey's posthoc t test.
Values in bold indicate $p<0.05$ comparing WT and the strain of interest.
Values in *italics* indicates $p<0.05$ comparing HDAC5-/- and DKO groups.

[00495] "MAR" denotes mineral apposition rate. "MS/BS" denotes mineralizing surface / bone surface. "BFR/BS " denotes bone formation rate / bone surface. "BFR/BV" denotes bone formation rate/ bone volume. "N.Ob/B.Pm" denotes number of osteoblasts per bone perimeter. "N.Oc/B.Pm" denotes number of osteoclasts per bone perimetetr. "OS/BS" denotes osteoid surface / bone surface. "O.Th" denotes osteoid thickness. "ES/BS" denotes eroded surface per bone surface. "Ob.S" denotes osteoblast surface. "Oc.S" denotes osteoclast surface.

PTH signals through HDAC4 and HDAC5 to suppress SOST

[004961 It was next asked whether PTH, a known suppressor of SOST expression (9), worked through HDAC4, HDAC5, or both. PTH treatment of Ocy454 cells caused translocation from the cytosol to the nucleus of both HDAC4 and HDAC5 (Figure 2A). When phosphorylated, class IIa HDACs are predominantly cytoplasmic through retention by 14-3-3 proteins (19). When dephosphorylated, class Ila HDACs translocate to the nucleus where they potently inhibit MEF2-driven gene expression in muscle (28, 29). In neurons, HDAC5 nuclear import is additionally inhibited by CDK5-mediated phosphorylation at S279 (30). PTH signaling reduced phosphorylation of HDAC4 at S246/S632 and, to a lesser extent, HDAC5 at S259/S279 (Figures 2B and 11A). Others have over-expressed HDAC5 in a rat osteosarcoma cell line to demonstrate that mutation of these serines to alanine led to PTH-independent nuclear import (31). PTH-induced HDAC4/5 dephosphorylation and nuclear translocation requires cAMP signaling, as evidenced by the fact that these events did not occur in cells lacking Gsa via CRISPR/Cas9-mediated genome editing (Figures 2C and 2D and Figures 11B to 1IE). As previously described (17, 32, 33), Gsa deficiency significantly increases sclerostin production by osteocytes. However, reducing MEF2C levels via shRNA or by over-expressing a constitutively nuclear super-repressor form of HDAC5 rescued this phenotype (Figure 11F to 11I), consistent with the model that Gsa deficiency increases sclerostin production via a gain-of-function MEF2C phenotype.

[00497] To determine the roles of HDAC4/5 in mediating PTH actions, osteocytes lacking HDAC4 (via CRISPR/Cas9-mediated deletion, Figures 12A to 12E), HDAC5 (via lentiviral-mediated shRNA), or both (Figure 2E) were generated. While cells lacking HDAC4 or HDAC5 alone showed normal suppression of SOST expression in response to PTH, deletion of both HDAC4 and HDAC5 abolished PTH-

induced SOST down-regulation (Figure 2F, left). Importantly, HDAC4/5-deficient cells showed preserved PTH-induced RANKL up-regulation (Figure 2F, right). Chromatin IP revealed that PTH signaling reduces MEF2C binding to the +45 kB downstream SOST enhancer (Figure 2G); this occurs rapidly, at time points prior to observed reductions in MEF2C mRNA levels (Figure 12F and (34, 35)). HDAC4/5-deficient cells showed increased MEF2C binding at baseline, and failed to reduce MEF2C SOST enhancer occupancy in response to PTH (Figure 2H).

[00498] To determine the relevance of HDAC4/5 in mediating PTH actions *in vivo*, HDAC4/5-deficient mice were treated with PTH, and acute effects were measured 90 minutes later. While bone RANKL levels increased comparably across all four genotypes (WT, HDAC5-/-, HDAC4f/f;DMP 1-Cre, and HDAC4f/f;HDAC5-/-;DMP1-Cre), HDAC4/5-deficient mice were unique in that SOST levels failed to decrease following PTH treatment (Figures 3A and 3B). At the protein level, PTH administration significantly decreased the numbers of sclerostin-immunoreactive cortical osteocytes in all genotypes tested except in HDAC4/5-deficient animals (Figures 3C and 3D). Taken together, these results indicate that HDAC4 and HDAC5 are downstream of PTH receptor signaling, and are required for PTH-mediated SOST suppression, both *in vitro* and *in vivo.*

100499] While SOST is a well-studied PTH target genes, it represents a small portion of the portion of transcriptome regulated by parathyroid hormone (Figure 6A). Underscoring this point, once daily intermittent PTH treatment leads to comparable gains in trabecular bone density in mice lacking HDAC4 in osteocytes, HDAC5, or both (Figure 13A). Therefore, although class I HDACs are required for acute PTH-induced changes in SOST expression, other signaling arms and target genes downstream of the PTH receptor may exist that are important for the pharmacologic effects of this hormone.

SIK2 is inhibited by PTH, and required for PTH-mediated decreased HDAC4/5 phosphorylation and gene regulation

100500] Next, the signaling mechanisms used between activation of the PTH receptor and HDAC4/5 dephosphorylation were addressed. In chondrocytes *in vitro,* PTHrP drives HDAC4 into the nucleus via PP2A-mediated dephosphorylation, which can be blocked by okadaic acid (36). Surprisingly, okadaic acid did not block PTH-mediated decreased HDAC4/5 phosphorylation or SOST suppression in Ocy454 cells

(Figures 13B and 13C). Similarly, PTH-induced decreases in HDAC4/5 phosphorylation and SOST suppression were intact when PP2A catalytic subunit levels were reduced via shRNA (Figures 13D and 13E). Okadaic acid and PP2A shRNA efficacy was confirmed in these experiments based on observed increases in HDAC4 S246 phosphorylation (Figures 13B and 13D). Taken together, these results suggest that, unlike in chondrocytes, in osteocytes PTH-stimu!ated decreased phosphorylation of HDAC4/5 is not mediated by activation of PP2A.

100501 1 To explore candidate kinases whose activity might mediate the actions of PTH on HDAC4/5, salt inducible kinases (SIKs), AMPK family members reported to function as class Ila HDAC N-terminal kinases (22, 37) were examined. Subcellular fractionation experiments revealed that both SIK2 and S1K3 proteins are predominantly cytoplasmic in osteocytes (Figure 13E). Combined silencing of both SIK2 and SIK3 in Ocy454 cells significantly decreased HDAC4/5 N-terminal phosphorylation (Figure 4A).

[00502] Cyclic AMP signaling in adipocytes and hepatocytes inhibits SIK2 activity via protein kinase A (PKA)-mediated phosphorylation, which in turn sequesters SIK2 from its substrates (38-40). PTH signaling in osteocytes triggered SIK2 phosphorylation at S343, S358, and T484 (Figure 4B). PKA-mediated SIK3 phosphorylation was not triggered by PTH signaling (Figure 4B). Notably, PTH-stimulated SIK2 S358 phosphorylation occurred rapidly, faster than the fall in HDAC4/5 phosphorylation levels (Figure 4C). Importantly, SIK2-silenced cells showed normal up-regulation of the PTH target gene CITED 1 (41) (Figure 4D). In contrast, PTH-induced decreases in HDAC4/5 phosphorylation (Figure 4E) and SOST suppression (Figure 4F) did not occur in SIK2-silenced cells. Interestingly, PTH-induced RANKL upregulation, an HDAC4/5-independent phenomenon (Figure 2F and Figure 3A) also did not occur in SIK2-deficient osteocytes (Figure 4G), suggesting that another SIK substrate may be involved in PTH-mediated RANKL gene induction. SIK3 deficient cells showed normal PTH responses (Figures 4D, 4F and 4G), as predicted by the fact that this protein is not phosphorylated in response to PTH signaling. Cyclic AMP responses to PTH were slightly blunted in SIK2-silenced Ocy454 cells but were clearly present at PTH levels above 4 nM (Figure 13F). However, forskolin-induced cAMP up-regulation was normal in SIK2 deficient cells, yet this agent failed to regulate SOST or RANKL expression in the absence of SIK2 (Figure 4H).

[00503] To determine the relevance of SIK2 in mediating PTH actions *in vivo,* mice lacking SIK2 in DMPl -expressing cells (including osteocytes) were treated with PTH, and acute effects were measured in bone 120 minutes later. Figure 4I shows that DMPl-Cre deletion of SIK2 led to a significant reduction in S1K2, but not PTH receptor, mRNA levels in bone. Similar to the results in Ocy454 cells, PTH-induced Cited 1 up-regulation was preserved in SIK2^{0cyK0} mice (Figure 4J). However, PTH-induced SOST and RANKL gene regulation did not occur in the absence of SIK2 (Figure 4K).

|00504| RANKL is a known PTH target gene; previous studies have suggested an important role for CREB, through binding to an enhancer 75 kB upstream of the transcription start site (13-15, 42, 43). While CREB itself is not a known SIK substrate, the CRTC CREB coactivator proteins are (21). All three CRTC proteins are expressed in osteocytes; therefore, levels of each were reduced individually using shRNA. CRTC2 silencing was sufficient to block PTH-induced RANKL up-regulation (Figure 4L). Figure 13G to 131 shows that PTH-induced cAMP generation was normal in CRTC2-deficient cells. PTH promoted CRTC2 nuclear translocation in a Gsa-dependent manner (Figure 2C), and CRTC2 inducibly associated with the -75 kB "D5" RANKL enhancer (44) following PTH treatment (Figure 4M). In summary, these results demonstrate that two key SIK substrates, HDAC4/5 and CRTC2, play major roles in PTH-mediated regulation of SOST and RANKL expression, respectively.

Small molecule SIK inhibitors regulate SOST and RANKL expression in osteocytes

100505] Gene ablation studies suggested that SIK inhibition may be needed for PTH to regulate SOST and RANKL expression, and PTH signaling may lead to PKA-mediated SIK2 inhibition. Therefore, it was asked whether acute inhibition of SIK kinase activity in otherwise normal cells or mice would be sufficient to mimic these actions of PTH. HG-9-91-0 1 is a small molecule kinase inhibitor with demonstrated biologic activity against S!Ks in cultured macrophages, dendritic cells, and hepatocytes (39, 40, 45, 46). However, HG-9-91-01 is not SIK-specific and is not suitable for *in vivo* use; therefore, analogs were screened for based on the goals of improved specificity and pharmacokinetics. These efforts ultimately led to the identification of YKL-04-1 14 and its closely related analog YKL-05-093 (Figure 5A).

The K_d of YKL-05-093 for SIK2 is 7.1 nM, and its activity against a panel of 96 recombinant kinases is shown in *Table 2* (here SIK refers to SIK1 and QSK refers to SIK3) and shown graphically in Figure 14A. YKL-04-114 treatment of Ocy454 cells led to rapid, dose-dependent decreases in HDAC4/5 phosphorylation (Figures 5B and 5C), and nuclear translocation of HDAC4 and CRTC2 (Figure 5D). YKL-04-114 and YKL-05-093 caused rapid and potent SOST suppression and RANKL up-regulation (Figure 5E) without increasing cAMP levels (Figure 14B). Optimal efficacy at the level of HDAC4/5 dephosphorylation (~1 μM, Figure 5C) and gene expression (~0.5 μM, Figure 5E) occurred at comparable doses.

[00506] *Table 2*. Results of YKL-05-093 profiling against 96 recombinant kinases

Gene Symbol	% of control activity at 71 nM
ABL1	0.2
ACVR1B	50
ADCK3	93
AKT1	92
ALK	23
AMPK-alpha1	94
ARK5	77
AURKA	12
AXL	68
BMPR2	87
BRAF	66
BRSK1	74
BTK	0.45
CDK11	88
CDK2	99
CDK3	80
CDK7	85
CDK9	88
CHEK1	42
CSF1R	0.85
CSNK1D	98
CSNK1G2	100
DCAMKL1	89
DYRK1B	93
EGFR	5.9
EPHA2	7.1

Gene Symbol	% of control activity at 71 nM
ERBB2	3.5
ERBB4	6.1
ERK1	100
FAK	90
FGFR2	8.9
FGFR3	24
FLT3	20
GSK3B	68
HCK	1.2
H1PK2	100
IGF1R	100
!KK-alpha	93
IKK-beta	84
INSR	56
JAK2	13
JNK1	97
JNK2	89
KIT	1.8
LCK	0.75
LKB1	85
MAP3K4	60
MAPKAPK2	85
MARK!	84
MARK3	40
MEK1	20
MEK2	12
MELK	36
MET	92
MKNKl	76
MLK1	12
p38-alpha	0.95
p38-beta	47
PAK1	6.6
PAK2	75
PAK4	88
PCTKl	9 1
PDGFRA	11
PDGFRB	0.35
PDPK1	55
PIK3C2B	100
PIK3CA	84
PIK3CG	80

Gene Symbol	**% of control activity** at 71 nM
PIM1	89
PIM2	97
PIM3	84
PKAC-alpha	100
PLKl	100
PLK3	90
PRKCE	92
QSK	5.3
RAF1	100
RET	3.6
RIOK2	77
RIPK2	16
ROCK2	70
RSK2	51
SIK	**0.6**
SIK2	10
SNARK	6
SRC	0
SRPK3	88
TGFBR1	90
TIE2	32
TRKA	74
TSSK1B	83
TYK2	49
ULK2	31
VEGFR2	26
YANK3	95
ZAP70	52

[00507] Importantly, treatment with YKL-05-093 did not decrease HDAC4 S246 phosphorylation or cause SOST suppression in osteocytes lacking SIK2 and SIK3 (Figures 5F to 5G). In addition, PTH and YKL-05-093-mediated stimulation of RANKL expression was abrogated in cells lacking CRTC2 (Figure 511). So although YKL-05-093 does target other kinases *in vitro,* its cellular actions studied here depend on the presence of SIK2 and SIK3.

[005081 Based on the model that YKL-05-093 functions as a SIK inhibitor downstream of PTH-stimulated cAMP generation, one would predict that the inhibitor would regulate gene expression in Gsa-deficient osteocytes. Indeed, YKL-05-093 treatment of Gsa-deficient Ocy454 caused SOST suppression and RANKL up-

regulation with effects similar to forskolin, except, as expected based on its inability to increase cellular **cAMP** levels (Figure 14B), YKL-05-093 did not increase SIK2 S358 phosphorylation (Figures 5 1to 5J).

|00509 1 The Ocy454 osteocyte cell line was treated for 90 minutes with the indicated compound at 10 uM dose (Figure 17). Phospho-HDAC4 S246 levels were monitored by immunoblotting (top band) compared to DMSO control. Several compounds reduce HDAC4 S246 phosphorylation, but compound 3-9 (YKL-04-1 14) showed the most clear results across multiple replicates. Table X shows the compounds tested in Figure 17.

|00510j *Table 2A*. Compounds tested in Figure 17

Compound Number recited in Figure 17	Compound
3	HG-11-136-01
?3	HG-11-136-01
3-1	YKL-04-103
3-2	YKL-04-104
3-3	YKL-04-105
3-4	YKL-04-106
3-5	YKL-04-107
3-6	YKL-04-108
3-7	YKL-04-112
3-8	YKL-04-113
3-9	YKL-04-114
3-10	YKL-04-114
3-11	YKL-04-118
3-12	YKL-04-125
3-13	YKL-04-136-1
3-14	YKL-04-136-2
3-15	YKL-04-136-3
3-16	YKL-04-136-4
3-17	YKL-04-136-5
3-18	YKL-04-136-6
3-19	YKL-04-136-7
3-20	YKL-04-136-8
3-21	YKL-04-136-9
3-22	YKL-04-136-10
3-23	YKL-04-136-11

100511 1 In Figure 18, analogs of YKL-04-1 14 were synthesized and tested in a similar assay as in Figure 17. YKL-05-093 showed clear activity with respect to reducing HDAC4 S246 levels

[00512] Analogs of YKL-05-093 were tested in multiple experiments (Figure 19). Among the tested compounds in Figure 19, YKL-05-093 was the compound that most reproducibly led to reduced HDAC4 S246 phosphorylation.

[005131 Figure 20 shows additional data showing the activity of YKL-05-093 and some analogs thereof in HDAC4 S246 phosphorylation assays.

[00514] In Figure 21, Ocy454 cells (osteocyte cell line, also known at 6-9 cells) were cultured at 37 °C for 2 weeks to permit osteocyte differentiation. The cells were then treated with the indicated compound (0.5 μM) for 3.5 hours, and gene expression was analyzed by RT-qPCR. SOST expression was reduced by the indicated compounds. RANKL expression was increased by the indicated compounds. YKL-04-114 and YKL-05-093 were most active in these experiments at reducing SOST and increasing RANKL amongst the indicated compounds. These effects did not occur in Ocy454 cells lacking SIK2 and SIK3. Therefore, these changes in gene expression may be due to on-target effects of the indicated compound.

[00515] The experiments of Figure 22A are similar to the experiments as shown in Figure 21, using additional analogs of YKL-05-093. Figure 22B shows SIK2 IC_{50} data generated from an *in vitro* kinase assay.

[00516] Figure 23 is a plot of the data from Figure 22A and 22B showing the SIK2 IC_{50} on the x-axis and the effects of RANKL and SOST on the y-axis. The relationship may be affected by factors like poor cellular penetration of some of the compounds that potently inhibit SIK2 in a pure *in vitro* assay.

Small molecule SIK inhibitors mimic PTH action *in vitro*

[00517] The ability of YKL-05-093 to mimic the effects of PTH with respect to SOST and RANKL gene regulation supports the hypothesis that the actions of YKL-05-093 might mimic the effects of PTH on many genes. Therefore, RNA-seq was perfomed on Ocy454 cells treated for four hours with vehicle, PTH (1 nM), or YKL-05-093 (0.5 μM) to determine the overlap in global gene regulation by these two agents. 446 genes were significantly (>2 fold, FDR<0.05) regulated by PTH, and 257 genes were significantly regulated by YKL-05-093. Of the 446 PTH-regulated genes, 142 (32%) were co-regulated in the same direction by YKL-05-093 (Figures 6A and 6B and *Table 3* for differentially expressed genes, and *Table 4* for all RNA-seq data). This significant overlap was not due to random chance (Figures 15A and 15B). Gene ontology analysis for the genes regulated by both PTH and YKL-05-093 is shown in

Figures 15C and 15D: many of the co-regulated genes fit into categories of interest such as "ossification" and "mesenchyme development".

[00518] *Table 3*. Results of YKL-05-093 profiling against 96 recombinant kinases

Gene Symbol	% of control activity at 71 nM
ABL1	0.2
ACVR1B	50
ADCK3	93
AKT1	92
ALK	23
AMPK-alpha1	94
ARK5	77
AURKA	12
AXL	68
BMPR2	87
BRAF	66
BRSK1	74
BTK	0.45
CDK11	88
CDK2	99
CDK3	80
CDK7	85
CDK9	88
CHEK1	42
CSF1R	0.85
CSNK1D	98
CSNK1G2	100
DCAMKL1	89
DYRK1B	93
EGFR	5.9
EPHA2	7.1
ERBB2	3.5
ERBB4	6.1
ERK1	100
FAK	90
FGFR2	8.9
FGFR3	24
FLT3	20
GSK3B	68
HCK	1.2

Gene Symbol	% of control activity at 71 nM
HIPK2	100
IGF1R	100
IKK-alpha	93
IKK-beta	84
INSR	56
JAK2	13
JNK1	97
JNK2	89
KIT	**1.8**
LCK	0.75
LKB1	85
MAP3K4	60
MAPKAPK2	85
MARK1	84
MARK3	40
MEK1	20
MEK2	12
MELK	36
MET	92
MKNK1	76
MLK1	12
p38-alpha	0.95
p38-beta	47
PAK1	6.6
PAK2	75
PAK4	88
PCTK1	91
PDGFRA	11
PDGFRB	0.35
PDPK1	55
PIK3C2B	100
PIK3CA	84
PIK3CG	80
PIM1	89
PIM2	97
PIM3	84
PKAC-alpha	100
PLK1	100
PLK3	90
PRKCE	92
QSK	**5.3**
RAF1	100

Gene Symbol	**% of control activity at 71 nM**
RET	3.6
RIOK2	77
RIPK2	16
ROCK2	70
RSK2	51
SIK	**0.6**
SIK2	10
SNARK	6
SRC	0
SRPK3	88
TGFBR1	90
TIE2	32
TRKA	74
TSSK1B	83
TYK2	49
ULK2	31
VEGFR2	26
YANK3	95
ZAP70	52

[00519] *Table 4.* **All** RBA-seq data

Up with PTH only	**Up with YKL-05-093 alone**	**Up with both PTH and YKL-05-093**	**Down with PTH only**	**Down with YKL-05-093 only**	**Down with both PTH and YKL-05-093**
2310043M15Rik	1700023H06Rik	Ackr3	1700001L05Rik	Arc	6330403L08Rik
Abtb1	1700023L04Rik	Acsl3	2310022B05Rik	Arrdc4	Adra1d
Aldh3a1	A930018M24Rik	Adrb2	2700038G22Rik	Atoh8	Cd200
Ankrd44	Adamts1	Alx3	9930013L23Rik	Bahcc1	Chst15
Arl4c	Adck3	Arl4d	Abi2	Bcl2	Cxcl12
Baalc	Adrb1	Arrdc3	Adamts18	Ccl2	Cyp26b1
Batf	Aim1	Avpi1	Ahrr	Ccl7	Dlk2
Bglap	Apbb1	BB557941	Akap6	Csf1	Egr2
Bglap2	AU021092	C2cd4c	Ankrd34a	Ctgf	Enc1
C1qtnf1	Bmf	Cebpd	Ano6	Dlx2	Esm1
Camk4	Bmp6	Col13a1	Apln	Dlx5	F3

Up with **PTH** only	**Up with YKL-05-093 alone**	**Up** with **both PTH** and **YKL-05-093**	**Down with PTH** only	Down **with YKL-05-093 only**	Down with **both PTH** and **YKL-05-093**
Cede 109b	Btbdl7	Crem	Bcar3	Dlx6	Fam 198b
Cede 152	C130050 OlSRik	Crispld2	Bmp2	Dmpl	Fjxl
Cda	Cd24a	Cxcll	Bok	Dusp4	Fzd5
Cebpb	Coll la2	Enpp6	Car8	Dusp6	Fzd8
Ch25h	Dhrs3	**Eya2**	Cd2ap	Egrl	Gml0715
Chstl2	Duspl	Fam 167a	CdkSrl	Eps8	Gml0717
Cited!	Fbxo32	Fam20a	Cdol	Etv-5	Gml0718
Clec2d	Fosl2	Fos	Chst3	Gcnt4	Gm 10800
Col2al	Gm 11837	Gadd45a	Chsyl	Gmlll68	Gm 10801
Cyplbl	Gm22314	**Gjal**	CmyaS	Gml6516	Gm13186
Cyp26al	**Gm22633**	Glisl	Deptor	Gm23296	**Gml3493**
Ddc	Gm24119	Gm2222()	Dixdcl	Gm25047	**Gm21738**
Dio3	Gm25395	Gm22288	**Dlx3**	Gm26982	Gm26507
Dio3os	Gm9949	Gm22421	Dtx4	Gm3200	Gm26870
Dnajcl2	Gprl33	Gm22623	Dusp7	Gm9987	Gm5763
Dpt	GprcSc	Gm22628	Eepdl	**Heyl**	Gprl76
Efnb2	Grhl3	Gm23287	E112	Hmga2	Gprin3
Emb	**Hgf**	Gm23445	Fam 101b	Hoxcl2	Hdac9
Faml34b	Hrc	Gm23927	Fam 102a	Hoxcl3	**Id3**
Fam 169b	Inhbb	Gm23947	Faml3c	Id1	I117rd
Faml98a	Kctd7	Gm23966	Fam 180a	Id2	Klf5
Fam69c	Kdr	Gm23971	Fam2 17b	Irf5	Lfng
Fas	Krt80	Gm24204	Fam43a	KlhdcSa	Lmcd 1
Fbxo3 1	Mnl	**Gm24316**	Faϕ 2	Krtapl-5	Nuakl
Flrt2	Ncfl	Gm24447	Fgd3	**Mical2**	Pdgfa
Foxfl	Nfil3	Gm24620	Fhodl	Nfkbie	Rasl11a
FxydS	Nr4a3	Gm24917	Foxdl	**PcdhlO**	Rgs3
Fzdl	Pdzrn3	Gm24968	Gadd45g	Pdpl	Shisa2
Gfral	Perl	Gm25101	Gcntl	Prkg2	Spry!
Gm10327	PlekhaS	Gm25514	**Glil**	Ptprj	Tbx2
Gm 10638	Ptgfr	Gm25682	Gml0136	**Rinl**	Thbsl
Gm13705	Rftnl	**Gm26072**	Gm10602	Rnfl 50	Tiam2
Gm 16062	Rhpn2	Gm26323	Gm 10722	Rspo3	Tmem22 9b
Gm22265	Serpinb6b	Gm26324	Gm 11944	Sacs	Vgll3
Gm22307	Sikl	Gm2633 1	Gml29	Serpin33f	
Gm22488	Sox4	Gng4	Gm15663	Serpina3	

Up with PTH only	Up with YKL-05-093 alone	Up with both PTH and YKL-05-093	Down with PTH only	Down with YKL-05-093 only	Down with both PTH and YKL-05-093
				g	
Gm22513	Spon2	Has2	Gm16185	Skil	
Gm22661	Ston2	Hdac4	Gm17045	Smad7	
Gm22980	Tcp11l2	Igf1	Gm17275	Smad9	
Gm22997	Tmie	Il1rl1	Gm20471	Snai2	
Gm23008	Usp2	Il6	Gm20655	Socs1	
Gm23137	Utp14b	Kcne4	Gm23388	Socs5	
Gm23140	Wnt7b	Kcnj2	Gm6478	Spred1	
Gm23143	Xylt1	Kcnk10	Gm6578	Spry4	
Gm23153	Ypel1	Limch1	Gm9869	Synj2	
Gm23201		Lpcat2	Hoxa4	Tmem2	
Gm23240		Lrrc17	Hps3	Tnfaip3	
Gm23511		Mcam	Hspb7	Tnfrsf12a	
Gm23523		Metazoa_SRP	Ihh		
Gm23686		Mrgprf	Inhba		
Gm24207		mt-Co3	Insc		
Gm24299		mt-Tl1	Irx1		
Gm24305		mt-Tm	Irx3		
Gm24317		N4bp2l1	Irx5		
Gm24407		Ncald	Kcnb1		
Gm24438		Nr4a1	KCTD12		
Gm24449		Nr4a2	Kif21b		
Gm24494		Nrp1	Klf4		
Gm24596		Pde4b	Klhl30		
Gm25099		Pde4d	Krt12		
Gm25107		Phex	Lbh		
Gm25135		Pim1	Lifr		
Gm25189		Plau	Lmo7		
Gm25327		Prex1	Lmod1		
Gm25380		Rasl10b	Lpar3		
Gm25414		Rgs2	Lyst		
Gm25681		Rnf122	Mars2		
Gm25739		Rprl2	Mef2c		
Gm25781		S1pr1	Mgat5		
Gm25793		Scg2	Mtus2		
Gm25970		Serpinb1a	Murc		
Gm26104		Shc2	Ndnf		

Up with PTH only	Up with YKL-05-093 alone	Up with both PTH and YKL-05-093	Down with PTH only	Down with YKL-05-093 only	Down with both PTH and YKL-05-093
Gm26107		Slc7a7	Neurl2		
Gm26202		Slpi	Nexn		
Gm6872		Snai1	Nhsl1		
Gm9889		Snora15	P2rx5		
Got1		Tmem100	Pak3		
Gpr153		Tnfrsf9	Panx3		
Grem2		Tnfsf11	Pawr		
Hopx		Trib2	Phospho1		
Ifngr1		Trp53inp1	Pitx2		
Il4ra		Tsc22d3	Polr3e		
Irak3		Tspan11	Pparg		
Itga11		Vdr	Ppm1e		
Itga9		Wnt4	Rassf3		
Itgb3		Ypel3	Rcan2		
Kremen1			Rcor2		
Krt31			Rnf144b		
Krt33b			Rnf43		
Ksr1			Rpgrip1l		
Lef1			Rtn4rl1		
Lif			Runx1		
Lrp8			Runx2		
Ly6a			Sap30		
Ly6c1			Satb2		
Megf10			Scn3a		
Mgp			Serpine1		
Mir3068			Slc22a23		
Mir5136			Slc25a13		
Mir677			Slc40a1		
Mmp13			Slc8a3		
mt-Atp6			Smpd3		
mt-Tv			Smtnl2		
mt-Tw			Sncaip		
Nap1l5			Snta1		
Net1			Snx7		
Notum			Sp7		
Osmr			Stc2		
Parvb			Swap70		
Pdk4			Tbc1d4		

Up with PTH only	Up with YKL-05-093 alone	Up with both PTH and YKL-05-093	Down with PTH only	Down with YKL-05-093 only	Down with both PTH and YKL-05-093
Pdpn			Tcf7		
Pgpep1l			Tmeff1		
Pitpnc1			Tmem119		
Pkdcc			Tmtc2		
Plaur			Tnfrsf11b		
Plxna2			Tnik		
Ppap2b			Trmt61a		
Ppfibp2			Wisp1		
Prr5			Wnt10b		
Ptp4a1			Zbtb16		
Rnu12			Zfp296		
Rnu73b					
Rny3					
Rprl3					
Scarna17					
Sfrp1					
Sfrp4					
Slc1a3					
Slc37a2					
Slc43a2					
Smim3					
Snora28					
Snora36b					
Snora47					
Snora62					
Snord100					
Snord104					
Snord110					
Snord19					
Snord35b					
Snord49a					
Snord49b					
Snord61					
Snord65					
Snord71					
Snord82					
Snord85					
Soga2					

Up with PTH only	Up with YKL-05-093 alone	Up with both PTH and YKL-05-093	Down with PTH only	Down with YKL-05-093 only	Down with both PTH and YKL-05-093
Stat3					
Tgfa					
Tll1					
Tnfaip6					
Tnfrsf19					
Vit					
Wdr45					
Wif1					
Wisp2					
Wnt9a					
Zfp52					
Zfp791					
Zhx2					

Differentially-expressed genes: >2-fold, FDR<Q.05.

1005201 Overall, six clusters of differentially-expressed genes were identified: those up-regulated by PTH alone (172 genes), YKL-05-093 alone (56 genes), and both PTH and YKL-05-093 (97 genes), and those down-regulated by PTH alone (132 genes), YKL-05-093 alone (59 genes), and both PTH and YKL-05-093 (45 genes). The appropriateness of gene categorization was assessed for selected genes from each of these 6 clusters (FAM69C, ADAMTS1, WNT4, KLHL30, DUSP6, and CD200, respectively) by RT-qPCR from independently generated samples (Figures 6C to 611). While YKL-05-093 regulation of many of its target genes not co-regulated by PTH did occur in cells lacking SIK2 and SIK3 (Figure 15E), regulation of WNT4 and CD200 (genes co-regulated by both PTH and YKL-05-093) by YKL-05-093 did not occur in SIK2/3 deficient cells (Figures 6I and 6J). In total, 13/19 genes measured showed SIK2/3-dependent regulation by YKL-05-093, while 6/19 genes measured showed regulation by YKL-05-093 independent of the presence of SIK2/3 (Figures 6I to 6J and 15E). Taken together, these results demonstrate that a major arm of PTH signaling in Ocy454 cells can be mimicked by SIK inhibition.

YKL-05-093 mimics PTH actions *in vivo*

[00521] While YKL-04-114 and YKL-05-093 had comparable activity *in vitro*, YKL-05-093 showed somewhat improved stability when exposed to murine hepatic microsomes *in vitro* (Figure 16). Therefore, mice were treated with YKL-05-093 and effects on gene expression in bone were assessed 2 hours later. Similar to acute PTH administration (Figures 3A to 3D), intraperitoneal YKL-05-093 administration led to dose-dependent SOST suppression and RANKL up-regulation in osteocyte-enriched bone RNA (Figures 7A and 7B). This was accompanied by reductions in sclerostin protein levels measured by immunohistochemistry (Figure 7C). Finally, expression of genes identified by RNA-Seq as co-regulated by PTH-1 and YKL-05-093 *in vitro* were measured: as shown in Figures 7D to 71, *in vivo* 20 μπιοϊ/kg YKL-05-093 treatment leads to significant regulation of VDR, WNT4, NR4A2, NUAK1, PDGFA, and CD200 expression in the directions predicted from the *in vitro* experiments. Therefore, acute YKL-05-093 treatment *in vitro* and *in vivo* engages a program of gene expression quite similar to one used by parathyroid hormone, thus identifying SIK inhibition as an important mechanism used by PTH to regulate gene expression in osteocytes.

Small molecule SIK inhibitors boost **bone formation and bone mass *in vivo***

100522 1 YKL-05-099 (25) was also tested. Developed in parallel efforts to design SIK inhibitors suitable for *in vivo* use, YKL-05-099 is well-tolerated and achieves free serum concentrations above its IC_{50} for SIK2 (34 nM) for >16 hours (25).

[00523 1 First, *in vitro* experiments were performed to characterize the effects of YKL-05-099 in Ocy454 cells. In these experiments, YKL-05-099 was compared side-by-side with YKL-05-093. As expected, YKL-05-099 leads to dose-dependent reduction in HDAC4 S246 phosphorylation (Figure 8A). Furthermore, YKL-05-099 treatment causes SOST down-regulation and RANKL up-regulation in a SIK2/3-dependent manner (Figure 8B). Like YKL-05-093, acute intraperitoneal administration of YKL-05-099 *in vivo* leads to SOST down-regulation and RANKL up-regulation (Figure 8C).

100524] Male mice were then treated with vehicle or YKL-05-099 (6 mg/kg) once daily via intraperitoneal injection for 2 weeks. Bone RNA from these animals revealed that RANKL levels were increased and there was a trend towards reduced SOST (Figure 8D). In addition, osteoblast marker genes (osteocalcin and COL1A1)

were significantly increased by YKL-05-099 treatment, suggesting possible positive effects on osteoblastic bone anabolism (Figure 8D). To determine effects on bone mass and cellular composition/activity, static and dynamic histomorphometry were performed. Indeed, once daily YKL-05-099 treatment increased cancellous bone mass (Figure 8E) and osteoid surface (Figure 8F), suggesting accelerated bone formation. Dynamic histomorphometry revealed that YKL-05-099 led increased mineralizing surface, a trend towards increased matrix apposition rate, and increased bone formation rate (Figures 8G to 8I and 8L). At the cellular level, YKL-05-099 treatment increased osteoblast numbers (Figures 8J and 8M) and reduced osteoclast numbers (Figure 8K). Other than the observed reduction in osteoclast numbers, these findings are quite similar to the effects of once daily PTH treatment.

Discussion

[0001] PTH is currently the only approved osteoporosis therapy that promotes new bone formation. While its effects on target cells in bone are broad, major target genes in osteocytes responsible for its ability to increase both bone formation and resorption are SOST and RANKL, respectively. Here, it was demonstrated that SIKs may act as gatekeepers to regulate a major arm of PTH signaling in osteocytes, including (but not limited to) these two important target genes. Tonic SIK activity may lead to constitutive phosphorylation and cytoplasmic localization of HDAC4/5 and CRTC2. Activation of protein kinase A, as may occur with activation of the PTH receptor (8), may lead to multisite phosphorylation on S1K2, modifications that inhibit its cellular activity (38, 40). This inhibition may reduce tonic HDAC4/5 and CRTC2 phosphorylation, which in turn leads to their nuclear localization and action on respective target genes (Figure 9).

[0002] HDAC4/5 are required for PTH-stimulated SOST repression in osteocytes, through effects on MEF2C binding to the +45 kB SOST enhancer. Previous overexpression studies have suggested that PTH signaling impinges on the upstream SOST enhancer (31, 51, 52): here, it is shown that HDAC4/5 are required for this effect using loss of function approaches *in vitro* and *in vivo*. At later time points, PTH treatment reduces in MEF2C mRNA levels (34, 35, 53), in addition to the post-translational effects on DNA binding observed here earlier (Figure 2G). Similarly, PTH induces both the rapid nuclear translocation of HDAC4 and, at later time points, increases in HDAC4 mRNA (Figures 6A to 6J and (54)). It is interesting that PTH

signaling has evolved two complementary mechanisms to inhibit MEF2C activity: HDAC4/5-mediated inhibition of binding of MEF2C to target genes and inhibition of transcription of the MEF2C gene. Since MEF2C autoregulation is known to occur (55), future studies will focus on whether class IIa HDACs regulate MEF2C-driven expression of MEF2C itself, and other targets of MEF2C in osteocytes (56, 57).

[0003] HDAC4/5 "DKO" mice display several phenotypes not present in either single knockout strain (Figures lOA to lOE). Notably, sclerostin transgenic mice (58, 59) do not display woven bone and increased osteocyte density, and sclerostin antibody did not increase bone mineral density (BMD) in DKO animals. Therefore, class IIa HDACs control expression of additional genes in osteocytes that potently regulate skeletal biology. In addition, as evidenced by the fact that HDAC4/5 "DKO" mice show a preserved bone anabolic effect of intermittent PTH treatment (Figure 13A), class II HDAC/SOST-independent pathways that mediate the pharmacologic effects of parathyroid hormone must exist.

[0004] Interesting parallels and distinct differences are noted between PTH-mediated SOST suppression in osteocytes and PTHrP-mediated suppression of expression of the Collagen X gene in growth plate chondrocytes (36). While both pathways may utilize a class Ila HDAC/MEF2 mechanism of action, the signaling events required for HDAC4 nuclear translocation may differ. PTH signaling in osteocytes may-involve inhibition of SIK activity, while in chondrocytes, PTHrP signaling may activate the cAMP-dependent phosphatase PP2A. That being said, a role for SIKs in PTHrP signaling in chondrocytes cannot be excluded given the fact that SIK3-deficiency (23) appears to phenocopy the effects of PTHrP overexpression (60). The experiments with okadaic acid and PP2A shRNA (Figures 13A to 13D) argue against a major role for PP2A in mediating PTH signaling in osteocytes. Because the inhibition of HDAC4/5 phosphorylation in response to PTH was shown to be substantial, any further action of PTH on PP2A or other phosphatases would be likely to have a modest effect on overall phosphorylation levels.

[0005] PTH signaling to regulate RANKL expression in osteoblasts and osteocytes has been studied extensively over the past decade. Many investigators have demonstrated a role for a cAMP/CREB pathway via the gene's upstream enhancers (14, 42, 44, 61). Herein it is shown an additional requirement for the presence of a CREB co-activator, CRTC2, for PTH-induced RANKL gene regulation. It is of interest that PTH action may require two pathways, one involving a direct PKA target

(CREB) and another that uses PKA-mediated SIK inhibition. Since SIK inhibition, through suppression of SOST expression, can also increase bone formation, one can speculate that this use of the SIK pathway may force PTH action to link bone resorption and bone formation.

[0006] A recent report has suggested that, in osteoblasts, PTH signaling promotes proteasomal degradation of HDAC4 which in turn allows MEF2C-driven activation of the RANKL promoter (26). No changes in HDAC4/5 levels are observed after PTH treatment, which may be explained by the differing time courses and cell types used. PTH may induce RANKL expression via its -75 kB enhancer through SIK-dependent CRTC2 nuclear translocation.

[0007] The use of SIK inhibitors uniquely allows us to examine the acute effects of changes in SIK enzyme activity in cells and mice. These experiments show that the effects of SIK inhibition are rapid enough to mediate the effects of PTH on SOST and RANKL expression. In this way, though the inhibitors are less specific than gene knockout or shRNA-mediated expression knockdown, they may complement the data derived from the genetic studies. While YKL-05-093 and YKL-05-099 do inhibit kinases other than SIKs when tested *in vitro,* many of its effects in Ocy454 cells were not observed when SIK2/3 proteins were absent.

[0008] The role of SIK2 and SIK3 (the predominant SIKs expressed in osteocytes) in bone biology *in vivo* remains incompletely understood. Global SIK2 knockout mice have been described to display phenotypes in melanocytes (62), neurons after ischemic injury (63), cardiomyocytes during hypertrophy (64), and in lipid homeostasis (65). Conditional SIK2 mutant alleles have been described as well (40, 66) to further study the role of this kinase in hepatocytes and in the pancreas. Global SIK2 knockout mice have no reported skeletal phenotype to date. SIK2 has been deleted from DMPl-Cre expressing cells and it has been observed that this gene may be required for the acute response of osteocytes to PTH. A detailed description of the global bone phenotype of the $SIK2^{0cyK0}$ strain remains to be determined. Global SIK3 deficient mice display a dramatic growth plate phenotype (23) that confounds study of osteocyte biology *in vivo.* A conditional SIK3 allele has been reported, and deletion in chondrocytes shows the cell-intrinsic role for SIK3 in these cells (67).

[0009] SIK inhibition downstream of cAMP signaling has long been appreciated to occur (38, 45, 46, 68), but the relative contribution of SIK inhibition to overall changes in gene expression due to Gsa-coupled GPCR signaling has not previously

been explored. Remarkably, 32% of genes regulated by PTH in osteocytes were co-regulated by YKL-05-093. While it is likely that many of these genes (like SOST and RANKL) are regulated in turn by HDAC4/5 and CRTC2, undoubtedly additional SIK2/3 substrates may be responsible for these widespread effects.

[0010] Recently, pterosin B was reported as a small molecule inhibitor of SIK3 with *in vivo* activity in a SIK3-dependent murine osteoarthritis model (67). Interestingly, this small molecule leads to ubiquitin-dependent SIK3 degradation, and therefore acts in a manner distinct to that of YKL-05-093 and YKL-05-099 which function as kinase inhibitors (25). While SIK2 deficiency was sufficient to abrogate responses to parathyroid hormone *in vitro* and *in vivo* (Figures 4A to 4M), combined SIK2 and SIK3 deficiency was required to blunt effects of YKL-05-093 and YKL-05-099. This is consistent was potential redundancy between these two kinases (40), and the fact that both inhibitors potently target SIK3 in addition to SIK2.

[0011] In many regards, YKL-05-099 treatment mimics the effects of once-daily PTH treatment *in vivo.* However, one notable exception is present. PTH treatment increases osteoclastic bone resorption, in part due to PTH-induced RANKL up-regulation (13). Although YKL-05-099 potently increases RANKL levels in bone (Figure 8D), osteoclast numbers are actually decreased by this treatment (Figure 8J). In addition to targeting SIK2, YKL-05-099 is known to inhibit the tyrosine kinase Src (25). Src deficiency leads to osteoclast defects and osteopetrosis (69). Therefore, combined SIK and Src inhibition may lead to the desirable therapeutic combination (16) of increased bone formation and reduced bone resorption. More detailed assessment of the long-term safety profile of YKL-05-099 will be required to determine if its profile of kinase inhibition will be well-tolerated over time.

[0012] Recombinant PTH is the only current osteoanabolic therapy approved for osteoporosis treatment. The data show that distinct signaling modules existed downstream of PTH receptor signaling, including a major arm involving SIK inhibition. SIK inhibition may be sufficient to reduce sclerostin levels and to mimic many of the other effects of PTH in osteocytes at the level of gene expression. Furthermore, *in vivo* SIK inhibition with YKL-05-099 boosted osteoblast numbers, osteoblast activity, and trabecular bone mass. Inhibitors of SIK action may provide a novel approach to mimic PTH action to stimulate bone anabolism.

Methods

Animal studies

[0013] All animals were housed in the Center for Comparative Medicine at the Massachusetts General Hospital, and all experiments were approved by the hospital's Subcommittee on Research Animal Care. HDACS-null mice (70) and HDAC4 f/f mice (71) were generously provided by Dr. Eric Olson (University of Texas Southwestern Medical Center, Dallas, TX) and were backcrossed to C57B/6 mice for at least 6 generations. DMPl-Cre mice (27) were generously provided by Dr. Jian (Jerry) Feng (Texas A&M University, Baylor College of Dentistry, Dallas, TX). "DKO" HDAC4/5 mice were of the following genotype: HDAC4f/f;HDAC5-/-;DMPl-Cre. SIK2 f/f mice were as described (40), and were bred to DMPl-Cre animals to generate $SI^{K}\ 2^{OcyKO}$ mice. ES cells carrying the targeted SOST allele $Sost^{tm1(KOMP)V,cg}$, in which the SOST coding sequence has been replaced by LacZ and floxed Neo cassette, were obtained from the Knockout Mouse Project (KOMP) Repository. Clone VG10069-BE8 was injected into blastocysts, and the resulting SOST+/- mice were crossed to IIDAC5 mutant animals to generate compound heterozygous mice. In all instances, skeletal phenotypes were evaluated in 8 week-old sex-matched littermates. For acute effects of PTH on bone gene expression, animals were treated with PTH (1-34, 300 μg/kg, subcutaneous administration) and then sacrificed 90 minutes later. For acute effects of YKL-05-093 on bone gene expression, animals were treated with the indicated doses of compound (dissolved in PBS + 25 mM HQ) or solvent via intraperitoneal injections, and sacrificed 2 hours later. Experiments with YKL-05-099 were performed in a similar fashion: compound was dissolved in PBS + 25 mM HC1 and injected I.P. once daily five times per week for a total of 10 injections. For *in vivo* sclerostin antibody treatment, mice were treated twice weekly with sclerostin antibody (50 mg/kg, subcutaneous administration, generously provided by Dr. Michael Ominsky, Amgen) for 6 weeks. Power calculations were performed based on pilot experiments in which standard deviations and magnitudes of effect sizes were estimated. For experiments in which mice were treated with either vehicle or PTH (or YKL-05-093), mice were assigned to alternating treatment groups in consecutive order.

Antibodies and compounds

|0014] Antibodies against phospho-HDAC4/5/7 S246/259/155 (3443), phospho-HDAC4 S632 (3424), MEF2C (5030), tubulin (2146), phospho-PKA substrate (9624), and PP2Acs (2259) were purchased from Cell Signaling Technology (Danvers, MA). HDAC4 (ab 12172) and GFP (ab6556) antibodies were from Abeam (Cambridge, MA). FLAG antibody (F1804) was from Sigma (St. Louis, MO). CRTC2 (ST 1099) and SP1 (07-645) antibodies were from EMD Millipore (Darmstadt, Germany). Gs,alpha antibody (C-18) was from Santa Cruz Biotechnology (Santa Cruz, CA). Phospho-HDAC5 S279 (30) antibody was a generous gift from Dr. Chris Cowan (McLean Hospital, Belmont, MA). Antibodies recognizing phosphorylated and total forms of SIK2 and SIK3 were as described (39, 40). The phospho-SIK3 (T469) antibody was generated by YenZym Antibodies by immunizing rabbits with mouse SIK3 peptide (Res 463-476 of mouse SIK3 (www.kinase.com) : *CLSMRRH-*p*T-VGVADPR (SEQ ID NO: 5), a terminal cysteine (*C) was added to the peptide sequence to allow peptide conjugation to carrier proteins and "//'denotes the phosphorylated residue). For sclerostin immunohistochemistry, biotinylated anti-sclerostin antibody (BAF1589) was purchased from R+D (Minneapolis, MN). Synthetic human PTH(l-34) was synthesized by Dr. Ashok Khatri (peptide/protein core facility, MGH). Forskolin (F6886), staurosporine (S5921), and okadaic acid (01 13) were from Sigma. Oligonucleotides were synthesized by the DNA synthesis group of the CCIB DNA Core Facility at MGH (Boston, MA).

Cell culture

[0015] For all experiments, a single cell subclone of Ocy454 cells (17, 18) was used. Cells were passages in alpha-MEM supplemented with 10% heat-inactivated fetal bovine serum and 1% antibiotics (penicillin/streptomycin, Fungizone) at 33°C with 5% C02. Cells were plated at 50,000 cells/ml and allowed to reach confiuency at 33˚C (typically in 2-3 days). At this point, cells were transferred to 37°C for subsequent analysis. For immunoblotting, cells were always analyzed after culture at 37°C for 7 days. For gene expression analysis, cells were analyzed after culture at 37°C for 14 days. Mycoplasma contamination was ruled out by PCR. Cells were routinely assayed for SOST expression at 37°C and examined for osteocytic morphology.

shRNA infections and CRISPR/Cas9-mediated gene deletion

[0016] See *Tables 5 and 6* for all shRNA and sgRNA targeting sequences used. For shRNA, lentiviruses were produced in 293T cells in a pLKO.1-puro (Addgene, plasmid 8453) backbone. Viral packaging was performed in 293T cells using standard protocols (www.broadinstitute.org/rnai/public/resources/protocols). For experiments with SIK2/SIK3 double knockdown, one shRNA was transferred into a blasticidin resistance-conferring backbone (Addgene, plasmid 26655). Cells were exposed to lentiviral particles (MOI 1=1) overnight at 33"C in the presence of polybrene (5 ug/ml). Media was then changed and puromycin (2 μg/ml) and/or blasticidin (4 μg/ml) was added. Cells were maintained in selection medium throughout the duration of the experiment. HDAC5 S/A cDNA was introduced via lentivims as described (18).

[0017] *Table 5.* shRNA target sequences

HDAC5	CATCGCTGAGAACGGCTTTAC	6
GNAS	TCGGGATGAGTTTCTGAGAAT	7
LacZ	CCAACGTGACCTATCCCATTA	8
SIK2	CTTGTTGGTGGAACGTCTAAA	9
SIK3	CGCACGGAAGTTATGGAAGAT	10
MEF2C	CCCTATGAATCTAGGAATGAA	11
CRTC1	ATAGGTCACCTGTCCGATAAT	12
CRTC2	CAAGGTGTAGAGGGAAATCTT	13
CRTC3	GACAATGTAGCACTGAATTAA	14

[0018] *Table 6.* sgRNA target sequences

HDAC4 #1	TGACGTGTAGAGAGGAAGTG	15
HDAC4 #2	ACTTACCCATACCAGTAGCG	16
GNAS #1	CCTCGGCAACAGTAAGACCG	17
GNAS #2	GATCCTCATCTGCTTCACAA	18

[0019] For sgRNA experiments, first Ocy454 cells were stably transduced with a hygromycin resistance-conferring Cas9-expressing lentivims to ensure no effects on sclerostin secretion. Sclerostin ELISAs were performed exactly as described in (18). For subsequent experiments, sgRNA sequences were subcloned into PX458 (a gift from Feng Zhang, Addgene plasmid 48138 (72)), a plasmid that co-expressed an sgRNA, Cas9, and eGFP. Ocy454 cells were transfected with this plasmid using Fugene HD (Promega, Madison, WI) (1 μg plasmid per well of a 6 well plate). 48

hours later, eGFP^{hi} cells were recovered by FACS-based sorting and plated in 96 well plates at 1 cell per well. Media was changed once weekly, and 3 weeks later colonies were identified by visual inspection. Colonies were then expanded and analyzed for loss of target protein expression by immunoblotting. For HDAC4 and Gsa targeting experiments, at least 3 independent clones (deriving from 2 independent sgRNA sequences) were analyzed and showed similar results. Allele-specific sequencing in mutant clones was performed by amplifying the genomic region of interest surrounding the targeted site by PGR. PGR products were then TOPO-TA cloned, and multiple bacterial colonies sequenced using T7 sequencing primer.

Real-time quantitative PGR

[0020] Total RNA was extracted from cultured cells using RNeasy (Qiagen, Venlo, Netherlands) following the manufacturer's instructions. For long bone RNA isolation, mice were sacrificed and both femurs were rapidly dissected on ice. Soft tissue was removed and epiphyses cut. Bone marrow cells were then removed by serial flushing with ice-cold PBS. TRIzol (Life Technologies) was added and sampled were frozen at -80C and then homogenized. RNA was then extracted per the manufacturer's instructions, and further purified on RNeasy microcolumns prior to cDNA synthesis. RNA with A260/280 ratio < 1.7 was not used for downstream analysis. For cDNA synthesis, 1 µg RNA was used in synthesis reactions according to the instructions of the manufacturer (Primescript RT, Takara). SYBR Green-based qPCR detection was performed using FastStart Universal SYBR Green (Roche, Basel, Switzerland) on a StepOne Plus (Applied Biosystems, Carlsbad, CA) thermocycler. All PGR primer sequences are listed in *Tables* 7 and *8*.

[0021] *Table 7.* RT-qPCR primer pairs

	Forward primer	SEQ ID NO:	Reverse primer	SEQ ID NO:
SOST	GCCTCATCTGCCTACTTGTG	19	CTGTGGCATCATTCCTGAAG	37
RANKL	GCTGGGCCAAGATCTCTAAC	20	GTAGGTACGCTTCCCGATGT	38
ß-actin	CCTCTATGCCAACACAGTGC	21	ACATCTGCTGGAAGGTGGAC	39
CITED1	CCAACCTTGGAGTGAAGGAT	22	CCAGAGGAGCTAGTGGGAAC	40

	Forward primer	SEQ ID NO:	Reverse primer	SEQ ID NO:
CRTCl	TCTGCAGACCAGGAG AACAC	23	GTGGATGTTGGTGAG GTCAG	41
CRTC2	CCATAGTCACCCATC ACTGC	24	GCACTCAGGACAGGA **GATGA**	42
CRTC3	**ATGGGTTTCTGTGAT GGTGA**	25	ACAGGGACTGGATCT CCTTG	43
FAM69C	TATTAGCCACATTGC CCTCA	26	ATGGCGAAGTTCTCA GGTTT	44
ADAMTS1	**GAAACCATGCTCGTA GCTGA**	27	AATTCCTAATGCTGG GATGC	45
WNT4	GGCCTTTGTATACGC CATCT	28	CACAGCCACACTTCT **CCAGT**	46
KLHL30	AGGTGCAATCTCAAC **ACAGC**	29	CiTAGGCCTCCATCTCC **ACAT**	47
DUSP6	CATGCAGAAGCTCAA CCTGT	30	AGGGTCCTTTCGAAG TCAAG	48
CD200	GAGCTGGGACTCTGG AACTC	31	GAGGGTAAGGCAAGC TGTTC	49
VDR	ACACTGCAGACCTAC ATCCG	32	AGCCAGCTTCTGGAT CATCT	50
NR4A2	ATCTCCTGACCGGCT CTATG	33	**TGGGTTGGACCTGTA** TGCTA	51
NUAK1	GTGGATGCTGATGGT GAATC	34	TGCCAAGAGTGGAGA CTCAG	52
PDGFA	CGAAGTCAGATCCAC AGCAT	35	GGGCTCTCAGACTTG **TCTCC**	53
MEF2C	ATCAGCAGGCAAAG ATTGTG	36	CTGTTATGGCTGGAC **ACTGG**	54

|0022] *Table 8*. **Primer pairs for ChlP qPCR** (RANKL **nomenclature is per Onal** *et al*., 2015)

	Forward primer	**SEQ ID NO:**	**Reverse primer**	**SEQ ID NO:**
SOST +45kB	GAGCCTGGTCTCAT TTGTTG	55	CCTCTCTAGGATGGC AGCAT	67
SOST promoter	CGCTGTGGTATGCT AACTGG	56	CTTACAAGTCGAGGC AGGTG	68
MEOX promoter	CCTCTGGGCAATTT GTCTCT	57	CTCCAGGGATTGAGA GAAGG	69
RANKL D2	CTTGGAAGGACTCC AGGAAA	58	CCTTTCTCAGAGCAC ACTGG	70
RANKL D3	AAATCCCATTTGCTT TCCAG	59	GAGCTGTGTCCTAGA AGAATTGTC	71
RANKL D4	TGGGAGACTCAGTT	60	TGTTGTTGGTTCGTT	72

	Forward primer	SEQ ID NO:	Reverse primer	SEQ ID NO:
	GTTGCT		GTCCT	
RANKL D5	GATGGAGTC AGGAT GCACAG	61	GAGCCCTGAGAACA GTGTGA	73
RANKL D6	GAAGAGAACATTGC TGGTTGC	62	TAAGGATGCTTTCCC AGCTC	74
RANKL D7	CACCTGTAATTCTA GCACGCA	63	TCACGCTCCTCTCAA ATTCA	75
RANKL T1	TGGTCCAGGTCAAG CAATAA	64	GGCAACACAAACCTC CTGTA	76
RANKL T2	CCTCTGGGAGCAAA TGAGAG	65	GGTGCATCTGTGGAT GGTAA	77
RANKL T3	CCTTGAATTCTTTGG ACTGGA	66	TACACTGTCCTTTCC TTGCG	78

Immunoprecipitation and Immunoblotting

[0023] Whole cell lysates were prepared using TNT buffer (20 mM Tris-HCT pH 8, 200 mM: NaCl, 0.5% Triton X-100 supplemented with 1 mM DTT, 1 mM NaF, and protease inhibitors (Pierce, catalog #88266). This lysis buffer was used for all experiments except those in which SIK2 and SIK3 phosphorylation was measured using phospho-specific antibodies: for those experiments, cells were lysed in buffer containing 50 mM Tris-HCT pH 7.5, 270 mM sucrose, 1 mM EDTA, 1 mM EGTA, and protease/phosphatase inhibitors. MEF2C (18) and SIK3 (39, 40) immunoprecipitations were performed as described. Subcellular fractionation was performed using commercially-available kit (Thermo Scientific, product number 78840) following the manufacturer's instructions. Lysates (15-20 μg cellular protein) were separated by SDS-PAGE and proteins were transferred to nitrocellulose. Membranes were blocked with 5% milk in TBST, and incubated with primary antibody overnight at 4˚C. The next day, membranes were washed, incubated with appropriate horseradish peroxidase (HRP)-coupled secondary antibodies, and signals detected with enhanced chemiluminescence (ECL, Pierce). All immunoblots were repeated twice with comparable results obtained.

Histology, immunohistochemistry, and analysis

[0024] Formalin-fixed paraffin-embedded decalcified tibia sections from 8 week-old mice were obtained. Sirius red staining was performed following standard procedures (73) using Sirius red and picric acid obtained from Sigma. Sections were visualized

under polarized light. Hematoxylin and eosin (H+E) staining was performed on some sections using standard protocols, and osteocyte density was assessed on cortical bone osteocytes in a medium power field 3 mm below the tibial growth plate. For anti-sclerostin immunohistochemistry, antigen retrieval was performed using proteinase K (20 μg/ml) for 15 minutes. Endogenous peroxidases were quenched, and slides were blocked in TNB buffer (Perkin Elmer), then stained with anti-sclerostin antibody at a concentration of 1:200 for one hour at room temperature. Sections were washed, incubated with HRP-coupled secondary antibodies, signals amplified using tyramide signal amplification (TSA), and HRP detection was performed using 3,3'-diaminobenzidine (DAB, Vector) for 2-3 minutes. Slides were briefly counterstained with hematoxylin prior to mounting. Quantification of sclerostin positive osteocytes was performed on a blinded basis. All photomicrographs were taken 3 mm below the growth plate on the lateral side of the tibia. All osteocytes were counted and then scored as either sclerostin-positive or negative. Sections from at least 4 mice per experimental group were analyzed. Quantification of immunostaining was done based on coded sample numbers in a completely blinded manner. Representative photomicrographs are displayed next to quantification in data figures.

Chromatin immunoprecipitations

[0025] ChIP assay was performed using a kit (EZ-Chip, Miilipore, 17-371, Billerica, MA) according to the manufacturer's instructions. Briefly, cells were grown at 37 °C for 7 days, followed by PTH treatment (25-50 nM) for the indicated times. Cells were then cross-linked with 1% formaldehyde for 10 minutes and then quenched with 0.125M glycine. Cells were lysed and sonicated with 10 pulses for 30 seconds each to fragment DNA to 200-800 bp fragments. DNA-protein complexes were precipitated using 1.5 μg antibodies (MEF2C, CRTC2, or control rabbit IgG) overnight at 4°C. Immune complexes were precipitated, DNA was purified, and real-time PGR was conducted using primer sets *{Tables 5* through *8)* to detect the +45 kB SOST enhancer and upstream RANKL enhancers. Data are expressed as relative enrichment for each antibody (above control IgG) for each primer set. Data shown represent triplicate biological repeats within experiments, and each experiment was performed at least twice.

cAMP radioimmunoassays

[0026] Cells, in 96 well plates, were treated with indicated ligands for 20 minutes at room temperature in the presence of the phosphodiesterase inhibitor 3-isobutyl-l-methylxanthine (IBMX, Sigma 15879, 2 mM). The medium was then removed and cells were lysed in 50 mM HQ and transferred to -80C. Thawed lysates were diluted 1:5 with dH20, and an 10 μï aliquot was assessed for cAMP content by radioimmunoassay using ^{125}I-cAMP analog as a tracer and unlabeled cAMP to generate a standard curve.

RNA-sequencing

[0027] Total RNA was subjected to rRNA depletion using RiboZero kit (Illumina) followed by NGS library construction using NEBNext Ultra Directional RNA Library Prep Kit for Illumina (New England Biolabs). Experimental duplicates were performed for each condition. Sequencing was performed on Illumina HiSeq 2500 instrument, resulting in an average of 33 million pairs of 50 bp reads per sample. Sequencing reads were mapped to the mouse reference genome (mm10/GRCm38) using STAR (bioinformatics .oxfordjournals .org/content/early/2012/10/25/bioinformatics.bts635). Gene expression counts were calculated using HTSeq v.0.6.0 (www.huber.embl.de/users/anders/HTSeq/doc/overview.html) based on a current Ensembl annotation file for mml0/GRCm38 (release 75). Differential expression analysis was performed using EgdeR package based on the criteria of >2-fold change in expression value versus control and false discovery rates (FDR) < 0.05. Venn diagrams from gene set analysis were generated using genes with > 1.5 fold change in expression values and FDR <0.05. Significance testing for gene set overlap was performed according to a standard hypergeometric distribution, p-values $<2.2*10^{-16}$. The accession number for the RNA-seq dataset reporter in this paper is GEO: GSE76932 (www.ncbi.nlm. nih.gov/geo/query/acc. cgi?acc=GSE76932).

[0028] ScanEDGE kinase assays paneling specificity across a panel of 96 representative kinases were performed by DiscoverX (Fremont, CA). For most assays, kinase-tagged T7 phage strains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. Bacteria were grown to log phase and infected with T7 phage from frozen stock (MOI = 0.4) and incubated with shaking at 32 °C until lysis (90-150 minutes). The lysates were centrifuged (6000 x g) and filtered (0.2 μm) to remove cell debris. The remaining kinases were produced in HEK-293 cells

and subsequently tagged with DNA for qPCR detection. Streptavidin coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washing with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 40x stocks in 100% DMSO and directly diluted into the assay. All reactions were performed in polypropylene 384 well plates in a final volume of 40 µl. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then resuspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 µM of the non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR. YKL-05-093 was screened in this assay at 71 nM (ten times its Kd for SIK2), and results are reported as "% control", where lower numbers indicate stronger hits.

Micro-CT

[0029] Assessment of bone morphology and microarchitecture was performed with high-resolution micro-computed tomography (µCT40; Scanco Medical, Bruttisellen, Switzerland). In brief, the distal femoral metaphysis and mid-diaphysis were scanned using 70 kVp peak x-ray tube potential, 113 mAs x-ray tube current, 200 ms integration time, and 10-µm isotropic voxel size. Cancellous bone was assessed in the distal metaphysis and cortical bone was assessed in the mid-diaphysis. The femoral metaphysis region began 1700 µm proximal to the distal growth plate and extended 1500 µm distally. Cancellous bone was separated from cortical bone with a semiautomated contouring program. For the cancellous bone region, bone volume fraction (BV/TV, %), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), trabecular number (Tb.N, 1/mm), connectivity density (Conn.D or ConnD, $1/mm^3$), and structure model index (SMI) were assessed. Transverse CT slices were also acquired in a 500 µm long region at the femoral mid-diaphysis to assess total cross-sectional area, cortical bone area, and medullary area (Tt.Ar, Ct.Ar, and Ma.Ar, respectively, all mm^2); bone area fraction (Ct.Ar/Tt.Ar, %), cortical thickness (Ct.Th,

mm), porosity (Ct.Po, %) and minimum (I_{min}, mm^4), maximum (I_{max}, mm^4), and polar (J, mm^4) moments of inertia. Bone was segmented from soft tissue using the same threshold, 300 mg HA/cm^3 for trabecular and 733 mg HA/cm^3 for cortical bone. Scanning and analyses adhered to the guidelines for the use of micro-CT for the assessment of bone architecture in rodents (74). For the primary spongiosa region (where intermittent PTH treatment has its predominant effect) analyzed in Figure 13A, coronal CT slices were evaluated in a 500 μm (50 slices) region located centrally in the bone. The region of interest began 1000 μm superior to the epiphysis and included all primary spongiosa and the medullary cavity. The primary spongiosa bone region was identified by semi-manually contouring the region of interest. Images were thresholded using an adaptive-iterative algorithm. The average adaptive-iterative threshold of control mice (WT, vehicle treated) for the region of interest (299 mgHA/cm^3) were then used to segment bone from soft tissue for all distal femur images. Micro-CT analysis was done based on sample numbers in a completely blinded manner.

Histomorphometry

[0030] Right tibia from 8-week-old mice were subjected to bone histomorphometric analysis. The mice were injected 20 mg/kg body weight of calcein and 40 mg/kg body weight of demeclocycline on 7 and 2 days before necropsy, respectively. The tibia was dissected and fixed in 70% ethanol for 3 days. Fixed bones were dehydrated in graded ethanol, then infiltrated and embedded in methylmethacrylate without demineralization. Undecalcified 4^m-thick longitudinal sections were obtained using microtome (RM2255, Leica Biosystems., IL, USA). Sections were left unstained for dynamic parameters measurement, and consecutive sections were stained with tartrate-resistant acid phosphatase and counterstained with toluidine blue for measurement of cellular parameters. A standard dynamic bone histomorphometric analysis of the tibial metaphysis was done using the Osteomeasure analyzing system (Osteometries Inc., Decatur, GA, USA). Measurements were performed in the area of secondary spongiosa, 200 μm below the proximal growth plate. The observer was blinded to the experimental genotype at the time of measurement. The structural, dynamic and cellular parameters were calculated and expressed according to the standardized nomenclature (75).

Example 3. Additional Biological assays

[00525] In Example 3, "YKL" refers to YKL-05-099, and the experimental conditions are described herein or as described in Example 2. Exemplary results of Example 3 are shown in Figures 24 to 37D.

YKL-05-099 uncouples bone formation and resorption by blocking M-CSF-**driven osteoclastogenesis**

[00526) It was recently reported that PTH signaling in osteocytes blocks the activity of the kinase, salt inducible kinase 2 (SIK2). Treatment of mice with YKL-05-099 once daily (single dose, 6 mg/kg) for 2 weeks led to effects similar to those of intermittent PTH: increased osteoblast numbers, increased bone formation, and increased bone mass. However, unlike PTH, YKL-05-099 treatment led to reductions in osteoclast numbers despite increased levels of RANKL. The goal of the current study is to understand how YKL-05-099 regulates osteoclast differentiation.

100527] 8-**week-old** male C57B/6 mice were treated with vehicle or different doses of YKL-05-099 (2 mg/kg, 6 mg/kg, 18 mg/kg) once daily for two weeks. Static and dynamic histomorphometry was performed (see Figure 24). Previous results of *in vitro* kinase profiling (DiscoverX) for YKL-05-099 were examined (see Figure 27). Murine bone marrow-derived macrophages were differentiated into osteoclasts in the presence of 10 different doses of YKL-05-099 (see Figure 25). Effects on osteoclast differentiation were assessed by TRAP secretion assays and counting multi-nucleated TRAP-positive cells (see Figure 26). M-CSF signaling in primary macrophages, was assessed by immunoblotting for MCSF-receptor Y723 phosphorylation and ERKl/2 phosphorylation (see Figure 27).

[00528] Compared to vehicle-treated mice, YKL-05-099 treatment caused dose-dependent increases in trabecular bone volume (veh 10.3±1.9 vs 18 mg/kg 16.3±2.0, $p<0.01$), increases in Ob.S/BS (veh 11.9±0.8 vs 18 mg/kg 16.8±1.3, $p<0.01$), and reductions in Oc.S/BS (veh 2.79±0.8 vs 18 mg/kg 1.59-1-0.4, $p<0.05$). It was hypothesized that YKL-05-099 might directly block osteoclastogenesis. M-CSF+RANKL-primed osteoclastogenesis was inhibited by YKL-05-099 treatment *in vitro* with an IC_{50} of 52 nM. In addition to SIK2, DiscoverX profiling data indicated that this compound could also target the M-CSF receptor. Acute YKL-05-099 pre-treatment (15 μM) of bone marrow-derived macrophages blocked M-CSF-induced M-CSF receptor Y723 auto-phosphorylation and downstream ERK phosphorylation.

[00529] YKL-05-099 may target bone formation and bone resorption by two distinct mechanisms. In osteocytes, this compound may block SIK2 and may boost bone formation, in part, by reducing sclerostin production. In pre-osteoclasts, this compound may block M-CSF receptor signaling. By boosting bone formation and inhibiting bone resorption, YKL-05-099 represents a promising osteoporosis treatment strategy.

The small molecule SIK inhibitor YKL-05-099 increases trabecular bone mass and bone formation in hypogonadal female mice

[00530] Whether YKL-05-099 boosts bone mass in oophorectomized (OVX) animals remains unknown. Furthermore, side-by-side comparison of PTH and YKL-05-099 treatment *in vivo* has not been performed. Here, it is determined if YKL-05-099 increases bone mass in OVX mice, and compared the skeletal effects of these two bone anabolic agents.

[00531] 48 female C57B/6 mice were subjected to sham surgery (SHAM; n=24) or oophorectomy (n=24) at 12 weeks of age. 8 weeks later, the mice were treated with either vehicle (n=8), YKL-05-099 (i.p., 18 mg/kg, n=8), or PTH (s.c, 1-34 (amino acids 1-34 of PTH), 100 mcg/kg, n=8) once per day for 4 weeks. The mice were assessed by micro-CT (μ-CT) of the femur and L5 vertebrae, and static/dynamic histomorphometry of the tibia. Exemplary results are shown in Figures 29A to 35.

[00532] Neither PTH nor YKL-05-099 altered growth or peripheral blood counts. OVX reduced trabecular BMD (Tb.BMD) in the distal femur (sham/veh vs OVX/veh p=0.041 (see Figure 30) and L5 vertebrae (p=0.00043), and reduced trabecular L5 BV/TV (p=0.00089) (see Figure 31A). In OVX mice, PTH and YKL-05-099 treatment increased trabecular bone mass at both skeletal sites (for example, distal femur Tb.BMD p=0.0047 veh vs PTH, p=0.00036 veh vs YKL) (see Figure 31B). Both PTH and YKL-05-099 increased osteoblast numbers (see Figure 32A) and bone formation rate (see Figure 33C) in OVX mice. Treatment effects of PTH and YKL-05-099 differed in two significant regards. First, while PTH tended to increase osteoclast activity, YKL-05-099 reduced eroded surfaces (see Figure 32C, p=0.41 veh vs PTH, p=0.0129 veh vs YKL). Second, while PTH increased amounts of non-mineralized osteoid, YKL-05-099 did not (see Figure 33D, p=0.00071 veh vs PTH, p=0.64 veh vs YKL).

[00533] In OVX mice, both YKL-05-099 and PTH increased trabecular bone mass (see Figure 30) and bone formation (see Figure 33C). Potential therapeutic advantages of YKL-05-099 may include its ability to reduce bone resorption and promote efficient osteoid mineralization.

Summary **of** OVX **results:** YXL **vs PTH**

[00534] OVX reduced BMD in the femur and reduced BMD and BV/TV in spine. PTH and YKL both increased bone mass/density in OVX mice. Both PTH and YKL increased osteoblast numbers and bone formation rate in OVX mice. YKL reduced osteoclasts, which is a direct anti-resorptive effect of YKL, and PTH increased osteoclasts. PTH increased osteoid but YKL did not. YKL may promote mineralization. YKL may also reduce marrow adipocytes.

In vivo toxicity **experiments**

[00535] In a 4 week treatment (weeks 20-24) 16 mice treated with vehicle, PTH, or YKL-05-099. There was normal weight gain in all groups. Blood was obtained for the complete blood count (CBC) measurement, and serum was obtained for the glucose, blood urea nitrogen (BUN), cholesterol, triglycerides, ALT, Creatine kinase (CK), amylase, and total protein measurements. Exemplary results are shown in Figures 36A to 37D. There were no effects of sham versus OVX on any of these parameters, so the data were analyzed with respect to drug (PTH or YKL-05-099) treatment. "WBC" refers to "white blood cell". "Hgb" refers to "hemoglobin". "Pit" refers to "platelet". "V vs Y" refers to "Vehicle vs. YKL-05-099." The hematology data showed no signal (see Figures 36A to 36D), suggesting that PTH and YKL-05-099 are not toxic under the test conditions. Serum toxicology data showed increased glucose and BUN (see Figures 37A to 37D).

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EQUIVALENTS AND SCOPE

[0031] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0032] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0033] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular

embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[0034] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A method of treating osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of an inhibitor of salt-inducible kinase (SIK).

2. A method of preventing osteoporosis in a subject in need thereof comprising administering to the subject in need thereof a prophylactically effective amount of an inhibitor of salt-inducible kinase (SIK).

3. A method of increasing the function of osteocytes in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

4. A method of increasing the number of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

5. A method of increasing the activity of osteoblasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

6. A method of inhibiting the resorption of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

7. A method of decreasing the number of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

8. A method of inhibiting the activity of osteoclasts in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

9. A method of increasing the mass of a bone in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

10. A method of down-regulating the expression of the gene SOST in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

11. A method of inhibiting the activity of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

12. A method of reducing the production of sclerostin in a subject in need thereof comprising administering to the subject in need thereof an effective amount of an inhibitor of salt-inducible kinase (SIK).

13. The method of any one of claims 1-12, wherein the effective amount, the therapeutically effective amount, or the prophylactically effective amount is further effective in inhibiting SIK.

14. The method of any one of claims 1-13 further comprising administering to the subject in need thereof an effective amount of an inhibitor of proto-oncogene tyrosine-protein kinase Src (Src).

15. The method of any one of claims 1-14 further comprising administering to the subject in need thereof an effective amount of an inhibitor of colony stimulating factor 1 receptor (CSFIR).

16. A pharmaceutical composition comprising:
an inhibitor of salt-inducible kinase (SIK);

an inhibitor of proto-oncogene tyrosine-protein kinase Src (Src): and

optionally a pharmaceutically acceptable excipient.

17. A pharmaceutical composition comprising:

an inhibitor of salt-inducible kinase (SIK);

an inhibitor of colony stimulating factor 1 receptor (CSFIR); and

optionally a pharmaceutically acceptable excipient.

18. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of treatment of osteoporosis.

19. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of prevention of osteoporosis.

20. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of increasing the function of osteocytes.

21. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of increasing the number of osteoblasts.

22. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of increasing the activity of osteoblasts.

23. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of inhibiting the resorption of a bone.

24. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of decreasing the number of osteoclasts.

25. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of inhibiting the activity of osteoclasts.

26. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of increasing the mass of a bone.

27. A kit comprising:

an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of down-regulating the expression of the gene SOST.

28. A kit comprising:

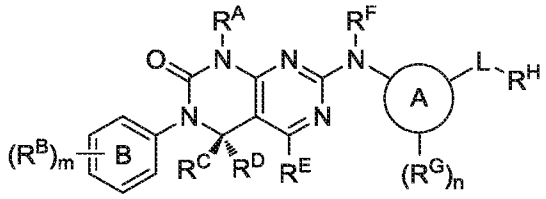
an inhibitor of salt-inducible kinase (SIK); and

instructions for administering the inhibitor of SIK to a subject in need of inhibiting the activity of sclerostin.

29. The method of any one of claims 1-15, pharmaceutical composition of any one of claims 16-17, or kit of any one of claims 18-28, wherein the SIK is salt-inducible kinase 2 (SIK2).

30. The method of any one of claims 1-15, pharmaceutical composition of any one of claims 16-17, or kit of any one of claims 18-28, wherein the SIK is salt-inducible kinase 3 (SIK3).

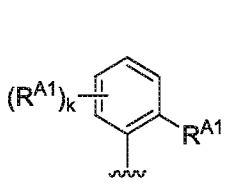
31. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of SIK is of the formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^A is substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,



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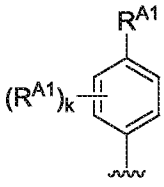


, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl;

each instance of R^{A1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom:

each instance of R^b is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^b are taken

together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, or 4;

each instance of R^B is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NC)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

m is 0, 1, 2, 3, 4, or 5;

R^c is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^D is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^E is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, Ci_{-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-N0_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$;

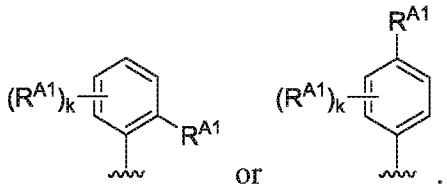
n is 0, 1, 2, 3, or 4, as valency permits;

L is a bond or a substituted or unsubstituted, Ci_{-6} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -C(=O)-, -O-, -S-, $-NR^b-$, -N=, or =N-; and

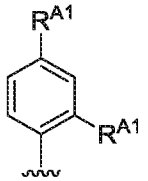
R^H is substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted heterocyclyl, -OH, or $-N(R^\circ)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening atoms to form

a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryi ring.

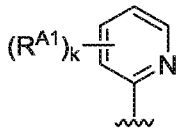
32. The method, pharmaceutical composition, or kit of claim 31, wherein R^A is



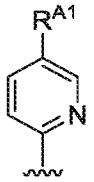
33. The method, pharmaceutical composition, or kit of claim 31, wherein R^A is



34. The method, pharmaceutical composition, or kit of claim 31, wherein R^A is



35. The method, pharmaceutical composition, or kit of claim 31, wherein R^A is



36. The method, pharmaceutical composition, or kit of any one of claims 31-35, wherein R^A is substituted or unsubstituted heterocyclyl, provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl.

37. The method, pharmaceutical composition, or kit of any one of claims 31-35, wherein R^A is substituted or unsubstituted tetrahydropyranyl.

38. The method, pharmaceutical composition, or kit of any one of claims 31-37, wherein at least one instance of R^B is halogen or substituted or unsubstituted, C_{1-6} alkyl.

39. The method, pharmaceutical composition, or kit of any one of claims 31-38, wherein Ring A is phenyl.

40. The method, pharmaceutical composition, or kit of any one of claims 31-38, wherein Ring A is pyrazole or pyridinyl.

41. The method, pharmaceutical composition, or kit of any one of claims 31-40, wherein L is a bond.

42. The method, pharmaceutical composition, or kit of any one of claims 31-40, wherein L is an unsubstituted C_{1-3} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -O- or -NR^b- .

43. The method, pharmaceutical composition, or kit of any one of claims 31-42, wherein R^H is substituted or unsubstituted heterocyclyl.

44. The method, pharmaceutical composition, or kit of any one of claims 31-42, wherein R^H is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyi, or substituted or unsubstituted piperazinyl.

45. The method, pharmaceutical composition, or kit of any one of claims 31-42, wherein R^H is substituted or unsubstituted, C_{1-6} alkyl.

46. The method, pharmaceutical composition, or kit of any one of claims 31-42, wherein R^H is -OH or -$N(R^C)_2$.

47. The method, pharmaceutical composition, or kit of any one of claims 31-46, wherein each instance of R^c is substituted or unsubstituted, C_{1-6} alkyl.

48. The method, pharmaceutical composition, or kit of any one of claims 31-47, wherein R^C is hydrogen.

49. The method, pharmaceutical composition, or kit of any one of claims 31-48, wherein R^D is hydrogen.

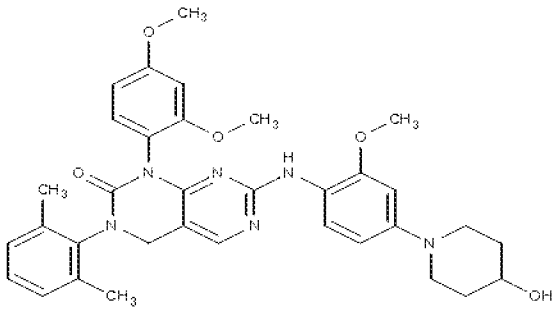
50. The method, pharmaceutical composition, or kit of any one of claims 31-49, wherein R^E is hydrogen.

51. The method, pharmaceutical composition, or kit of any one of claims 31-50, wherein R^F is hydrogen.

52. The method, pharmaceutical composition, or kit of any one of claims 31-51, wherein at least one instance of R^G is substituted or unsubstituted, C_{1-3} alkyl, halogen, or -OR ^{a}, wherein R^a is substituted or unsubstituted, C_{1-6} alkyl.

53. The method, pharmaceutical composition, or kit of any one of claims 31-51, wherein at least one instance of R^G is substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

54. The method, pharmaceutical composition, or kit of claim 31, wherein the inhibitor of SIK is of the formula:



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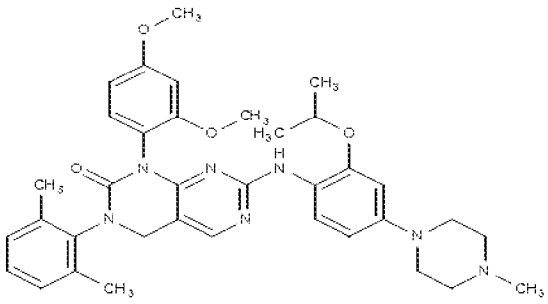

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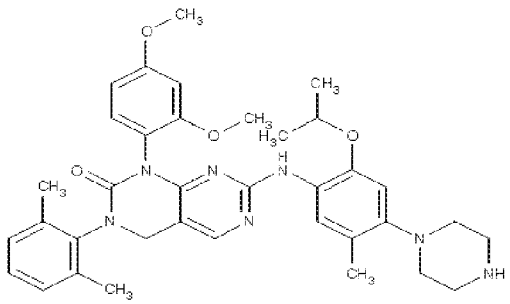

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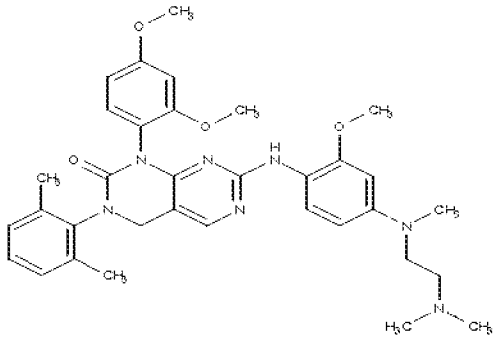

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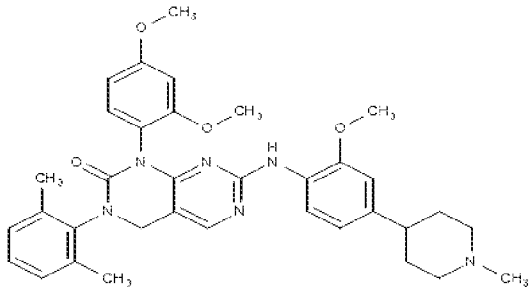

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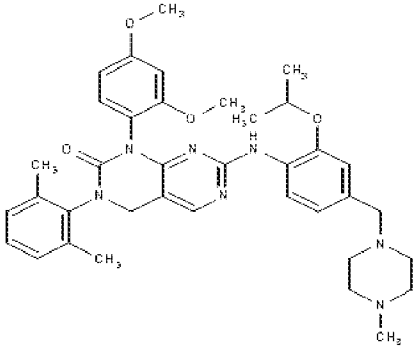

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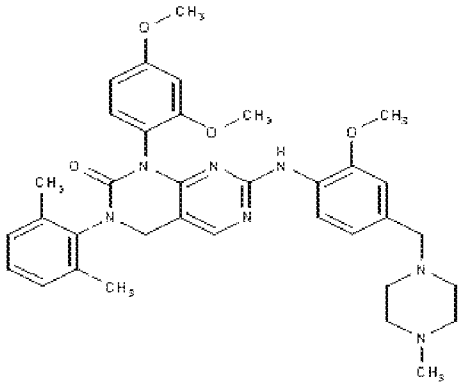

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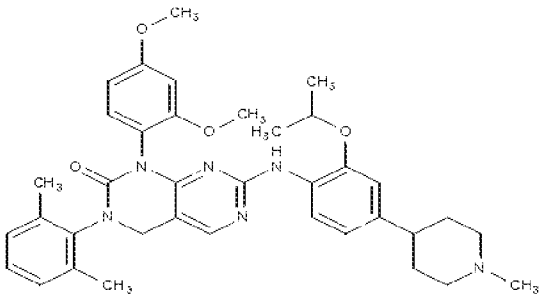

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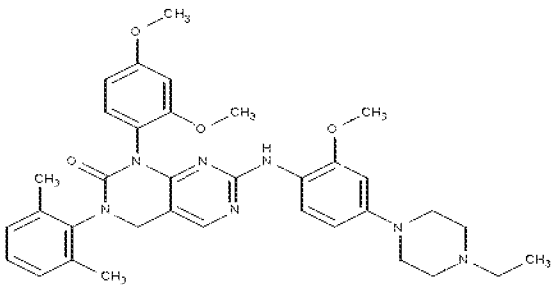

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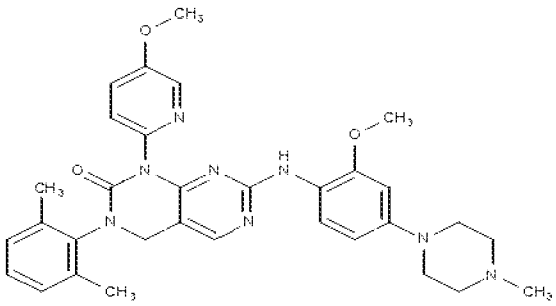

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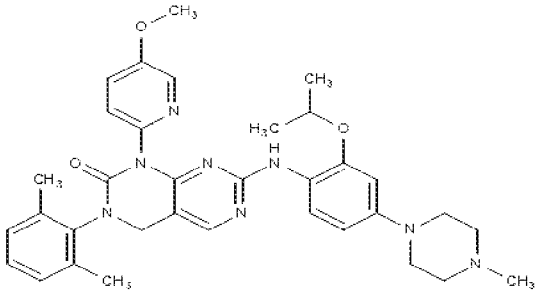

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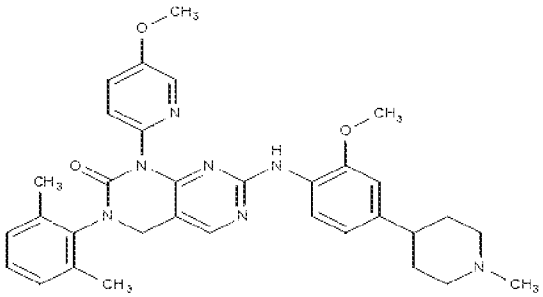

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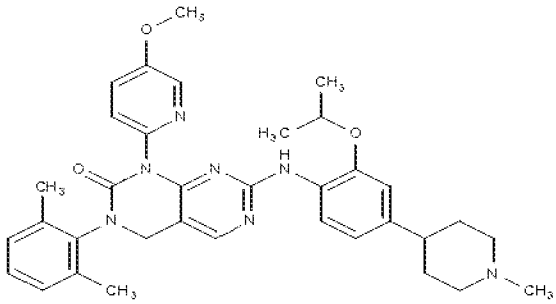

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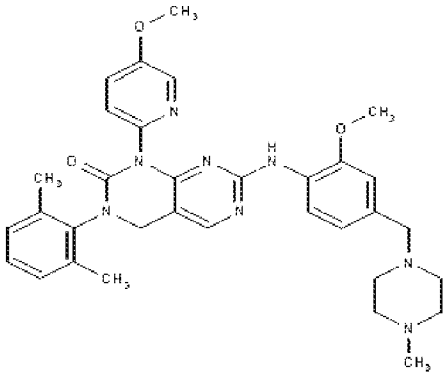

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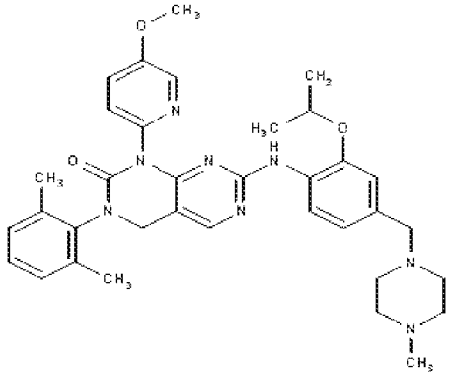

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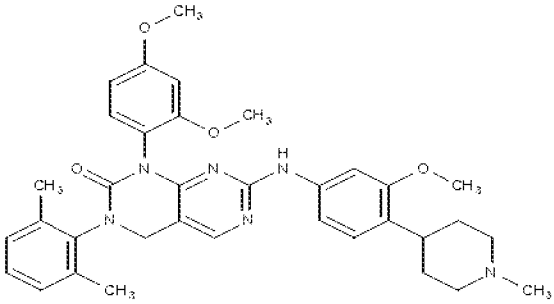

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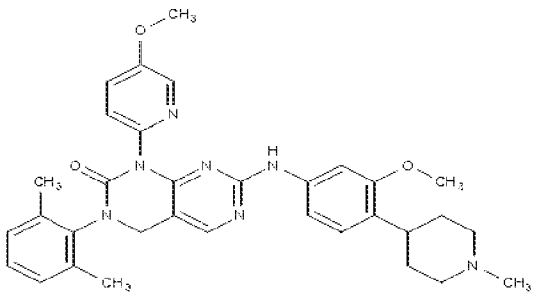

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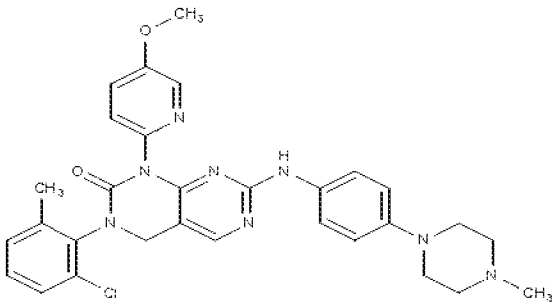

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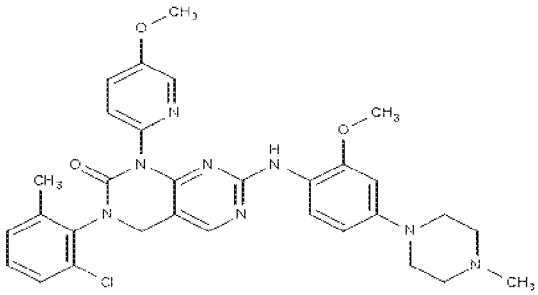

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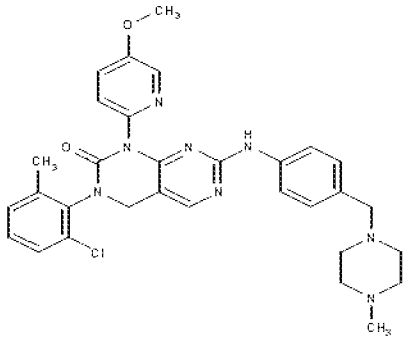

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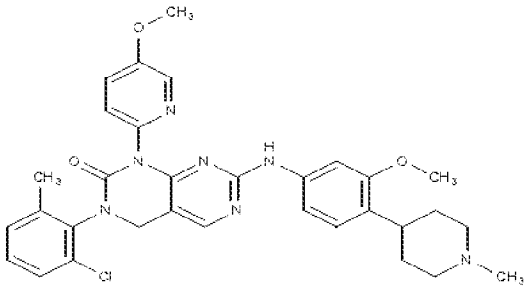

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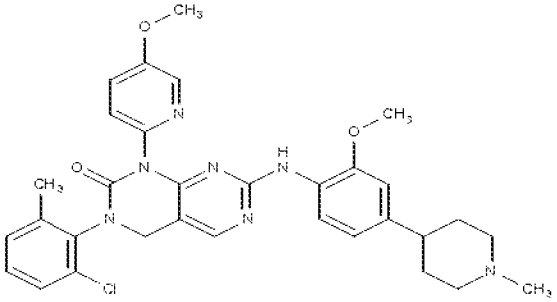

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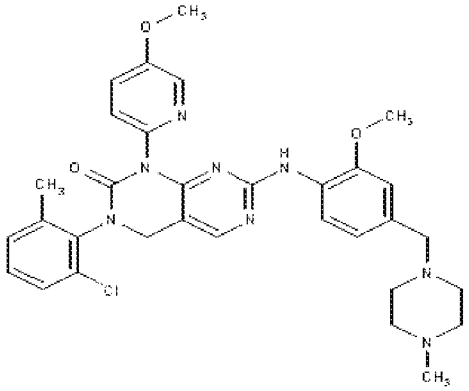

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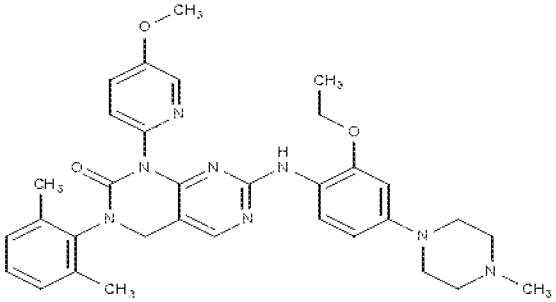

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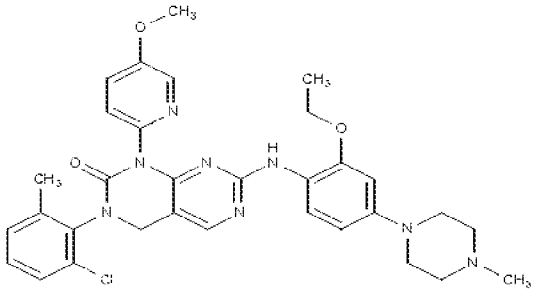

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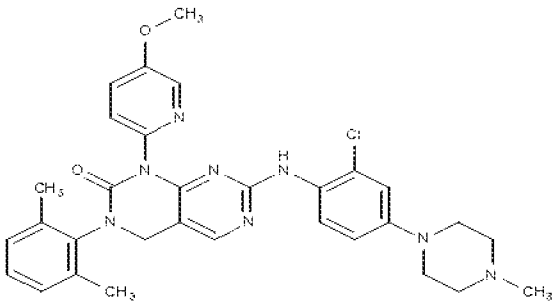

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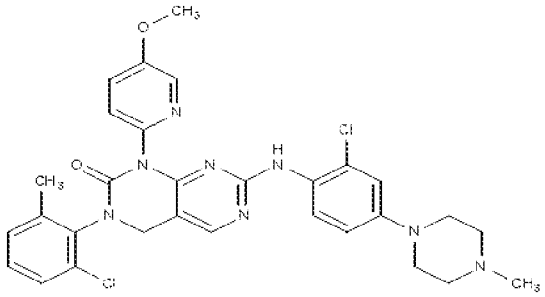

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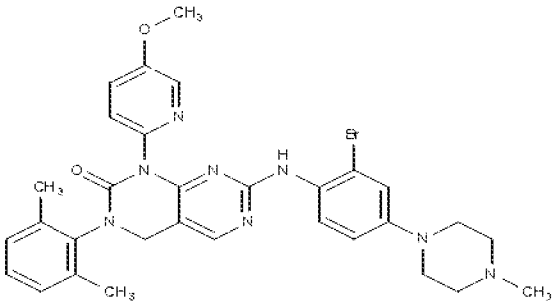

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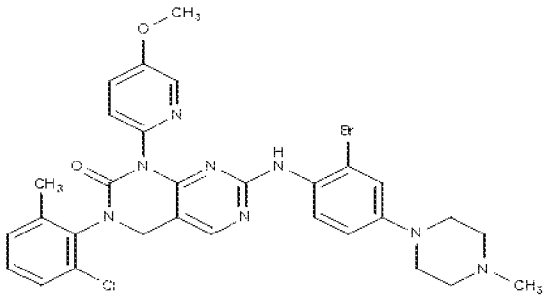

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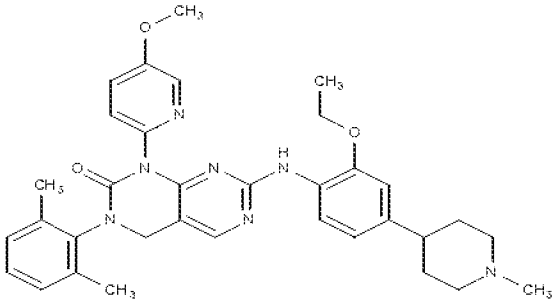

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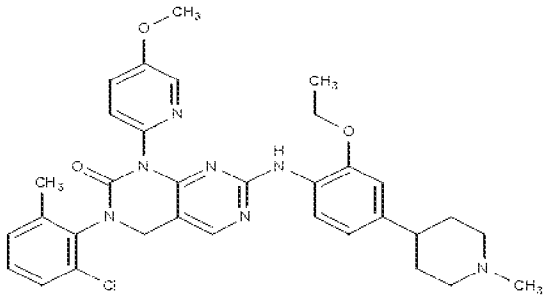

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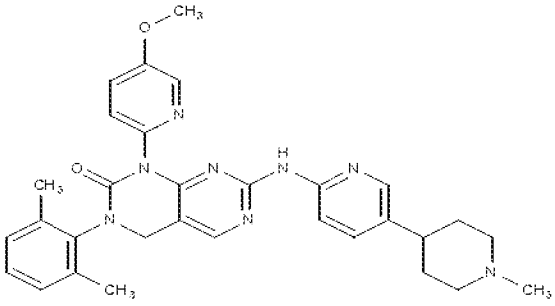

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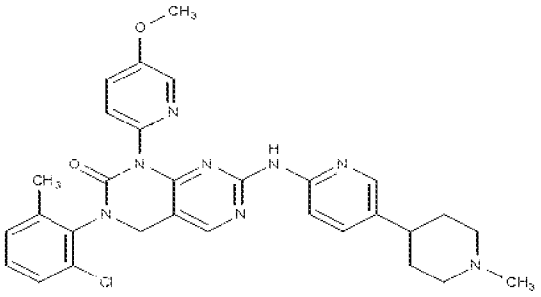

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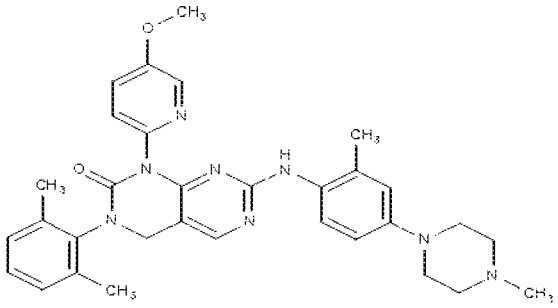

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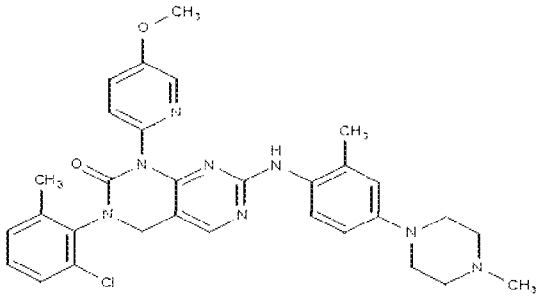

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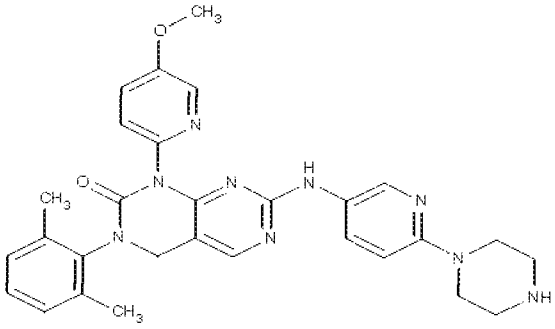

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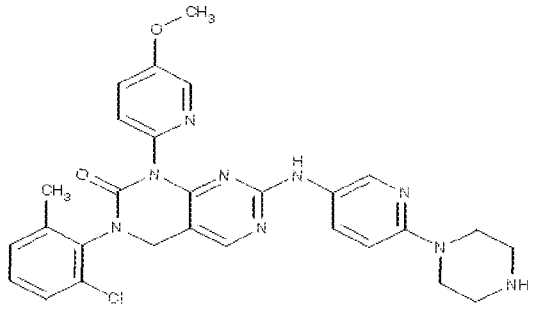

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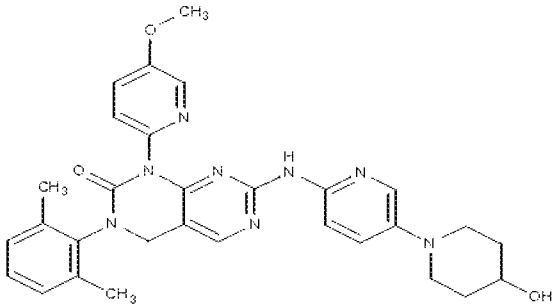

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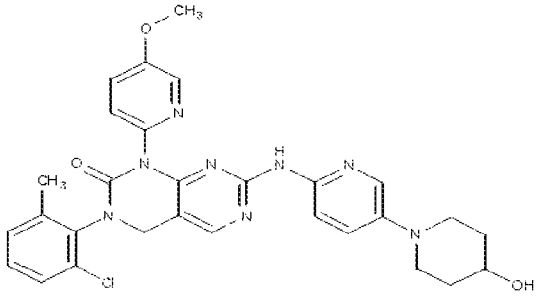

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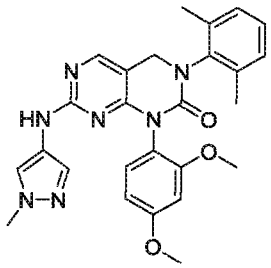
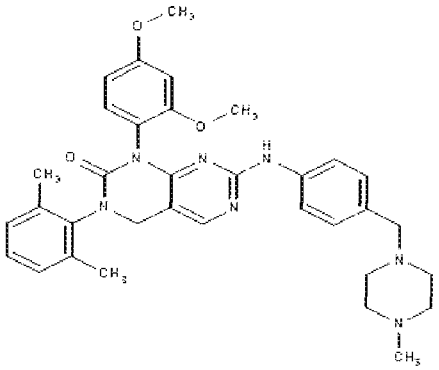


(Example 2),



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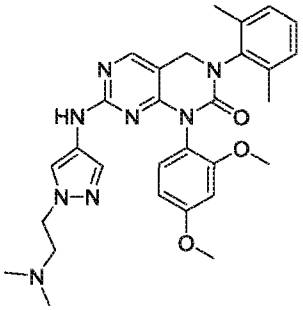

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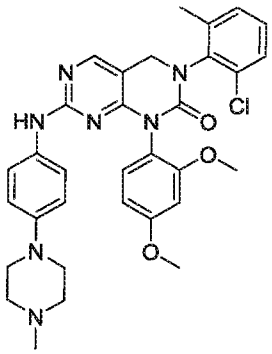
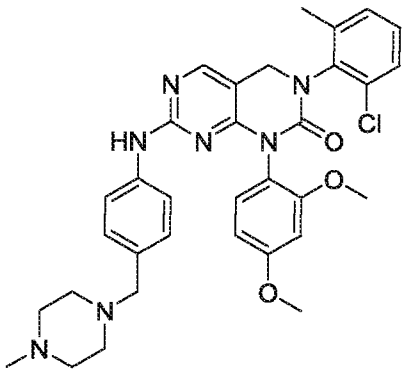
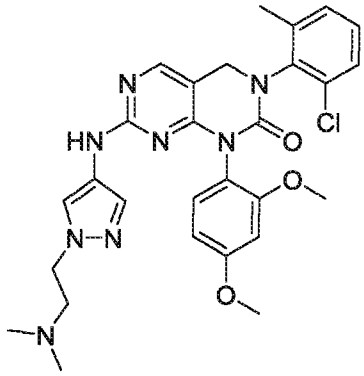


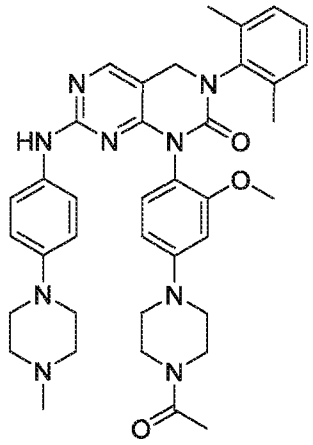
(YKL-04- 136-3 or SBl-D-03),



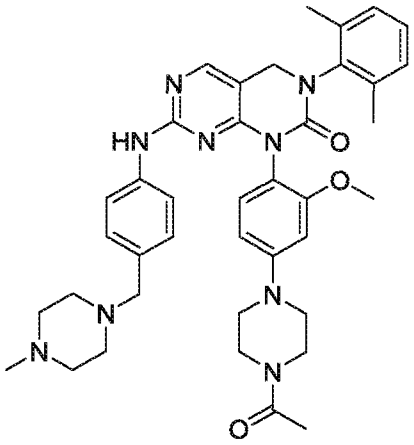
(YKL-04-136-9 or SB1-D-04),



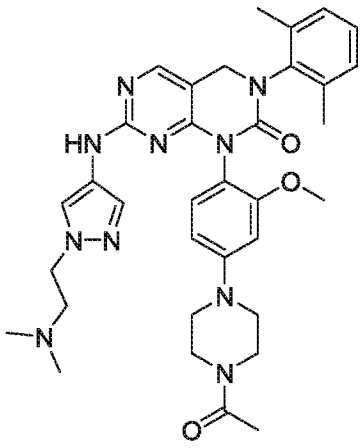
(YKL-04- 136-4 or SBl-D-05),



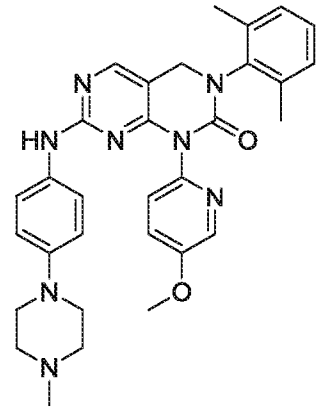
(YKL-04- 136-5 or SB1-D-06),



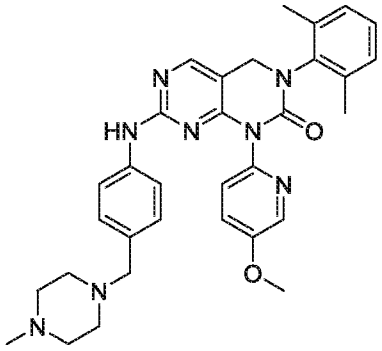
(YKL-04- 136-1 1 or SBl-D-07),

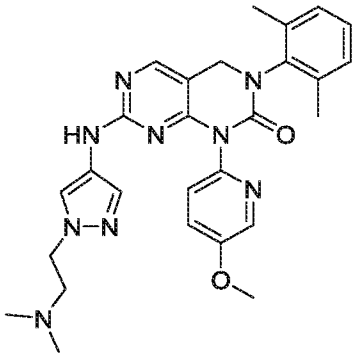


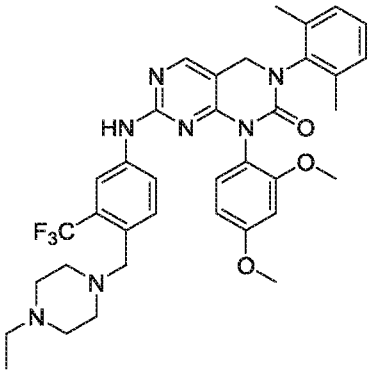
(YKL-04-136-7 or SB1-D-08),



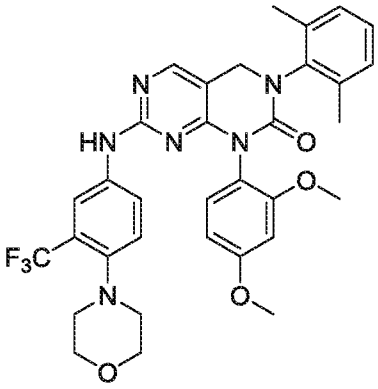
(YKL-04-136-6 or SB1-D-09),



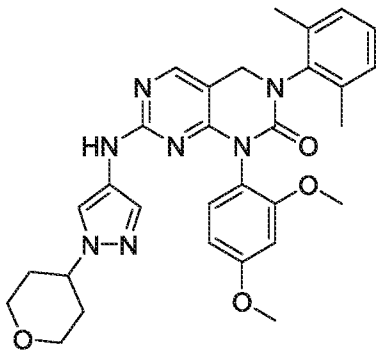




(YKL-04-136-10 or SB1-D-10), (YKL-04-136-8 or SB1-D-11), (YKL-04-103),



(YKL-04-104),



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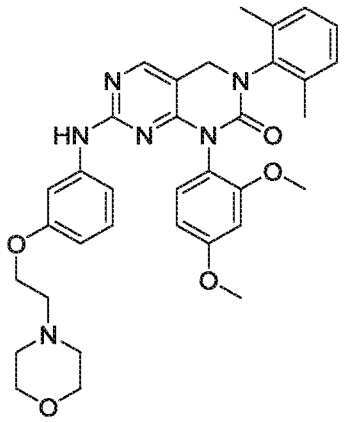
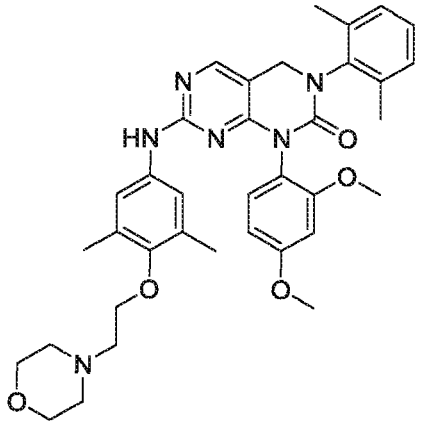
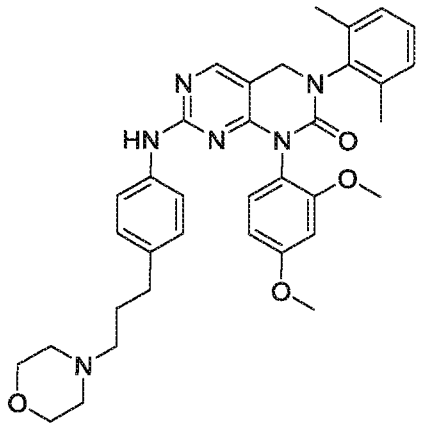


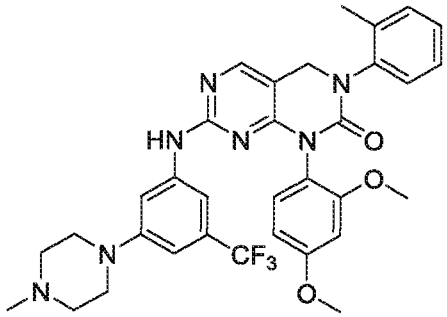
(YKL-04-106),



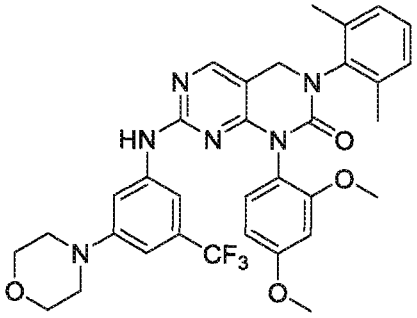
(YKL-04-107),



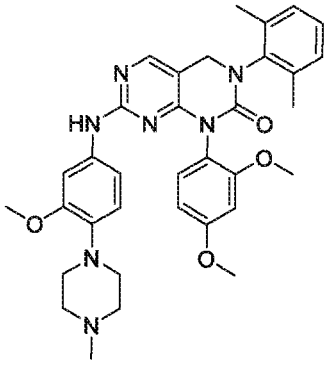
(YKL-04-108),



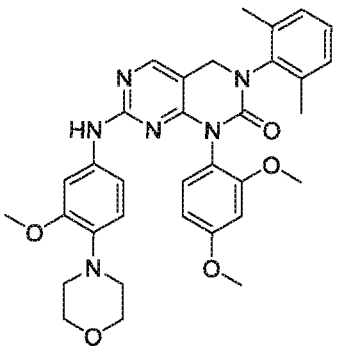
(YKL-04-112),



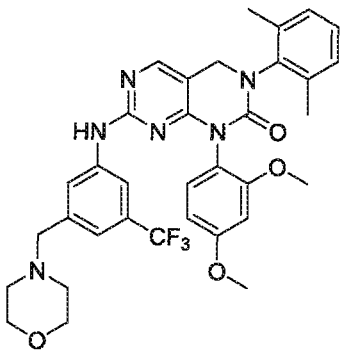
(YKL-04-113),



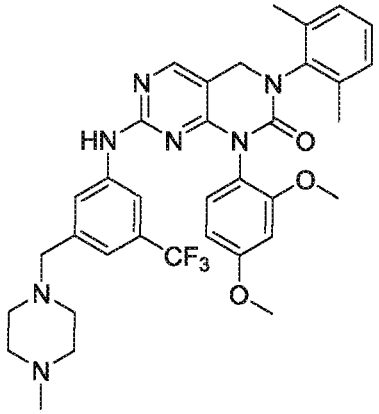
(YKL-04-114),



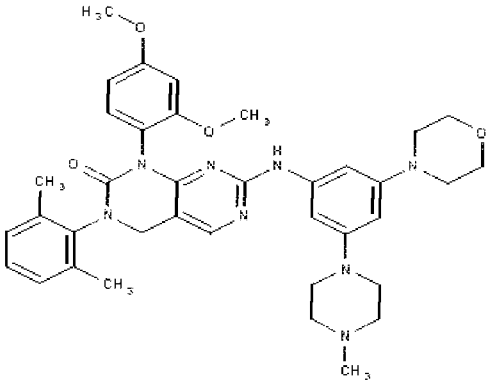
(YKL-04-115),



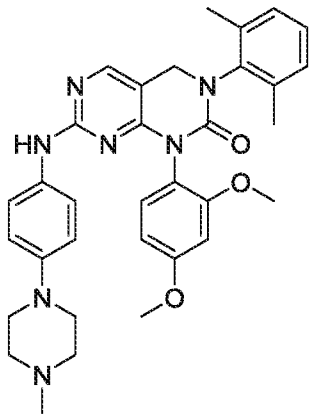
(YKL-04-118),



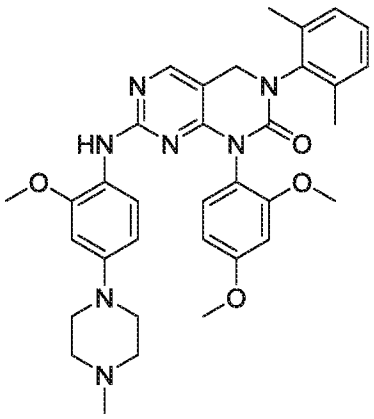
(YKL-04-125),



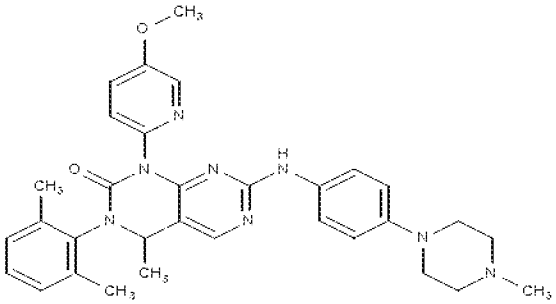
(HG-11-143-01),



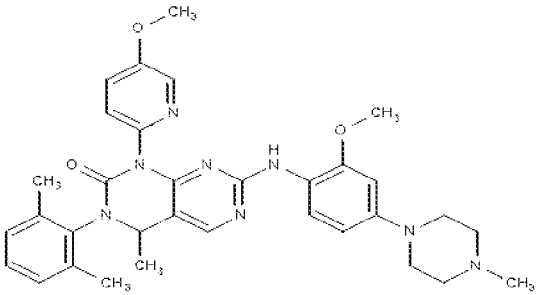
(HG-1 1-136-01),



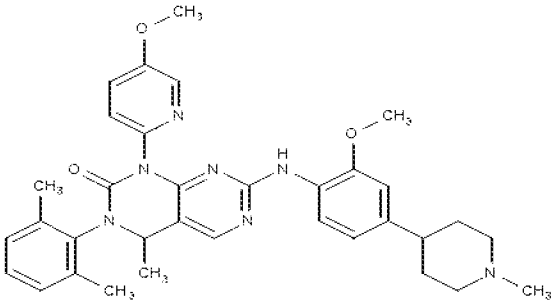
(HG-1 1-139-01),



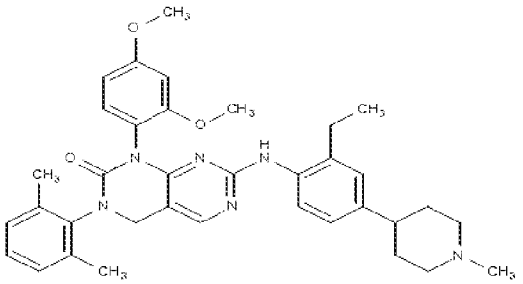
(YKL-06-038, YKL 06-038, or SB1-D-40),



(YKL-06-039 or SBl-D-42),



(YKL-06-040),



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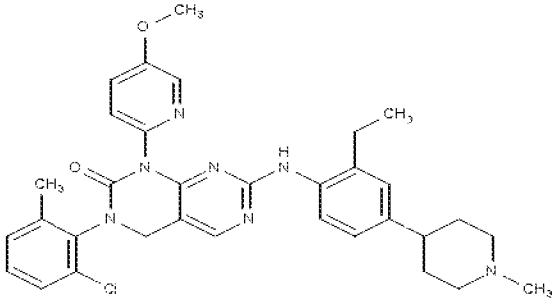
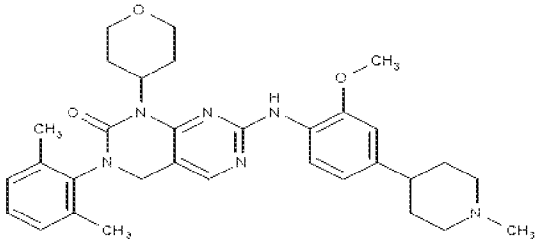
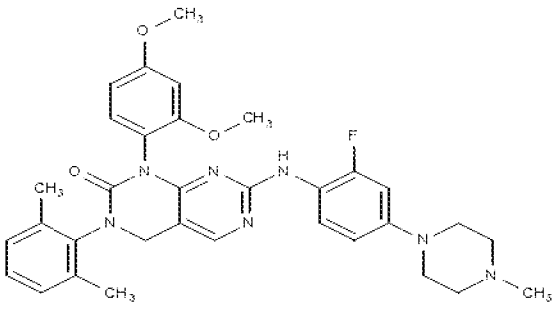


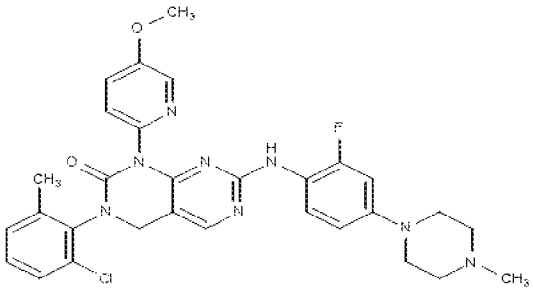
(YKL-06-045),



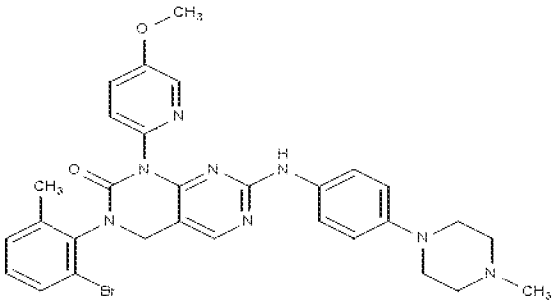
(YKL-06-051),



(YKL-06-054),



(YKL-06-055),



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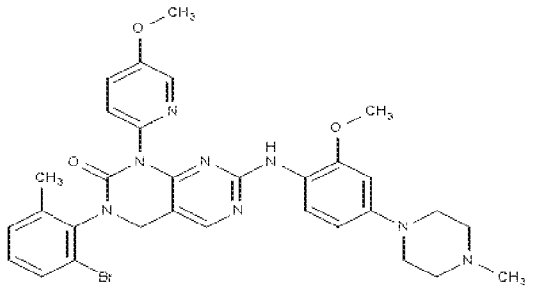
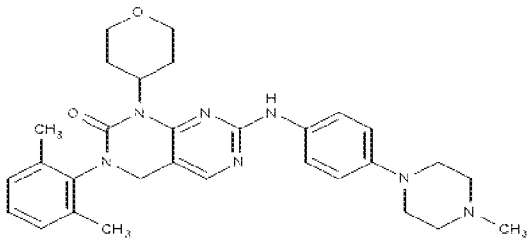
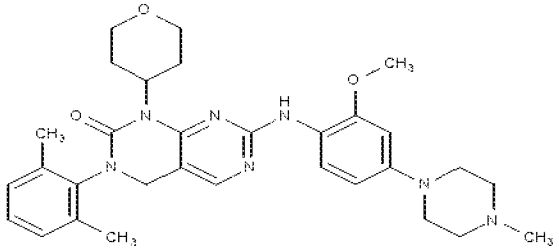


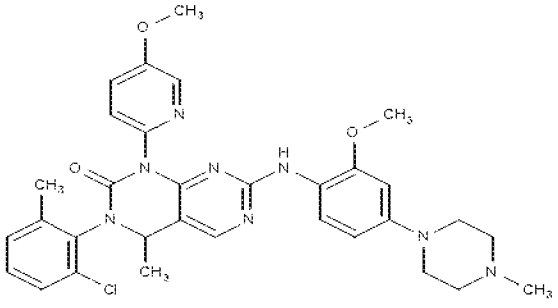
(YKL-06-057 or SB1-D-43),



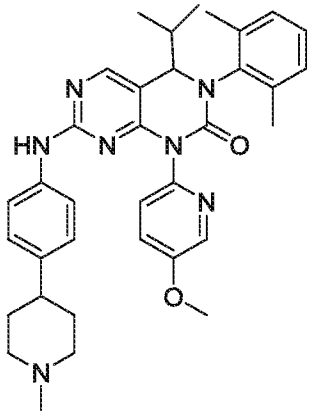
(YKL-06-077 or SBl-D-57),



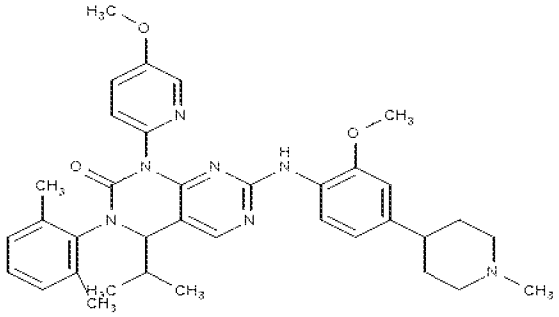
(YKL-06-078 or SBl-D-58),



(YKL-G6-080-1 or SB1-D-60),



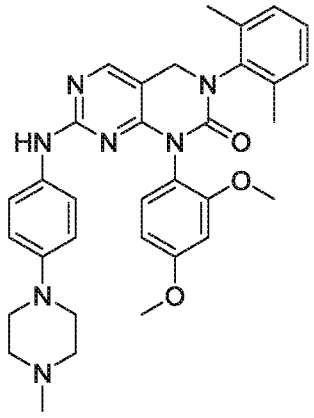
(YKL-06-081-1 or SB1-D-61),



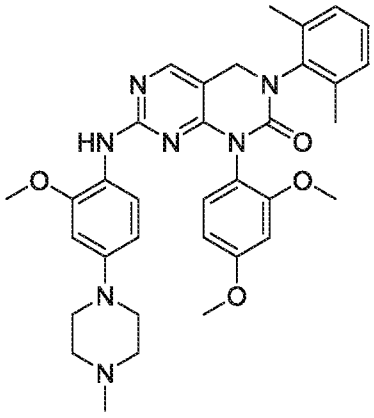
(YKL-06-082 or **SB1-D-62),**

or a pharmaceutically acceptable salt thereof.

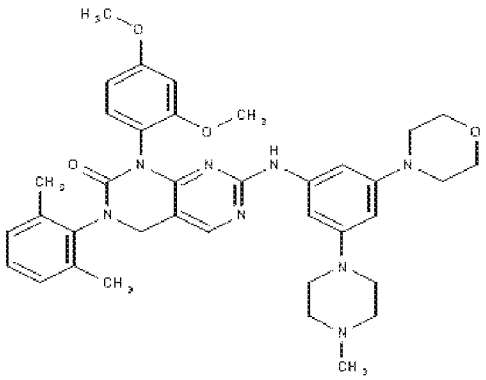
55. The method, pharmaceutical composition, or kit of claim 31, wherein the inhibitor of SIK is of the formula:



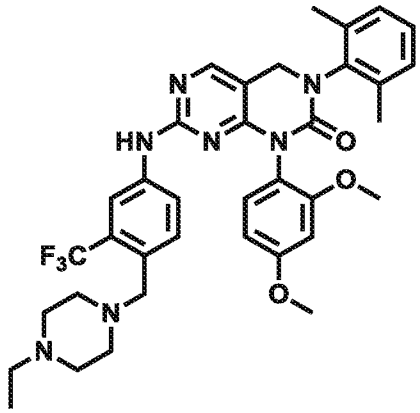
(HG-11-136-01),



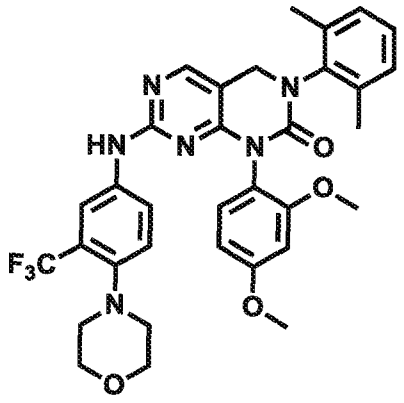
(HG-11-139-01),



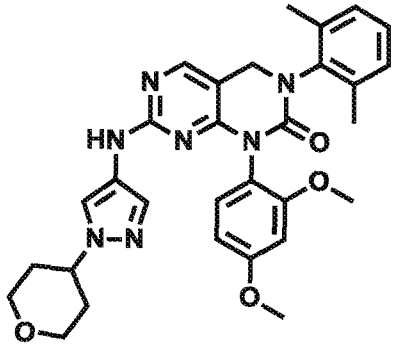
(HG-1 1-143-01),



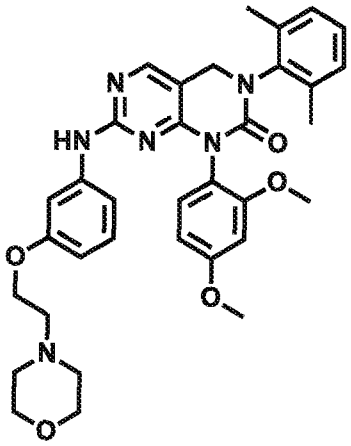
(YKL-04-103),



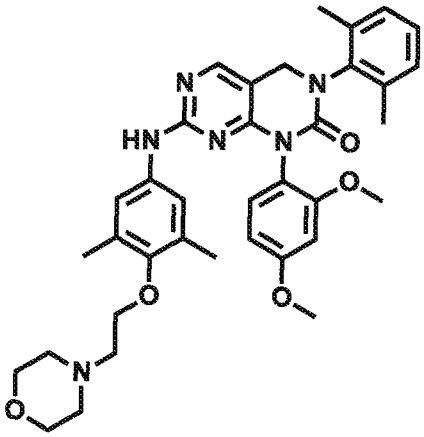
(YKL-04-104),



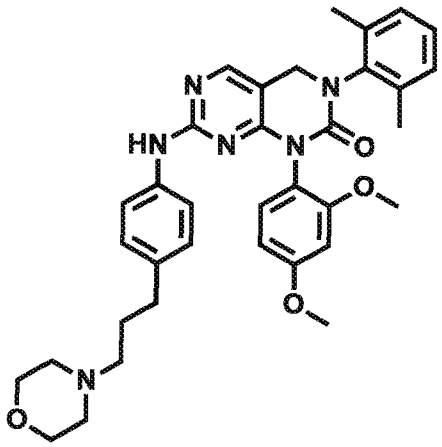
(YKL-04-105),



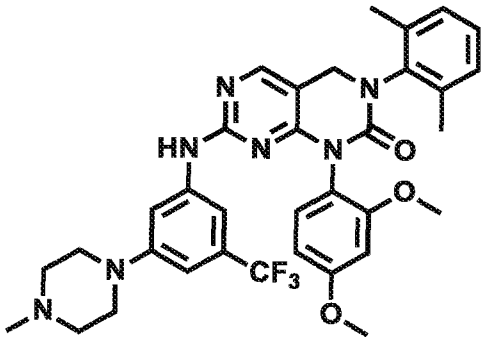
(YKL-04-106),



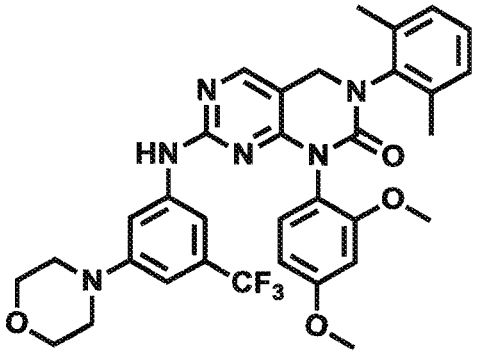
(YKL-04-107),



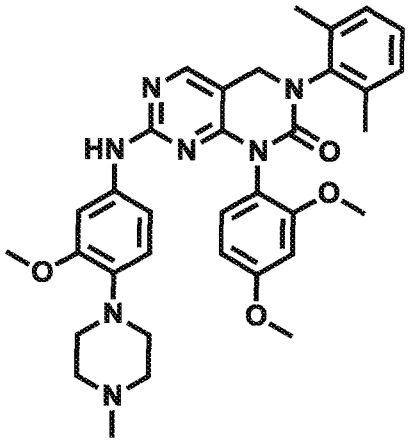
(YKL-04-108),



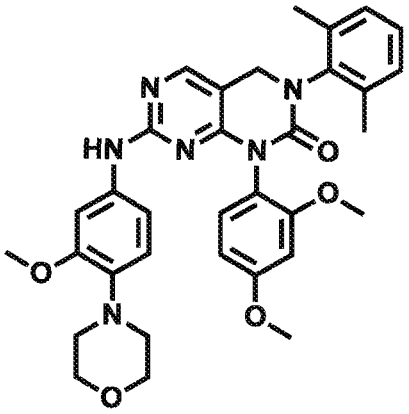
(YKL-04-1 12),



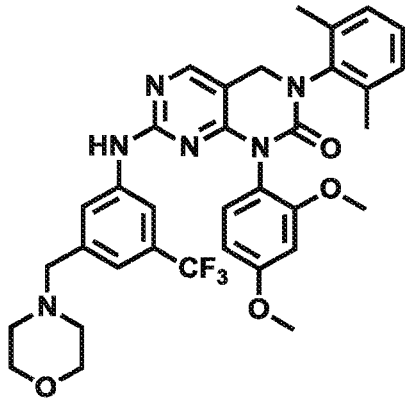
(YKL-04-113),



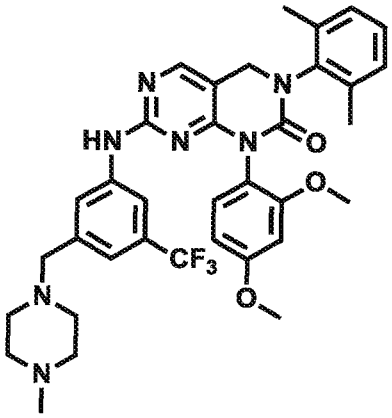
(YKL-04- 114),



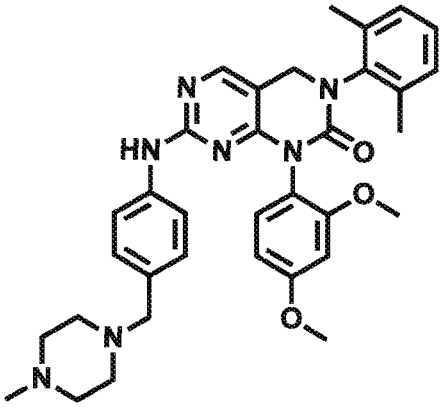
(YKL-04-115),



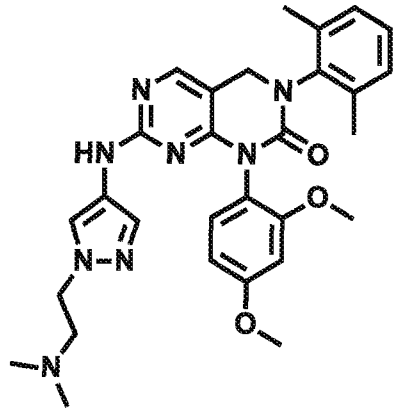
(YKL-04-118),



(YKL-04- 125),



(YKL-04- 136-1),



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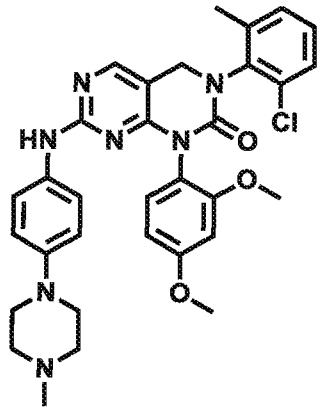
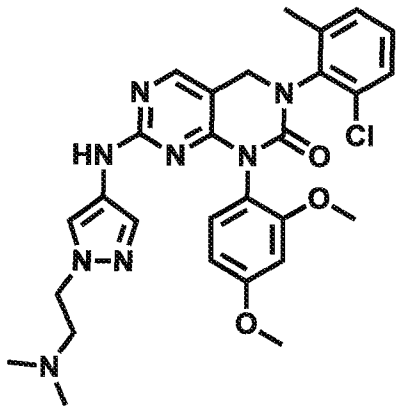
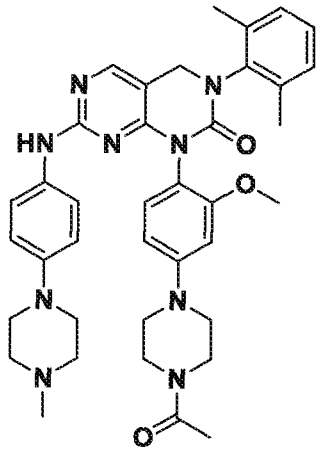


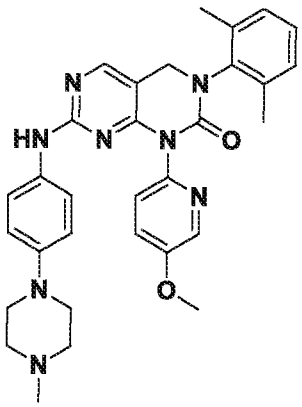
(YKL-04-136-3),



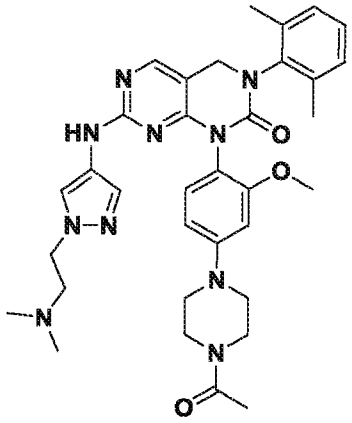
(YKL-04-136-4),



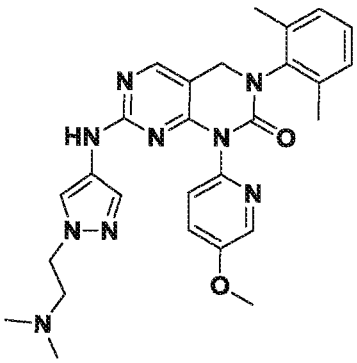
(YKL-04-136-5),



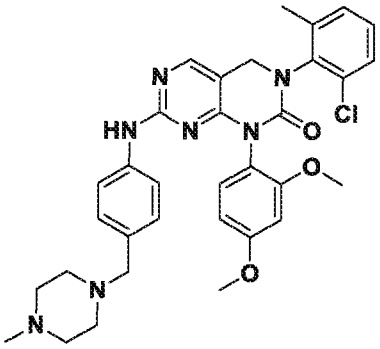
(YKL-04-136-6),



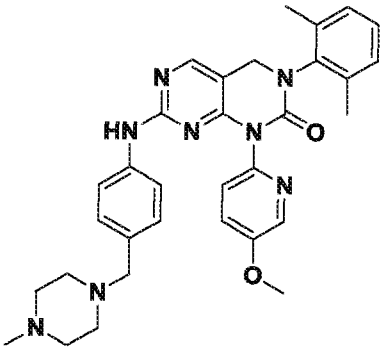
(YKL-04-136-7),



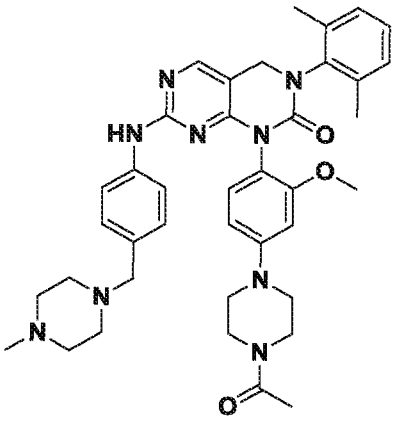
(YKL-04-136-8),



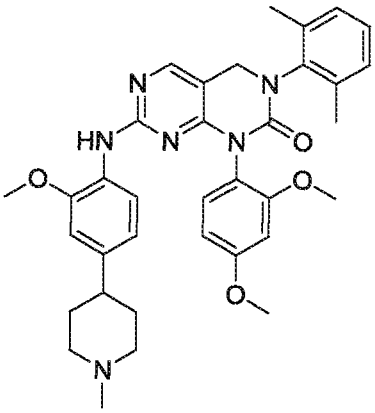
(YKL-04-136-9),



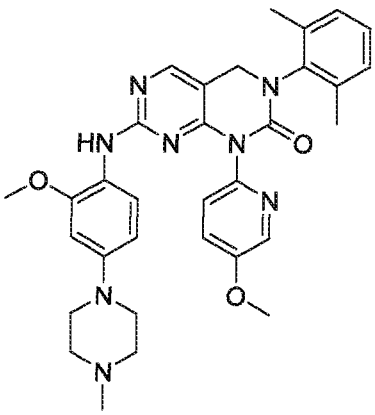
(YKL-04-136-10),



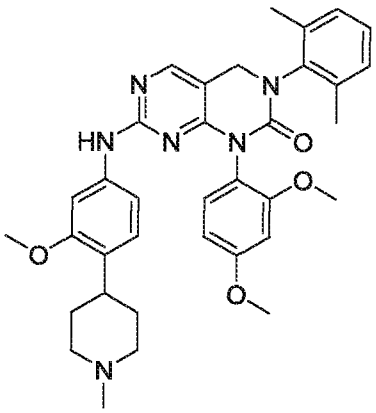
(YKL-04-136-11),



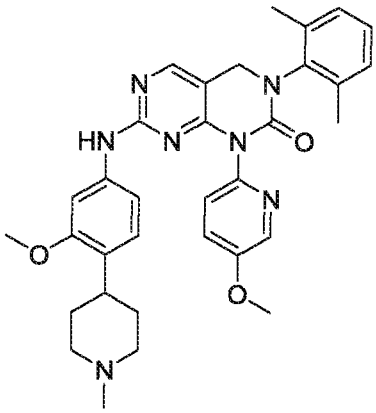
(YKL-05-068),



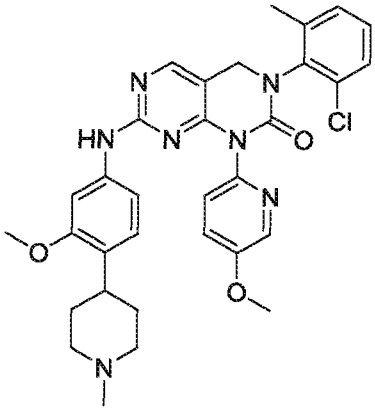
(YKL-05-077),



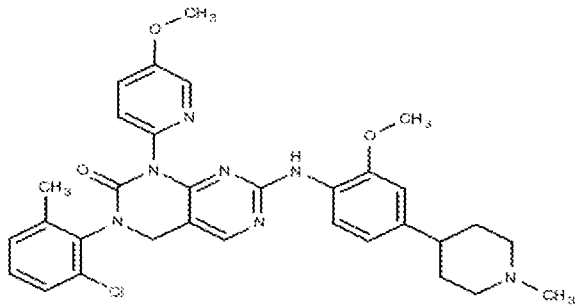
(YKL-05-093 or YKL 05-093),



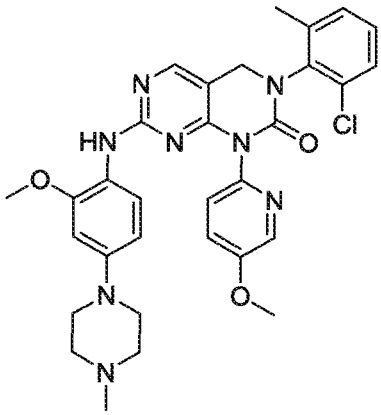
(YKL-05-094),



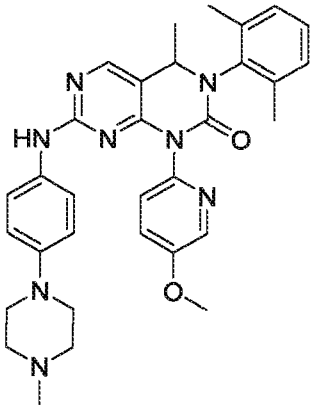
(YKL-05-098),



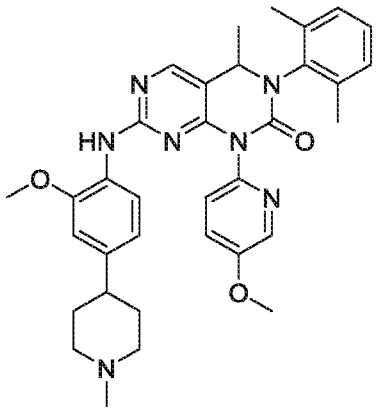
(YKL-05-99 or YKL-05-099),



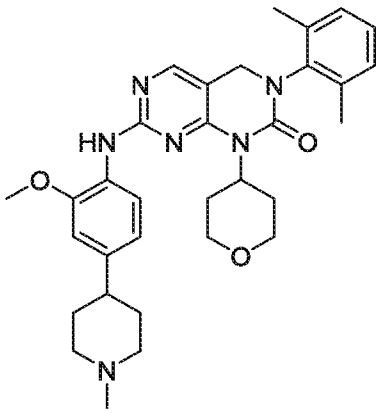
(YKL-05-096),



(YKL-06-038),



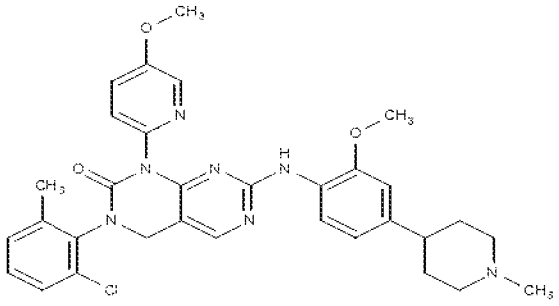
(YKL-06-040),



(YKL-06-051 or YKL 06-051),

or a pharmaceutically acceptable salt thereof.

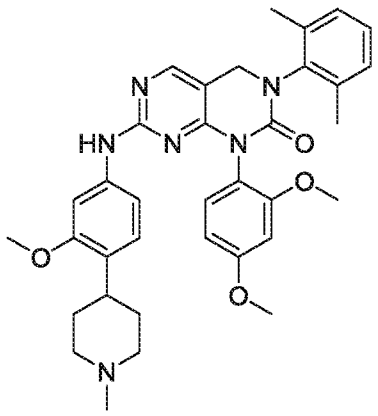
56. The method, pharmaceutical composition, or kit of claim 31, wherein the inhibitor of SIK is of the formula:



(YKL-05-99 or YKL-05-099),

or a pharmaceutically acceptable salt thereof.

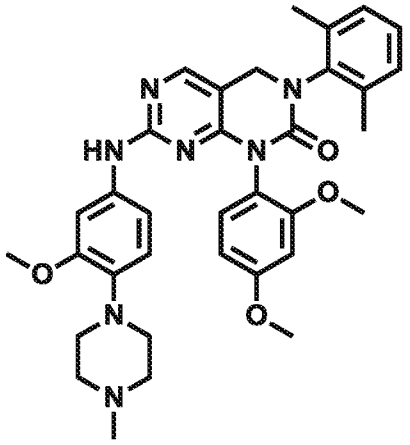
57. The method, pharmaceutical composition, or kit of claim 31, wherein the inhibitor of SIK is of the formula:



(YKL-05-093 or YKL 05-093),

or a pharmaceutically acceptable salt thereof.

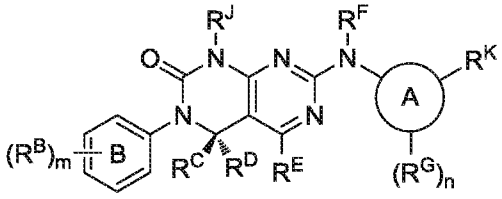
58. The method, pharmaceutical composition, or kit of claim 31, wherein the inhibitor of SIK is of the formula:



(YKL-04-114),

or a pharmaceutically acceptable salt thereof.

59. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of SIK is of the formula:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^J is substituted or unsubstituted carbocyclyl;

each instance of R^B is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(==0)R^a$, $-C(=0)OR^a$, $-C(==0)N(R^b)_2$, -N0 $_2$, $-NR^bC(=<))R^a$, $-NR^bC(=0)OR^a$, $-NR^bC(=0)N(R^b)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^b)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted alkynyl, **substituted or unsubstituted** carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

each instance of R^b is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^b are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

m is 0, 1, 2, 3, 4, or 5;

R^c is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^D is hydrogen, halogen, or substituted or unsubstituted, Ci_{-6} alkyl;

R^E is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^b)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^b)R^a$, $-C(==NR^b)OR^a$, $-C(==NR^b)N(R^b)_2$, $-C(=0)R^a$, $-C(=0)OR^a$, $-C(=0)N(R^b)_2$, $-N0_2$, $-NR^bC(=O)R^a$, $-NR^bC(O)0R^a$, $-NR^bC(=0)N(R^b)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^b)_2$;

n is 0, 1, 2, 3, or 4, as valency permits; and

R^K is unsubstituted methyl, substituted or unsubstituted heterocyclyl, $-QR^a$, or $-N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

60. The method, pharmaceutical composition, or kit of claim 59, wherein R^J is substituted or unsubstituted, 4- to 6-membered carbocyclyl.

61. The method, pharmaceutical composition, or kit of claim 59, wherein R^J is substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

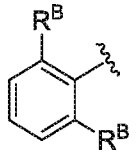
62. The method, pharmaceutical composition, or kit of any one of claims 59-61, wherein R^K is substituted or unsubstituted heterocyclyl.

63. The method, pharmaceutical composition, or kit of any one of claims 59-61, wherein R^K is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

64. The method, pharmaceutical composition, or kit of any one of claims 59-61, wherein R^K is $-N(R^c)_2$.

65. The method, pharmaceutical composition, or kit of any one of claims 59-64, wherein each instance of R^c is substituted or unsubstituted, C_{1-6} alkyl.

66. The method, pharmaceutical composition, or kit of any one of claims 59-65, wherein at least one instance of R^G is $-OR^a$, wherein R^a is substituted or unsubstituted, C_{1-6} alkyl.

67. The method, pharmaceutical composition, or kit of any one of claims 59-66, wherein Ring B is of the formula: 

; or m is 0.

68. The method, pharmaceutical composition, or kit of any one of claims 59-67, wherein at least one instance of R^B is halogen or substituted or unsubstituted, C_{1-6} alkyl.

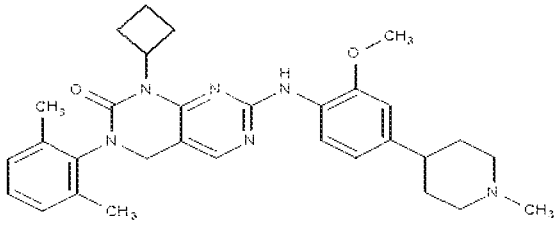
69. The method, pharmaceutical composition, or kit of any one of claims 59-68, wherein R^C is hydrogen.

70. The method, pharmaceutical composition, or kit of any one of claims 59-69, wherein R^D is hydrogen.

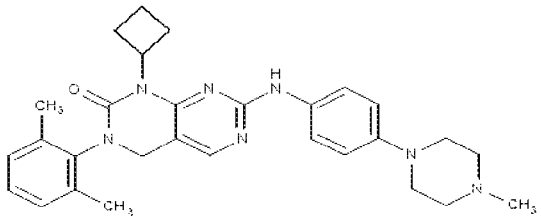
71. The method, pharmaceutical composition, or kit of any one of claims 59-70, wherein R^E is hydrogen.

72. The method, pharmaceutical composition, or kit of any one of claims 59-71, wherein R^F is hydrogen.

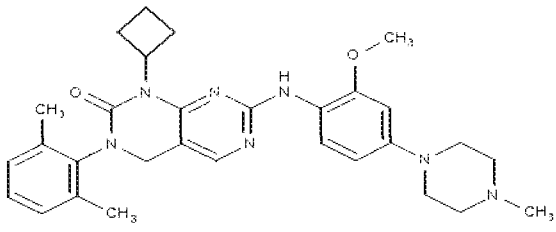
73. The method, pharmaceutical composition, or kit of claim 59, wherein the inhibitor of SIK. is of the formula:



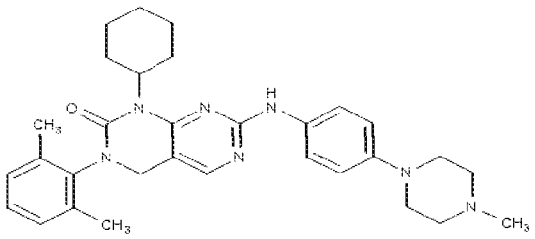
(YKL-06-050),



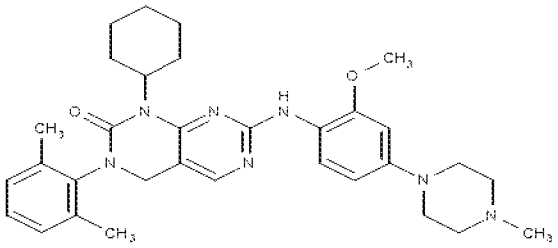
(YKL-06-060),



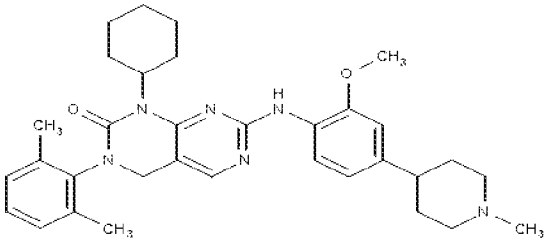
(YKL-06-061),



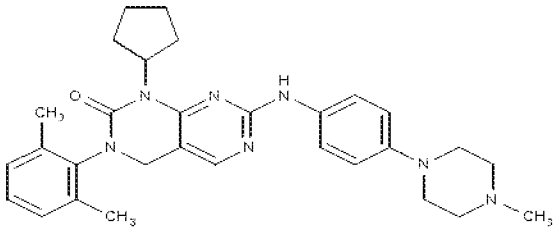
(YKL-06-062),



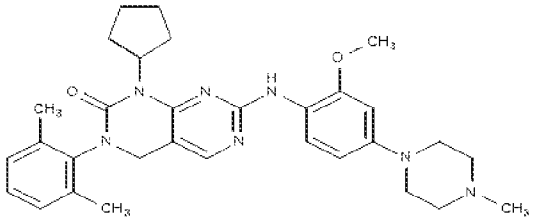
(YKL-06-063),



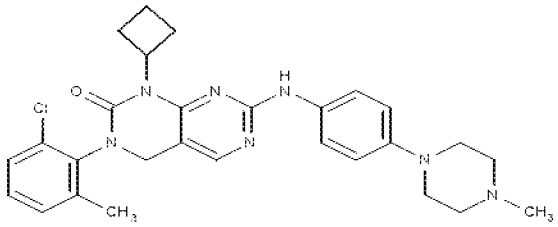
(YKL-06-064),



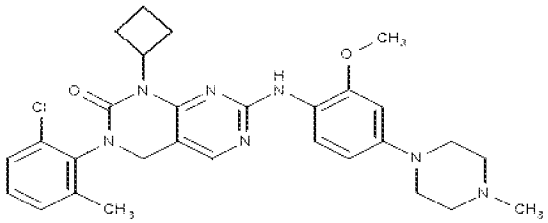
(YKL-06-075),



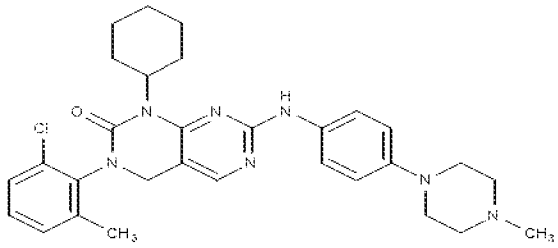
(YKL-06-076),



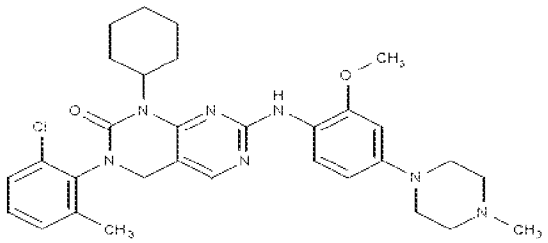
(YKL-06-088),



(YKL-06-089),



(YKL-06-090),

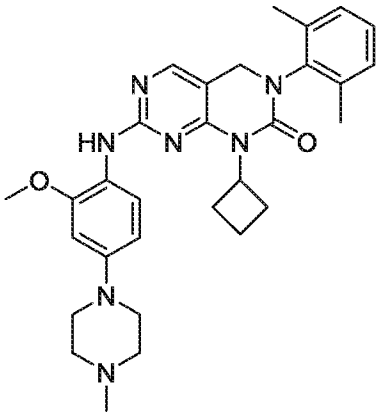


(YKL-06-091),

or a pharmaceutically acceptable salt thereof.

74. The method, pharmaceutical composition, or **kit** of claim 59, wherein the

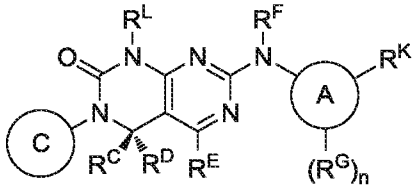
inhibitor of SIK is of the formula:



(YKL-06-061),

or a pharmaceutically acceptable salt thereof.

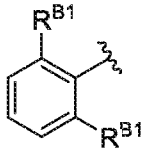
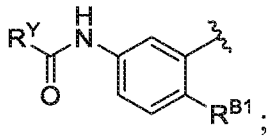
75. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of SIK is of the formula:



(III),

or a pharmaceutically acceptable salt thereof, wherein:

R^L is substituted or unsubstituted alkyl;

Ring C is unsubstituted phenyl or of the formula:  or  ;

each instance of R^{B1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^d)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^d)R^a$, $-C(==NR^d)OR^a$, $-C(=NR^d)N(R^d)_2$, $-C(=O)R^a$, $-C(=0)OR^a$, $-C(=0)N(R^d)_2$, $-N0_2$, $-NR^dC(=0)R^a$, $-NR^dC(==O)OR^a$, $-NR^dC(==0)N(R^a)_2$, $-OC(=0)R^a$, $-OC(=0)OR^a$, or $-OC(=0)N(R^d)_2$;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

each instance of R^d is independently hydrogen, -C(=0)R^a, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^d are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

R^C is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^D is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^E is hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

R^F is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

Ring A is substituted or unsubstituted phenyl; substituted or unsubstituted, polycyclic aryl; substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl; or substituted or unsubstituted, polycyclic heteroaryl;

each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^a, -$N(R^b)_2$, -SR^a, -CN, -SCN, -C(=NR^b)R^a, -C(=NR^b)OR^a, -C(=NR^a)$N(R^a)_2$, -C(=0)R^a, -C(=0)OR^a, -C(=0)$N(R^a)_2$, -N0$_2$, -NR^bC(=0)R^a, -NR^bC(=0)OR^a, -NR^bC(=0)$N(R^a)_2$, -OC(=0)R^a, -OC(=0)OR^a, or -OC(=0)$N(R^b)_2$;

each instance of R^b is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^b are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

n is 0, 1, 2, 3, or 4, as valency permits;

R^K is unsubstituted methyl, substituted or unsubstituted heterocyclyl, -QR^a, or -$N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of

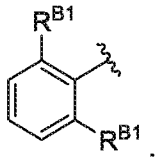
R^c are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; and

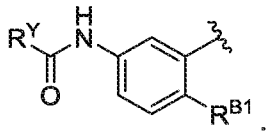
R^Y is substituted phenyl.

76. The method, pharmaceutical composition, or kit of claim 75, wherein R^L is substituted or unsubstituted, C_{1-6} alkyl.

77. The method, pharmaceutical composition, or kit of claim 75 or 76, wherein Ring C is unsubstituted phenyl.

78. The method, pharmaceutical composition, or kit of claim 75 or 76, wherein Ring C is of the formula:



79. The method, pharmaceutical composition, or kit of claim 75 or 76, wherein Ring C is of the formula:  .

80. The method, pharmaceutical composition, or kit of any one of claims 75-79, wherein R^K is substituted or unsubstituted heterocyclyl.

81. The method, pharmaceutical composition, or kit of any one of claims 75-79, wherein R^K is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

82. The method, pharmaceutical composition, or kit of any one of claims 75-79, wherein R^K is $-N(R^C)_2$.

83. The method, pharmaceutical composition, or kit of any one of claims 75-82, wherein each instance of R^c is substituted or unsubstituted, C_{1-6} alkyl.

84. The method, pharmaceutical composition, or kit of any one of claims 75-83, wherein each one of R^C and R^D is hydrogen.

85. The method, pharmaceutical composition, or kit of any one of claims 75-83, wherein one of R^C and R^D is hydrogen, and the other of R^C and R^D is substituted or unsubstituted, C_{1-6} alkyl.

86. The method, pharmaceutical composition, or kit of any one of claims 75-85, wherein R^E is hydrogen.

87. The method, pharmaceutical composition, or kit of any one of claims 75-86, wherein R^F is hydrogen.

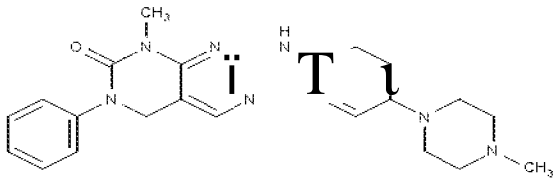
88. The method, pharmaceutical composition, or kit of any one of claims 75-87, wherein Ring A is substituted or unsubstituted phenyl.

89. The method, pharmaceutical composition, or kit of any one of claims 75-87, wherein Ring A is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl.

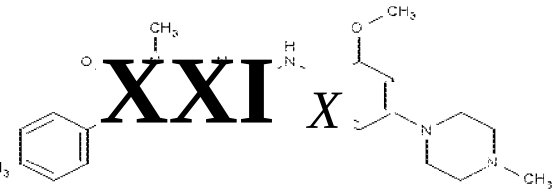
90. The method, pharmaceutical composition, or kit of any one of claims 75-87, wherein Ring A is substituted or unsubstituted pyridyl or substituted or unsubstituted pyrazolyl.

91. The method, pharmaceutical composition, or kit of any one of claims 75-90, wherein at least one instance of R^G is halogen, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted heterocyclyl, or -OR^a.

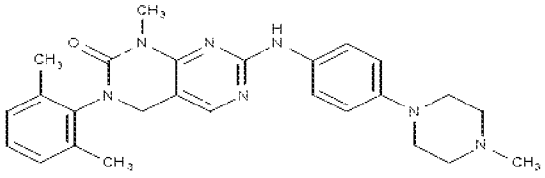
92. **The method, pharmaceutical composition, or kit of claim** 75, **wherein the inhibitor of SIK is of the formula:**



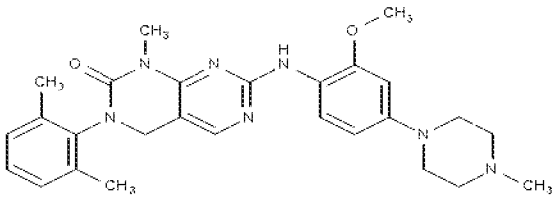
(HG-1 1-137-01),



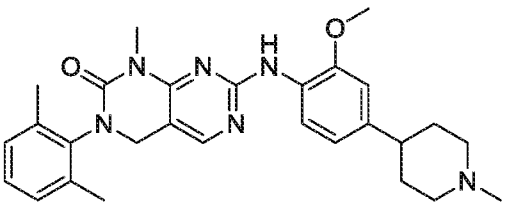
(HG- 11-139-02),



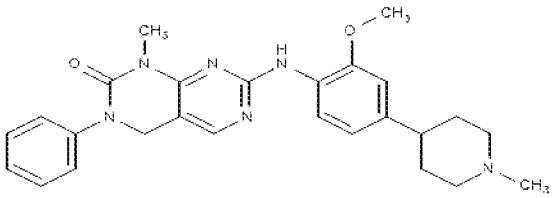
(YKL-06-029),



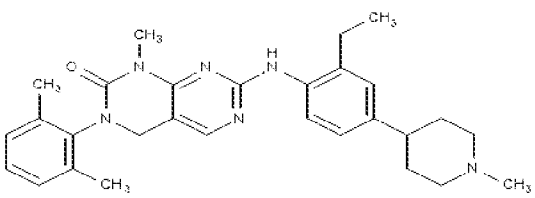
(YKL-06-030),



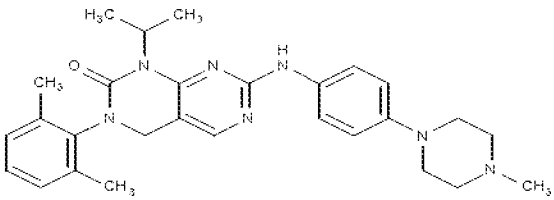
(YKL-06-031),



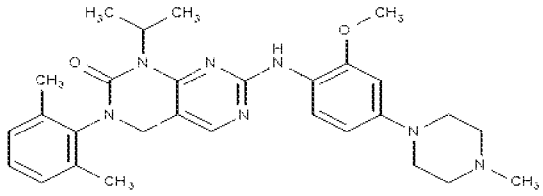
(YKL-06-033),



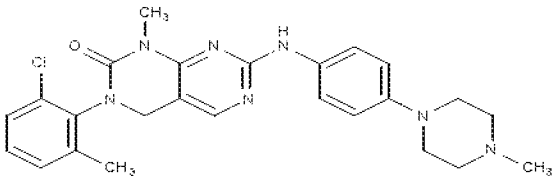
(YKL-06-046),



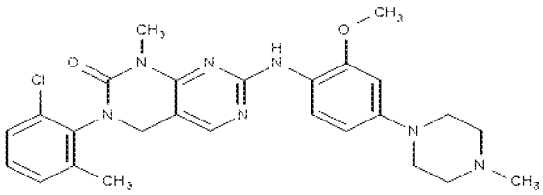
(YKL-06-058),



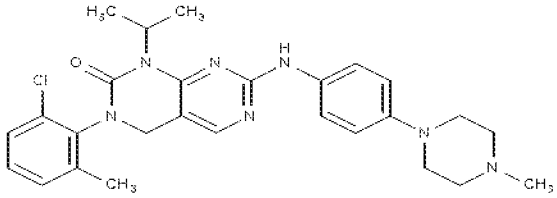
(YKL-06-059),



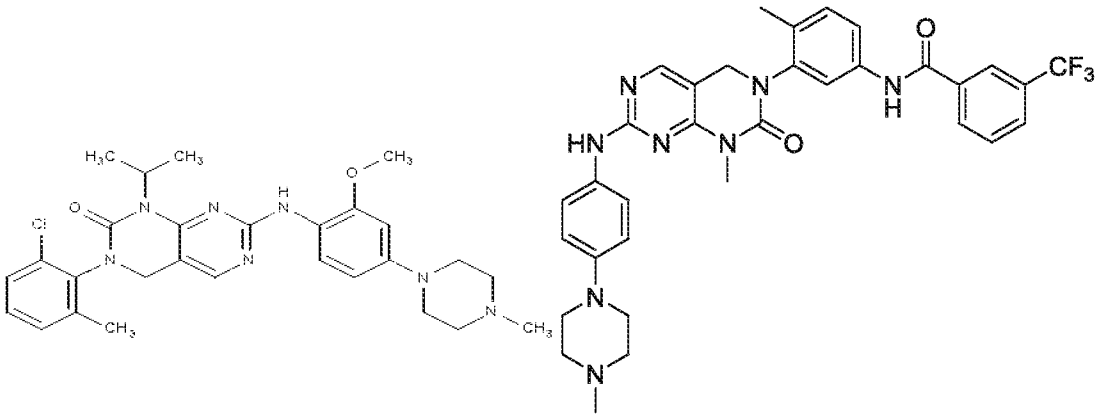
(YKL-06-084),



(YKL-06-085),

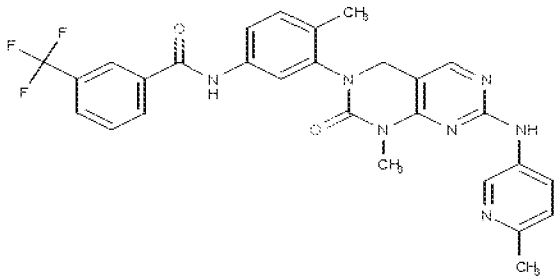


(YKL-06-086),



(YKL-G6-087),

(HG- 11-23-01),

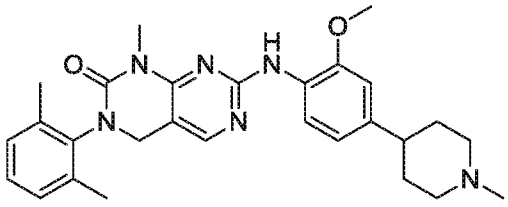


(HG-4-34-01),

or a pharmaceutically acceptable salt thereof.

93. The method, pharmaceutical composition, or kit of claim 75, wherein the

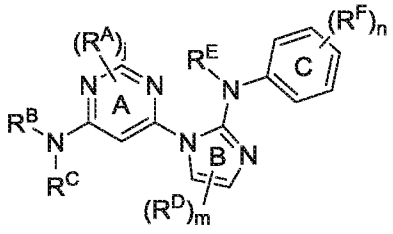
inhibitor of SIK is of the formula:



(YKL-06-03 1),

or a pharmaceutically acceptable salt thereof.

94. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of **SIK** is of the formula:



(IV),

or a pharmaceutically acceptable salt thereof, wherein:

each instance of $\mathbf{R}^{A}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $\mathbf{-OR^{A1}}$, -$N(R^{A1})_2$, $\mathbf{-SR^{A1}}$, **-CN, -SCN, -** $\mathbf{C(=NR^{A1})R^{A1}}$, $\mathbf{-C(=NR^{A1})OR^{A1}}$, -$C(==NR^{A1})N(R^{A1})_2$, –$\mathbf{C(=0)R^{A1}}$, -$C(=O)OR^{A1}$, - $\mathbf{C(=0)N(R^{A,})_2}$, -$N0_2$, $\mathbf{-NR^{A1}C(=0)R^{A1}}$, - $\mathbf{NR^{A1}C(=0)OR^{A1}}$, -$NR^{A1}C(=O)N(R^{A1})_2$, -$OC(=O)R^{A1}$, -$OC(=O)OR^{A1}$, **or -** $OC(=O)N(R^{A1})_2$, wherein each instance of $\mathbf{R^{A1}}$ is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{A1} are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

j is 0, 1, or 2;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

R^C is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^D is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, **-OR^{D1}, -**$N(R^{D1})_2$, **-SR^{D1},** -CN, -SCN, -C(=NR ^{D1})R^{D1}, **-C(=NR^{D1})OR^{D1}, - C(=NR^{D1})N(R^{D1})$_2$, -C(=O)R ^{D1}, -C(=O)OR ^{D1}, -C(=O)N(R ^{D1})$_2$, -N0 $_2$, - NR^{D1}C(=O)R^{D1},** – NR^{D1}C(=O)OR ^{D1}, -NR ^{D1}C(=O)N(R ^{D1})$_2$, **-OC(=O)R ^{D1}, -OC(=O)OR^{D1},** or-OC(=O)N(R ^{D1})$_2$, wherein each instance of R^{D1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

m is 0, 1, or 2;

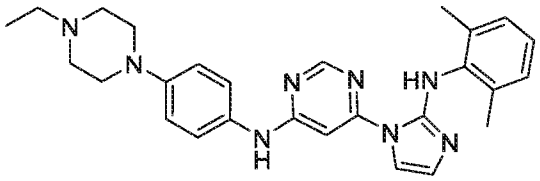
R^E is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^F is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, - OR^{F1}, - $N(R^{F1})_2$, -SR ^{F1}, **-CN,** -SCN, -C(=NR ^{F1})R^{F1}, -C(=NR ^{F1})OR^{F1}, -C(=NR ^{F1})N(R^{F1})$_2$, - **C(=O)R^{F1},** -C(=O)OR ^{F1}, -C(0)N(R ^{F1})$_2$, -N0 $_2$, - **NR^{F1}C(=O)R^{F1},** -NR ^{F1}C(=O)OR ^{F1}, -NR ^{F1}C(=O)N(R ^{F1})$_2$, -OC(=O)R ^{F1}, -OC(=O)OR ^{F1}, or -OC(=O)N(R ^{F1})$_2$, wherein each instance of R^{F1} is independently hydrogen, substituted or unsubstituted acyl,

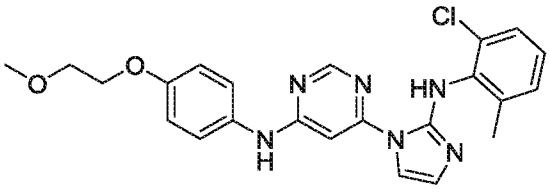
substituted or unsubstiluted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{F1} are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; and

n is 0, 1, 2, 3, 4, or 5.

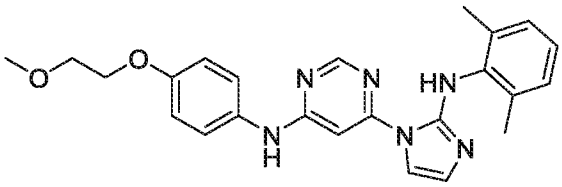
95. The method, pharmaceutical composition, or kit of claim 94, wherein the inhibitor of SIK is of the formula:



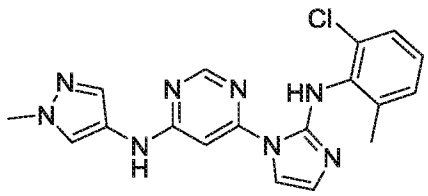
(IV-1 or HG-10-7-01),



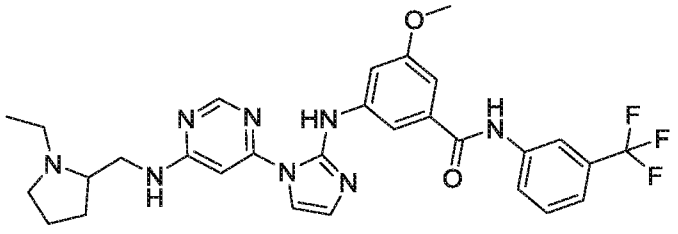
(IV-2),



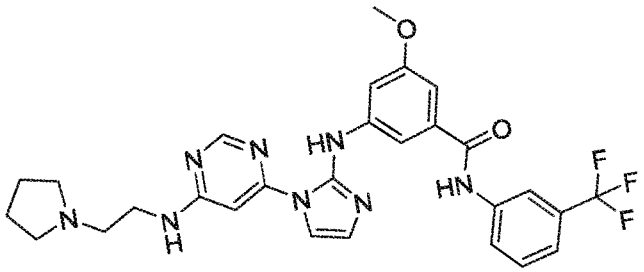
(IV-3),



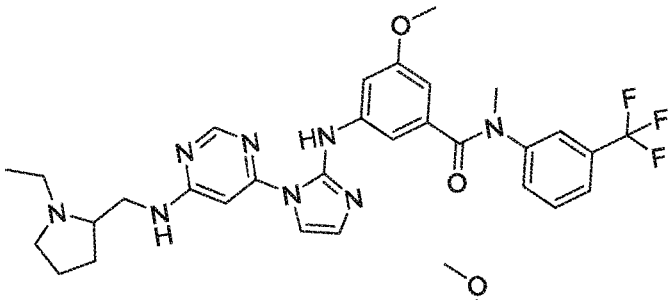
(IV-4),



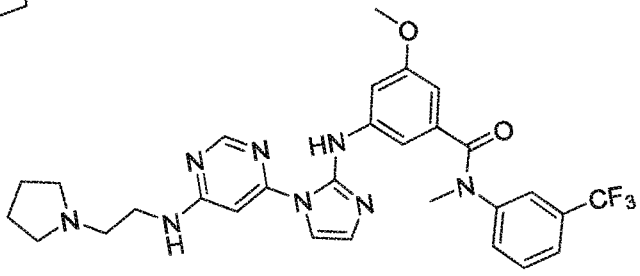
(IV-5),



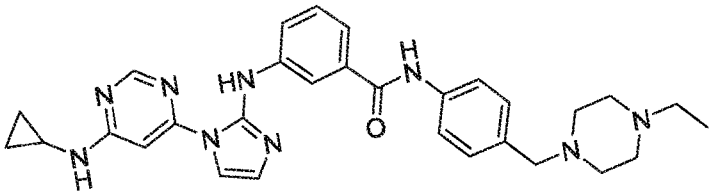
(IV-6),



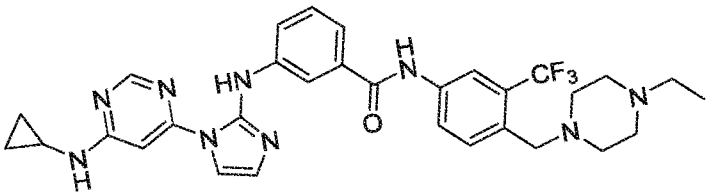
(IV-7),



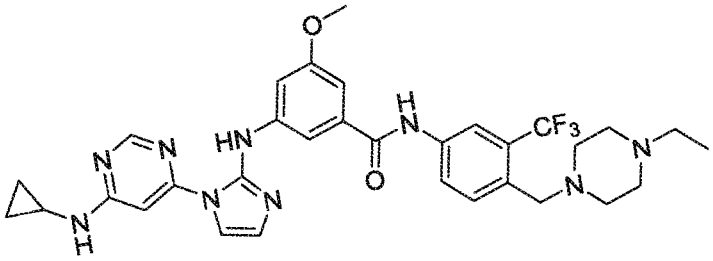
(IV-8),



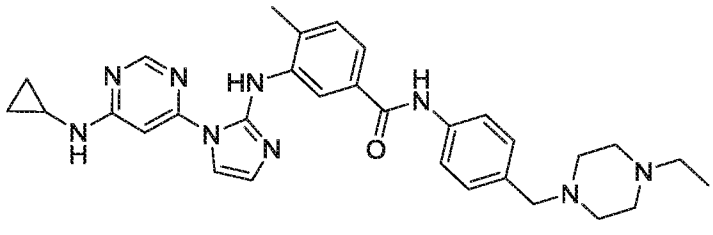
(IV-9),



(IV-10),



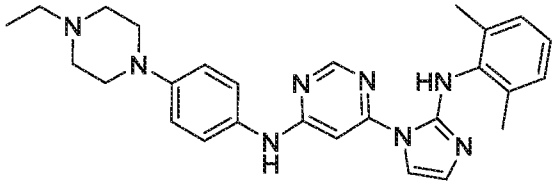
(IV-11),



(IV-12),

or a pharmaceutically acceptable salt thereof.

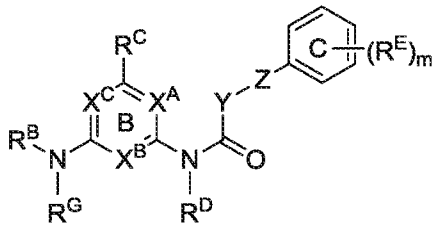
96. The method, pharmaceutical composition, or kit of claim 94, wherein the inhibitor of SIK is of the formula:



(IV-1 or HG-10-7-01),

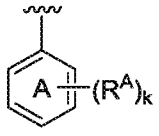
or a pharmaceutically acceptable salt thereof.

97. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of SIK is of the formula:



(V),

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R}^G$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl, or of the formula:  ;

each instance of $\mathbf{R}^A$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, **-OR^a**, -$N(R^a)_2$, **-SR^a**, -CN, -SCN, -C(=NR^a)R^a, -C(=NR^a)OR^a, -C(=NR^a)$N(R^a)_2$, -C(=O)R^a,

-C(=0)OR a, -C(=0)N(R a)$_2$, -N0 $_2$, -NR aC(=0)R a, -NR aC(=0)OR a, -NRaC(=0)N(R a)$_2$, -OC(=0)R a, **-OC(=0)ORa,** or -QC(=0)N(R a)$_2$, or two R^A groups are joined to form a substituted or unsubstituted carbocyclic ring, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted aryl ring, or substituted or unsubstituted heteroaryl ring;

each instance of Ra is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two Ra groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, 4, or 5;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^c is independently N or CR^X, wherein each instance of R^X is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR a, -N(R a)$_2$, -SR a, -CN, -SCN, -C(=NR a)Ra, -C(=NR a)ORa, -C(=NR a)N(Ra)$_2$, -C(=0)R a, -C(=G)OR a, -C(=0)N(R a)$_2$, -N0 $_2$, -NR aC(=0)R a, -NR aC(=0)OR a, -NR aC(=0)N(R a)$_2$, -OC(=0)R a, -OC(=0)OR a, or-QC(=0)N(R a)$_2$;

or: X^B is CR^X, and R^G and R^X of X^B are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

Rc is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR a, -N(R a)$_2$, -SR a, -CN, -SCN, -C(=NR a)Ra, -C(=NR a)ORa, -C(=NR a)N(Ra)$_2$, -C(0)R a, -C(=0)OR a, -C(=0)N(R a)$_2$, **-N0 $_2$,** -NR aC(=0)R a, -NR aC(=0)OR a, -NR aC(=0)N(R a)$_2$, -OC(=0)R a, -OC(=0)OR a, or-OC(=0)N(R a)$_2$;

R^D is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

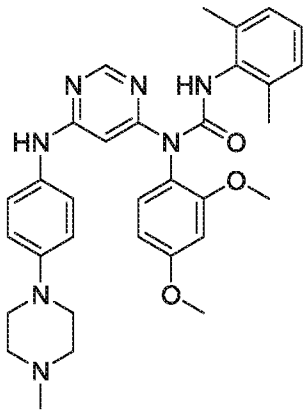
Y is -O- or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

Z is a bond or $-C(R^Z)_2-$, wherein each instance of R^Z is independently hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

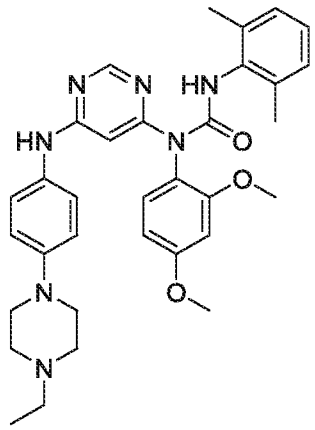
each instance of R^E is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-NR^aS(=O)R^a$, $-NR^aS(=O)OR^a$, $-NR^aS(=O)N(R^a)_2$, $-NR^aS(=O)_2R^a$, $-NR^aS(=O)_2OR^a$, $-NR^aS(=O)_2N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

m is 0, 1, 2, 3, 4, or 5.

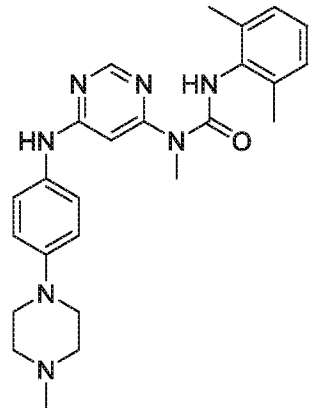
98. The method, pharmaceutical composition, or kit of claim 97, wherein the inhibitor of SIK is of the formula:



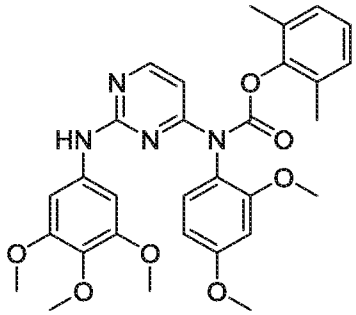
(V-1 or HG-9-91-01),



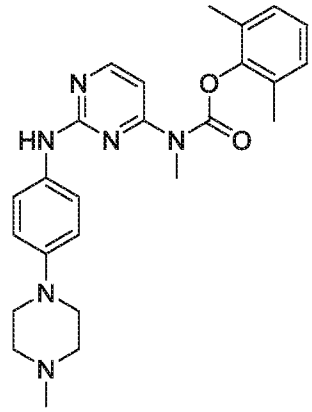
(**V**-2 or HG-1 0-1 1-01),



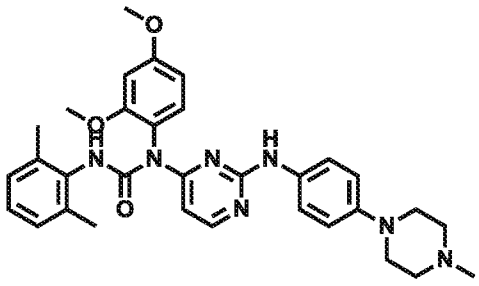
(**V**-3 or HG-9- 148-01),



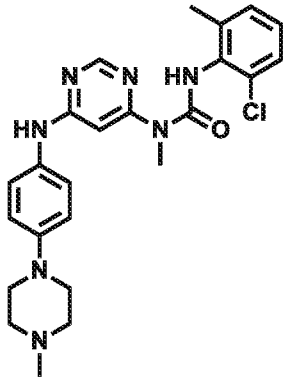
(**V-4** or HG-9-88-01),



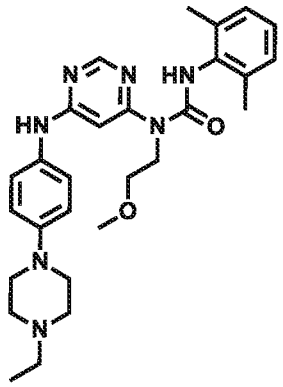
(**V-5** or HG-9-150-01),



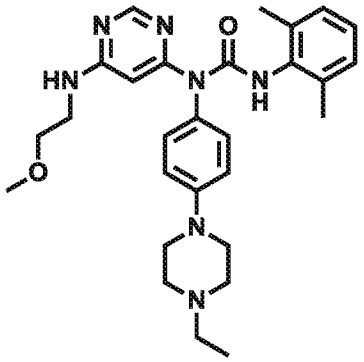
(HG-9-96-01),



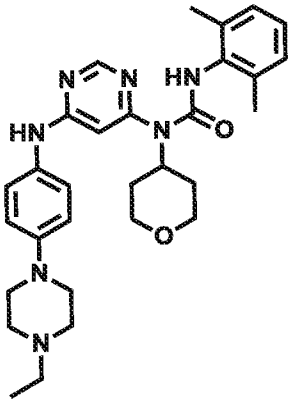
(HG-9- 148-02),



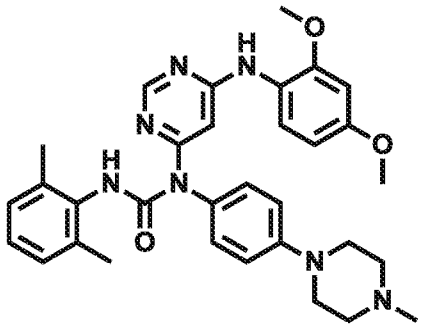
(HG-10-8-01),



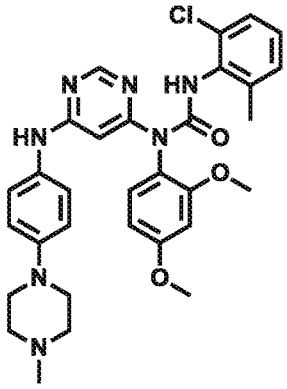
(HG-10-8-02),



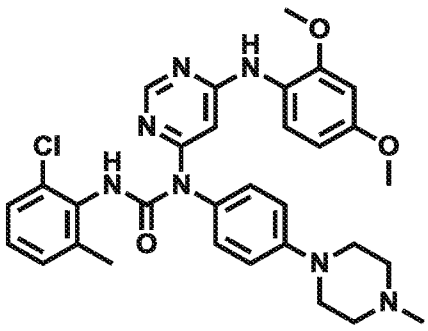
(HG-10-9-01),



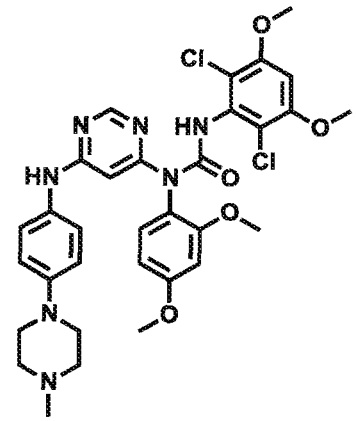
(HG-10-15-02),



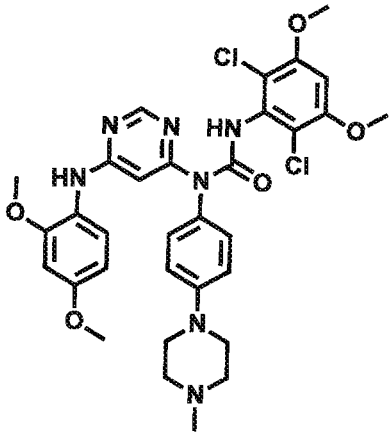
(HG-10-15-03),



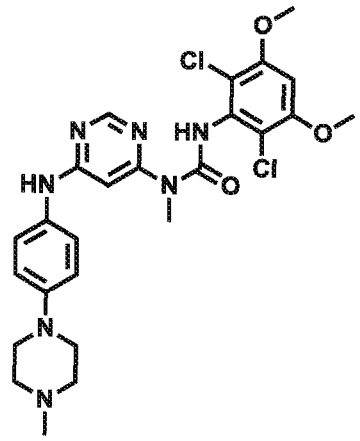
(HG-10-15-04),



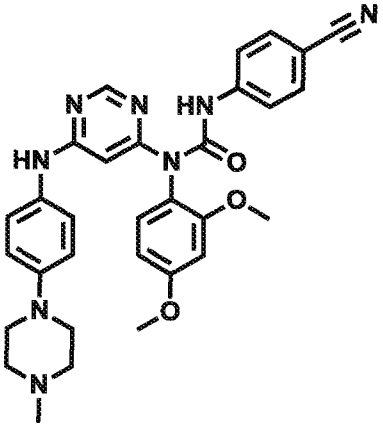
(HG-10-27-01),



(HG-10-27-02),



(HG-10-28-01),



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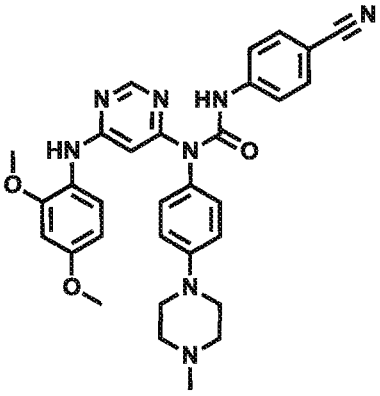

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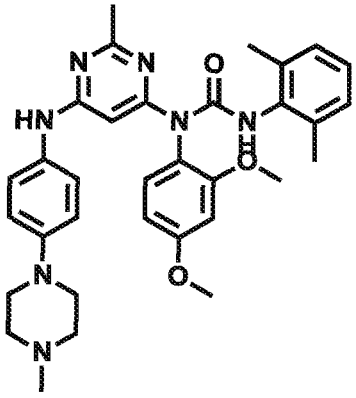
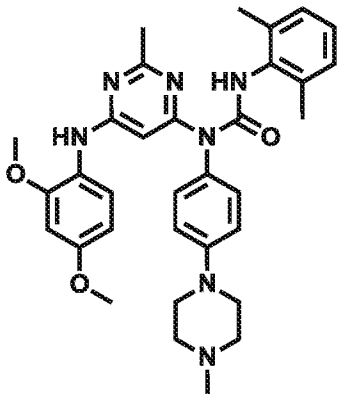
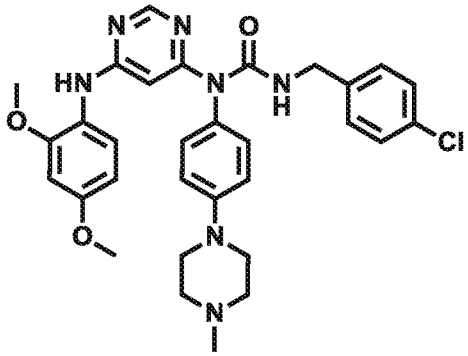


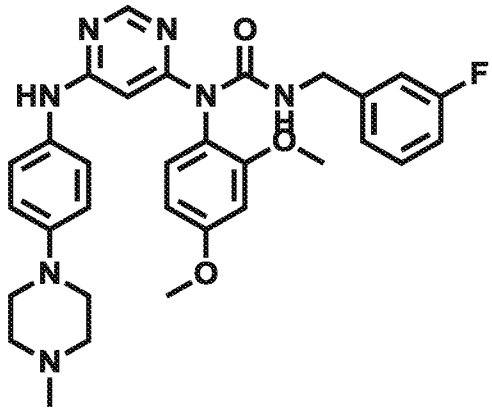
(HG-10-36-01),



(HG- 10-36-02),



(HG 10-59-02),



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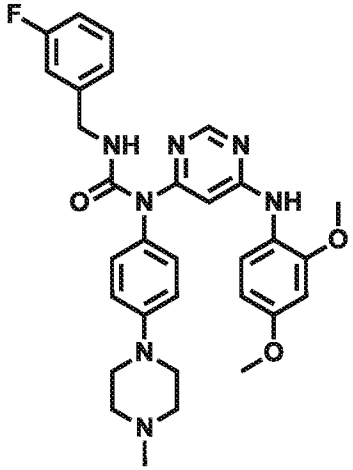

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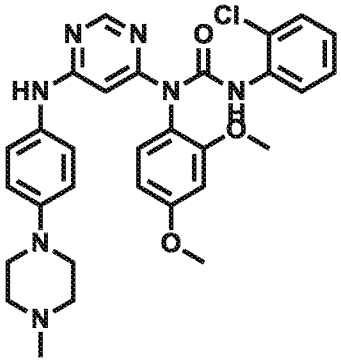

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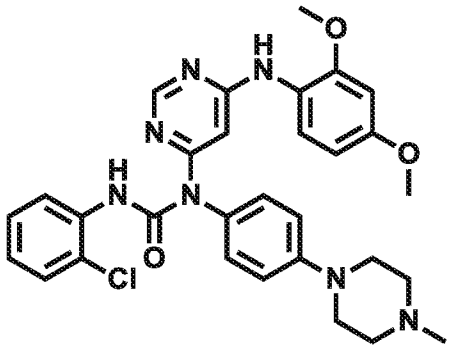

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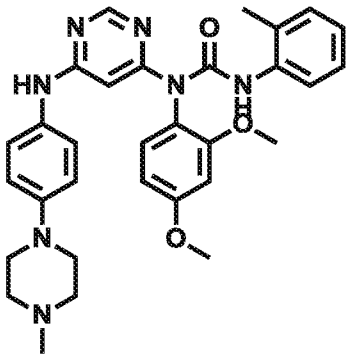

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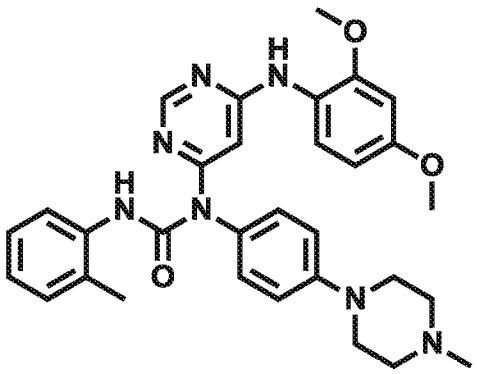

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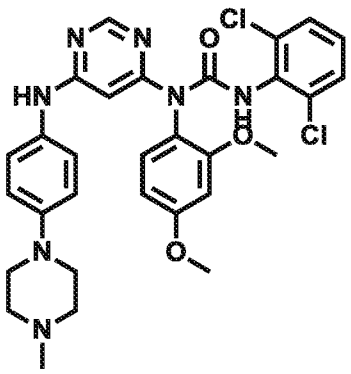

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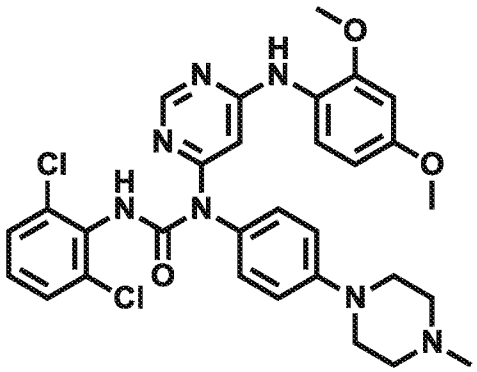

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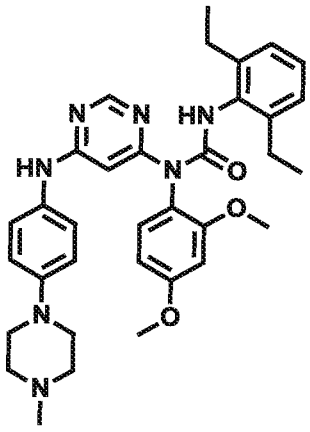

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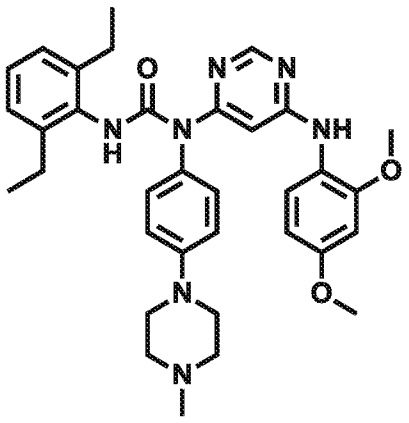

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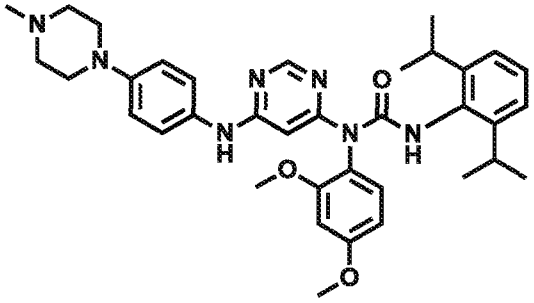

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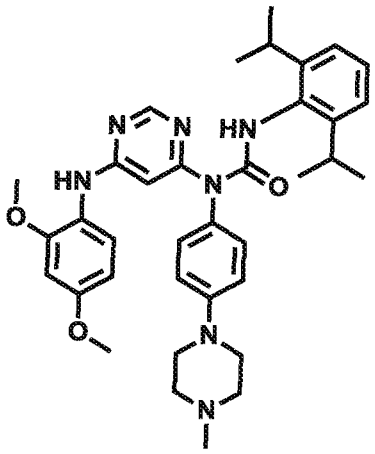

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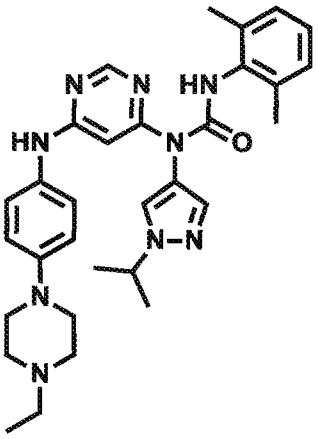

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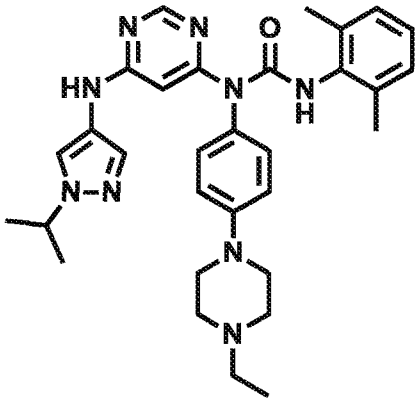

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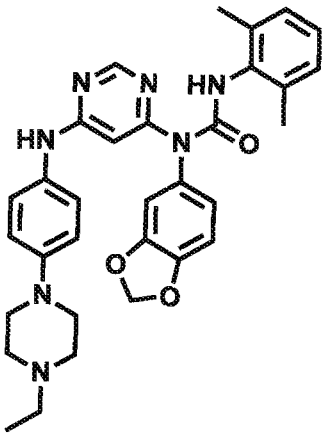

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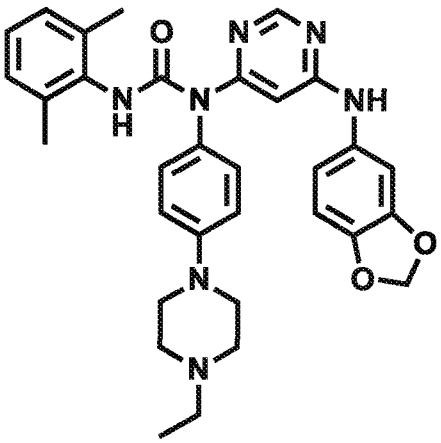

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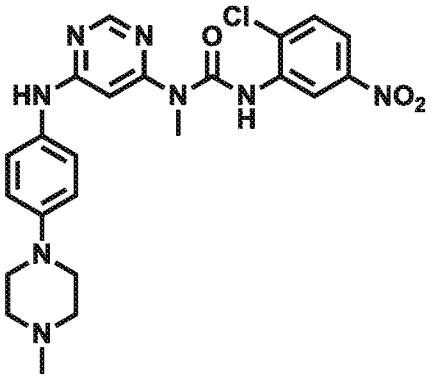

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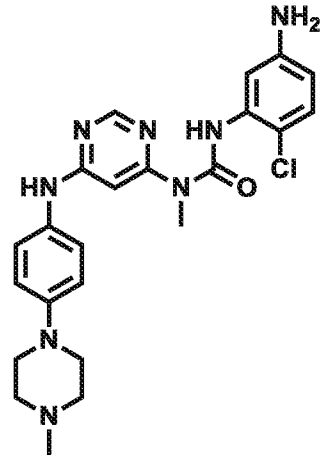

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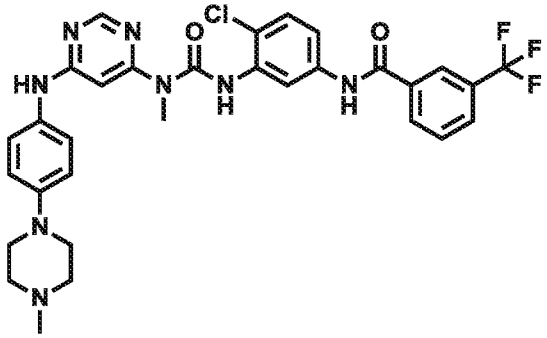

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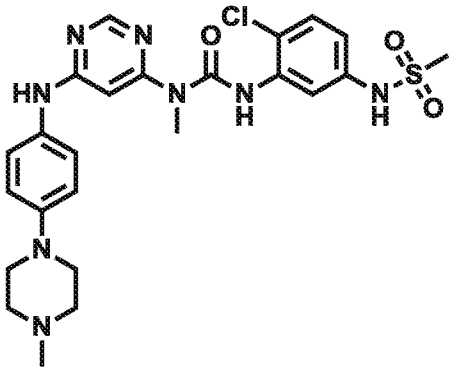

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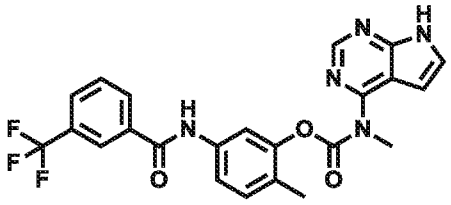

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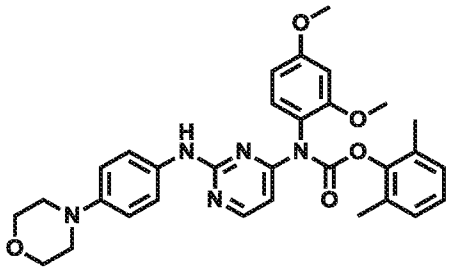

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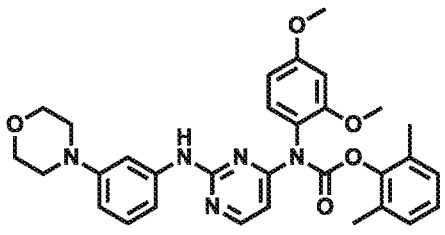

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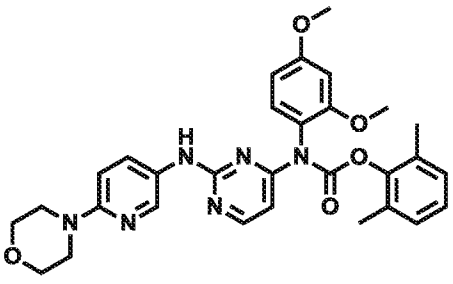

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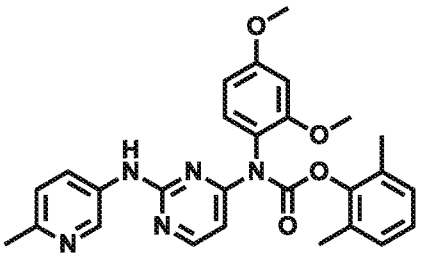

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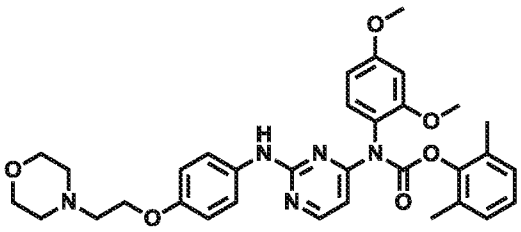

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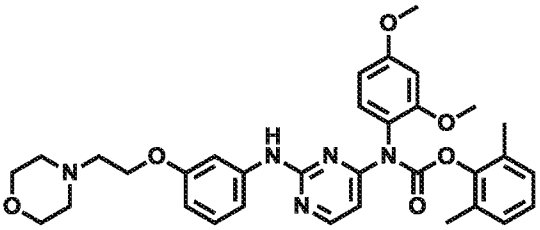

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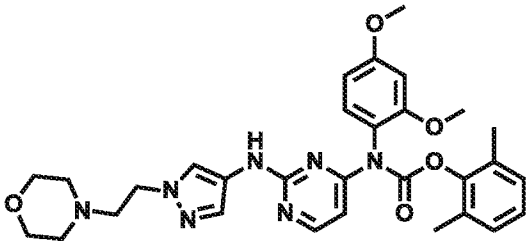

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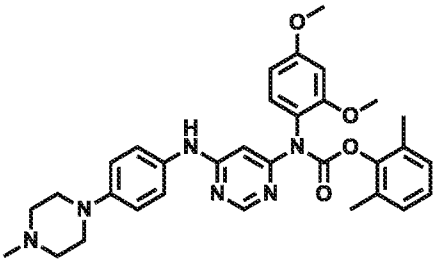

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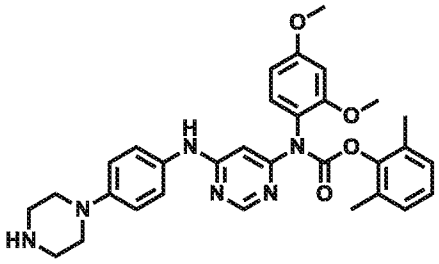

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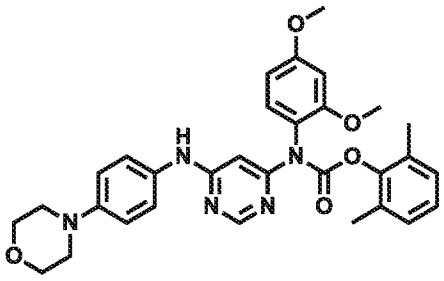

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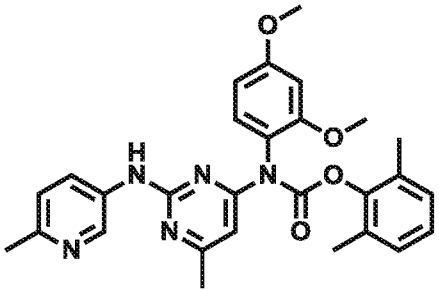

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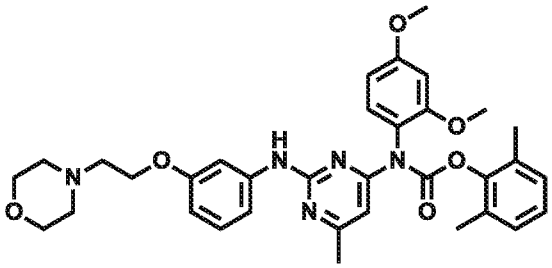

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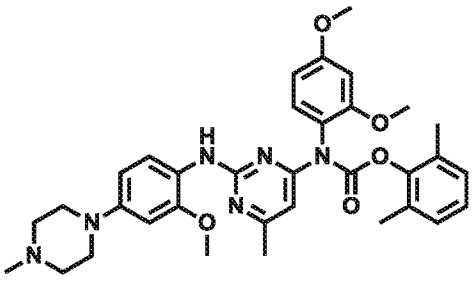

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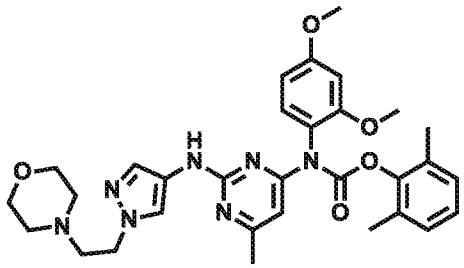

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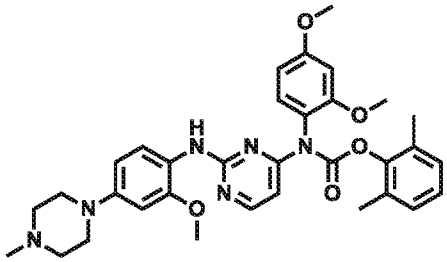

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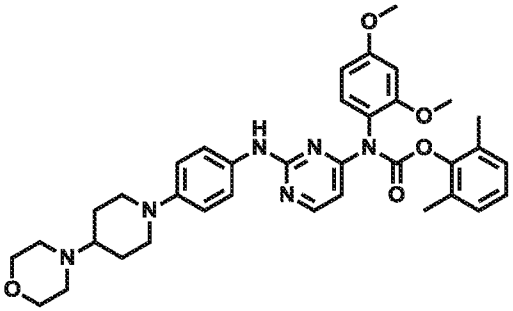

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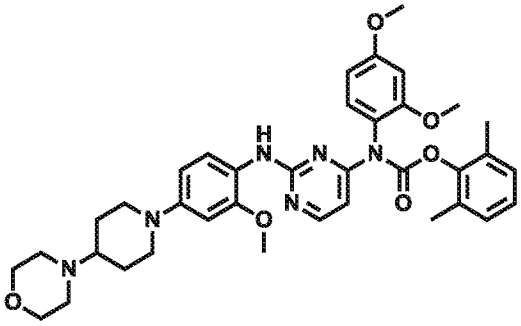

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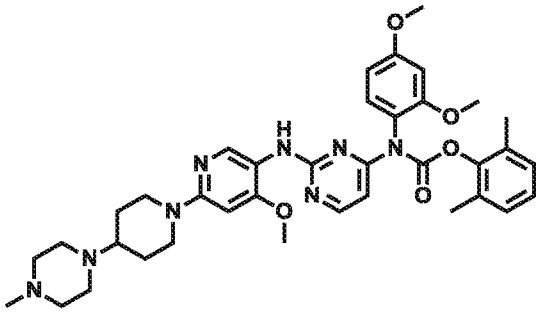

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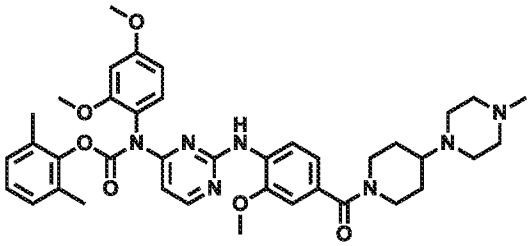

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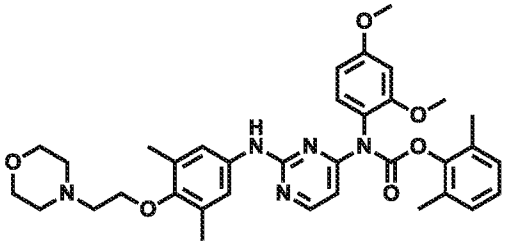

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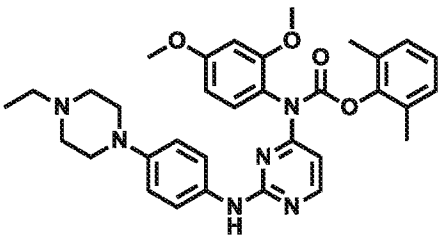

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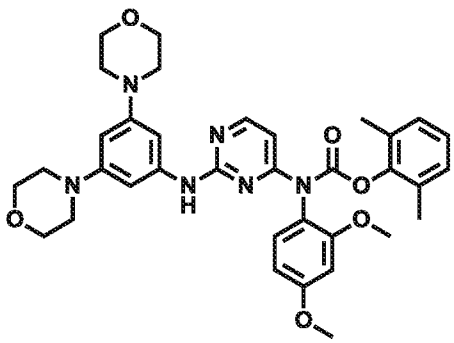

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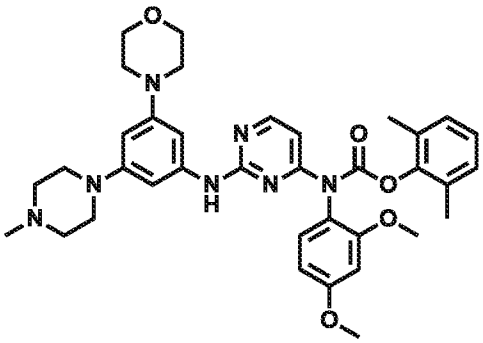

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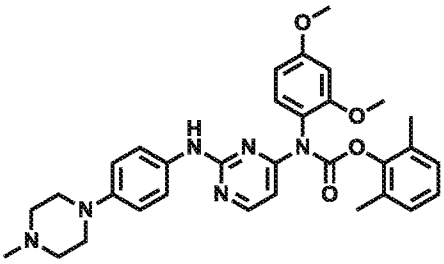

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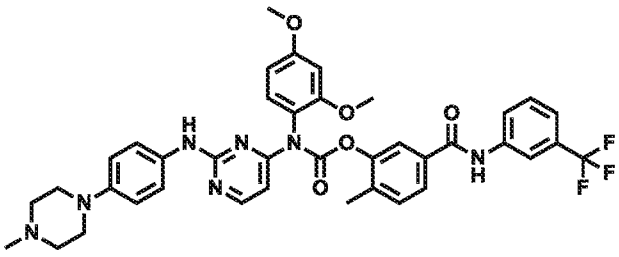

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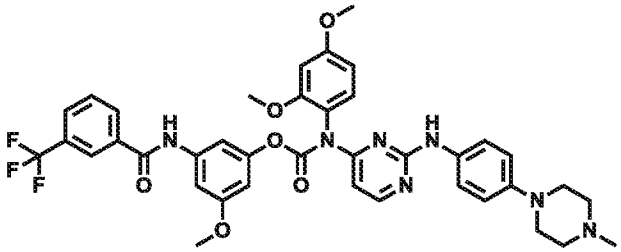

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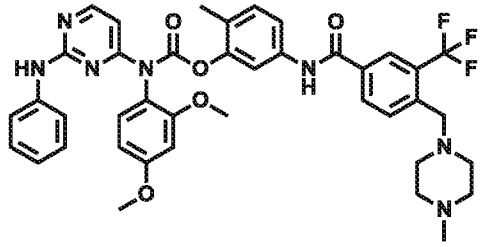

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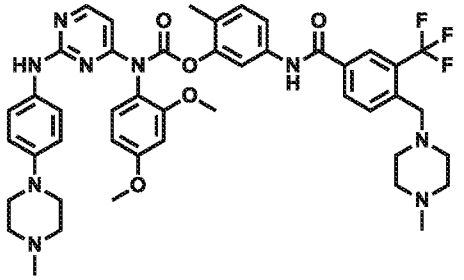

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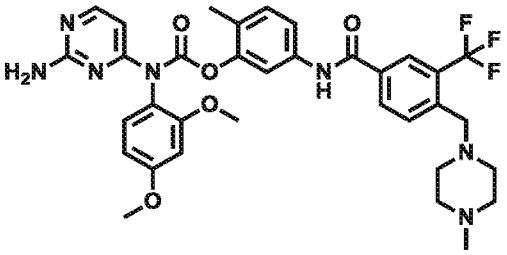
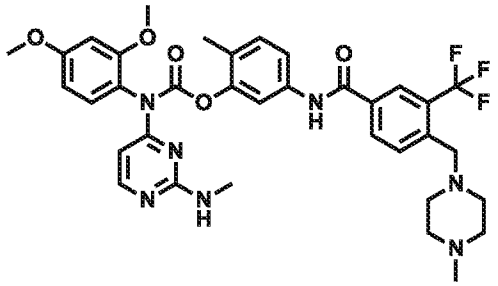
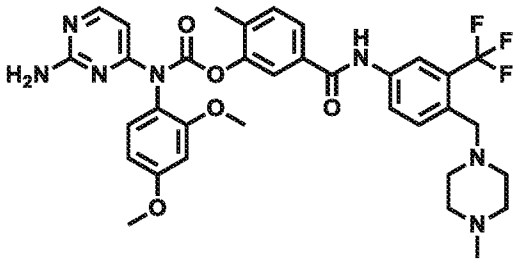


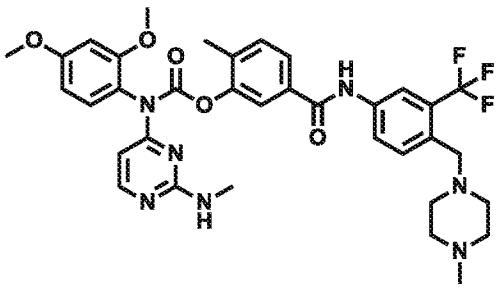
(WH4-199-1),



(WH4-199-2),



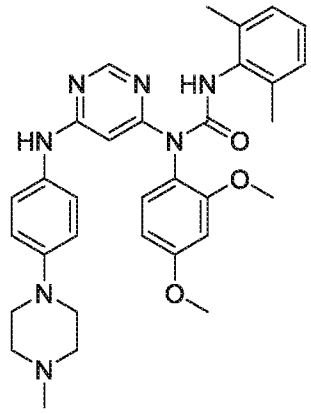
(WH4-200-1),



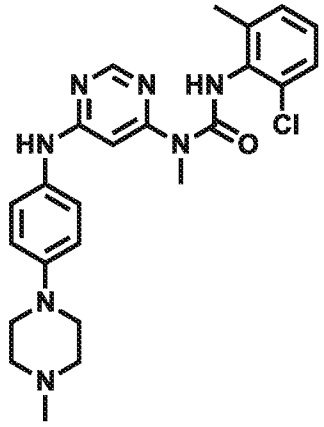
(WH4-200-2),

or a pharmlaceutically acceptable salt thereof.

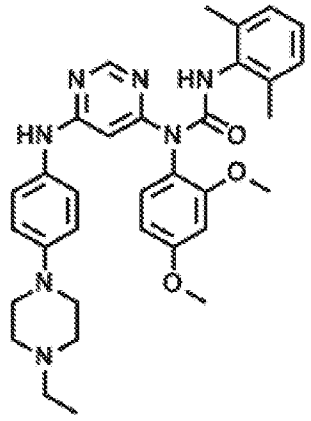
99. The method, pharmaceutical composition, or kit of claim 97, wherein the inhibitor of SIK is of the formula:



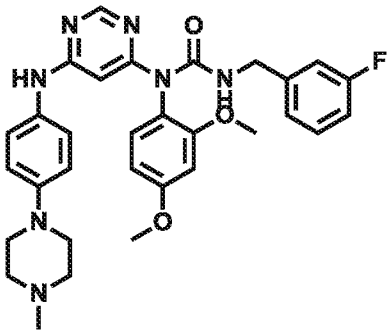
(**III-1** or HG-9-91-01),



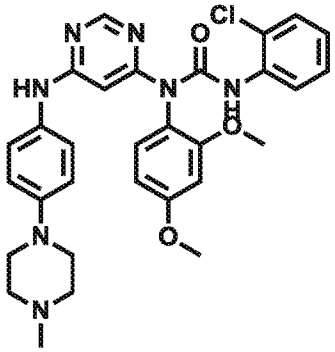
(HG-9-148-02),



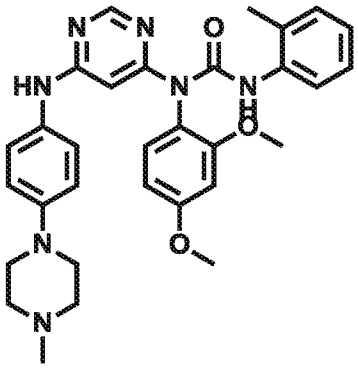
(HG-10-11-01),



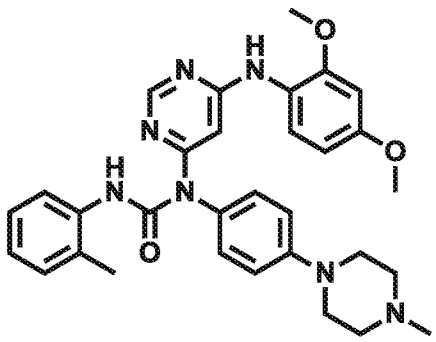
(HG-10-60-01),



(HG- 10-6 1-01),



(HG- 10-62-01),



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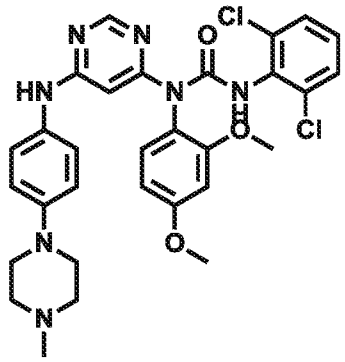

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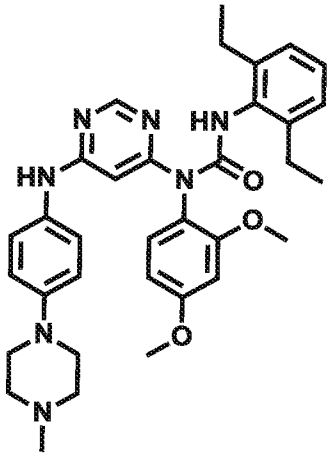
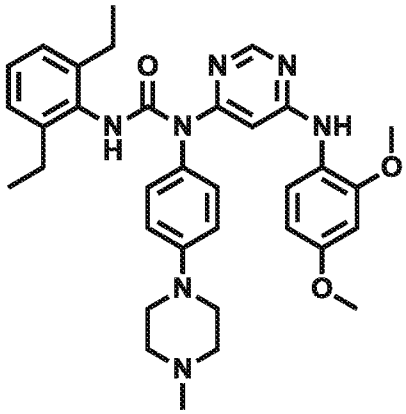


(HG-10-64-01),



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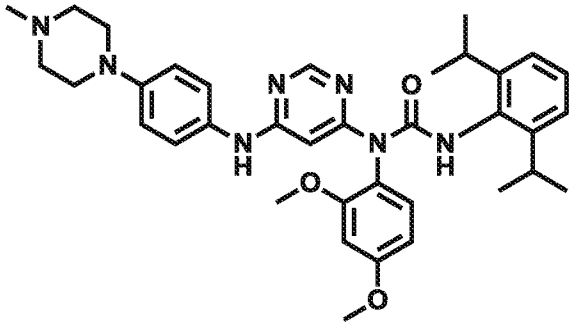

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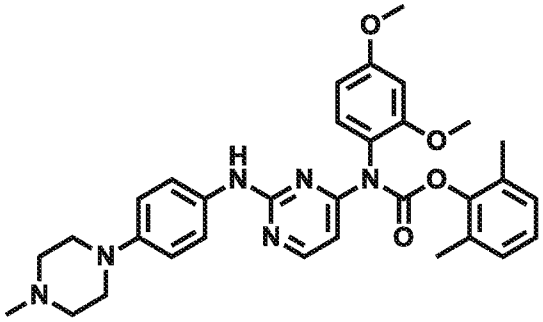
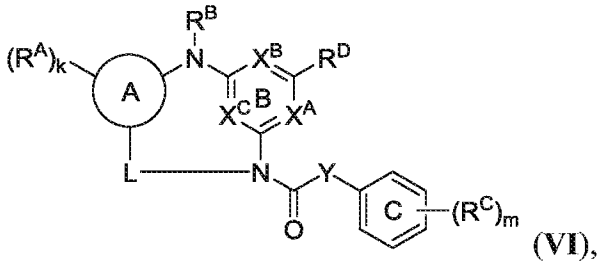


(WH1-4-023),

or a pharmaceutically acceptable salt thereof.

100. The method of any one of claims 1-15 and 29-30, pharmaceutical composition of any one of claims 16-17 and 29-30, or kit of any one of claims 18-30, wherein the inhibitor of SIK is of the formula:



(VI),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a substituted or unsubstituted phenyl ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur;

each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, -CN, -SCN, $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, or $-OC(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

k is 0, 1, 2, 3, or 4;

L is a substituted or unsubstituted, saturated or unsaturated C_{3-10} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with -O-, -S-, $-NR^N-$, -N=, or =N-, wherein each instance

of R^N is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, C_{i_6} alkyl, or a nitrogen protecting group;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, $C_{i\text{-}6}$ alkyl, or a nitrogen protecting group;

each of X^A, X^B, and X^c is independently N or CR^X, wherein R^X is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{X1}$, $-N(R^{X1})_2$, $-SR^{X1}$, -CN, -SCN, $-C(=NR^{X1})R^{X1}$, $-C(=NR^{X1})OR^{X1}$, $-C(=NR^{X1})N(R^{X1})_2$, $-C(=0)R^{X1}$, $-C(=0)OR^{X1}$, $-C(=0)N(R^{X1})_2$, $-N0_2$, $-NR^{X1}C(=0)R^{X1}$, $-NR^{X1}C(=0)OR^{X1}$, $-NR^{X1}C(=0)N(R^{X1})_2$, $-OC(=0)R^{X1}$, $-OC(=0)OR^{X1}$, or $-OC(=0)N(R^{X1})_2$, wherein each instance of R^{X1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{X1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

Y is -O- or $-NR^Y-$, wherein R^Y is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted, $C_{1\text{-}f}$ alkyl, or a nitrogen protecting group;

or when Y is $-NR^Y-$ and X^A is CR^X, R^Y and R^X of X^A are joined to form a substituted or unsubstituted, monocyclic, 5- to 7-membered heterocyclic ring that is fused with Ring B;

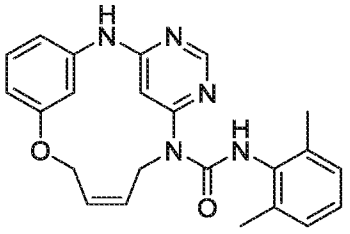
each instance of R^c is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C1}$, $-N(R^{C1})_2$, $-SR^{C1}$, -CN, -SCN, $-C(=NR^{C1})R^{C1}$, $-C(=NR^{C1})OR^{C1}$, $-C(=NR^{C1})N(R^{C1})_2$, $-C(=0)R^{C1}$, $-C(=0)0R^{C1}$, $-C(=0)N(R^{C1})_2$, $-N0_2$, $-NR^{C1}C(=0)R^{C1}$, $-NR^{C1}C(=0)0R^{C1}$, $-NR^{C1}C(=0)N(R^{C1})_2$, $-OC(=0)R^{C1}$, $-OC(=0)OR^{C1}$, or $-OC(=0)N(R^{C1})_2$, wherein each instance of R^{C1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted

alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyi, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{C1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

m is 0, 1, 2, 3, 4, or 5; and

R^D is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyi, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{D1}$, $-N(R^{D1})_2$, $-SR^{D1}$, -CN, -SCN, $-C(=NR^{D1})R^{D1}$, $-C(=NR^{D1})OR^{D1}$, $-C(==NR^{D1})N(R^{D1})_2$, $-C(=0)R^{D1}$, $-C(=0)OR^{D1}$, $-C(=0)N(R^{D1})_2$, $-N0_2$, $-NR^{D}C(=0)R^{D1}$, $-NR^{D1}C(0)GR^{D1}$, $-NR^{D1}C(=0)N(R^{D1})_2$, $-OC(=0)R^{D1}$, $-OC(=0)OR^{D1}$, or $-OC(=0)N(R^{D1})_2$, wherein each instance of R^{D1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyi, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

101. The method, pharmaceutical composition, or kit of claim 100, wherein the inhibitor of SIK is of the formula: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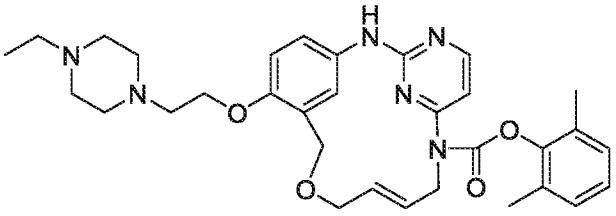
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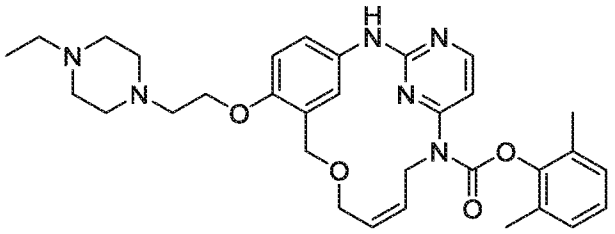
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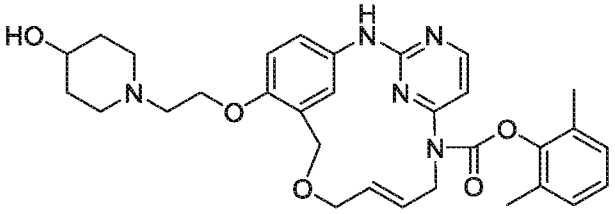
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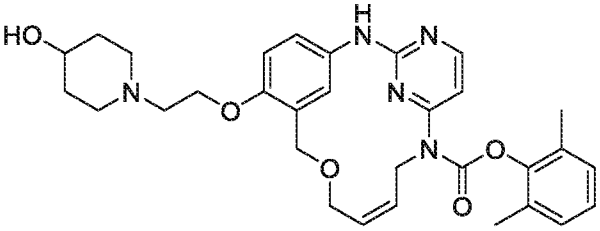
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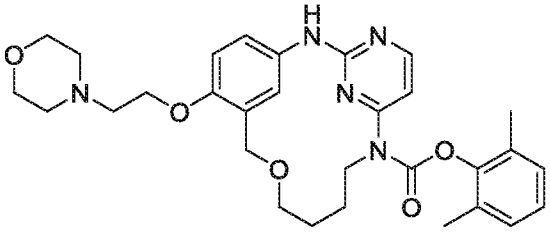
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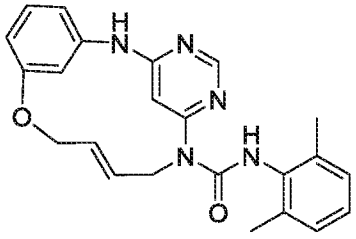
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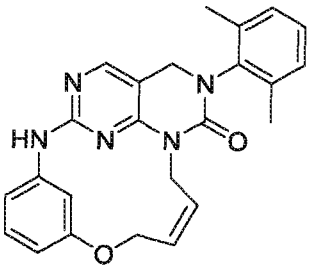

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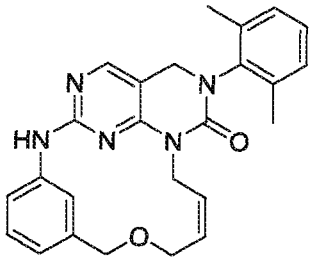

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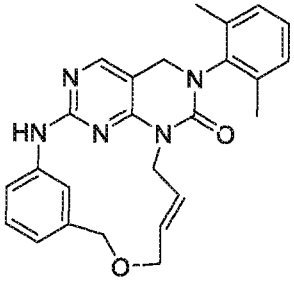

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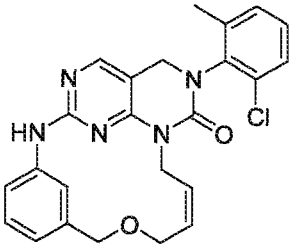

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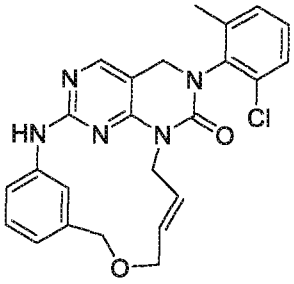

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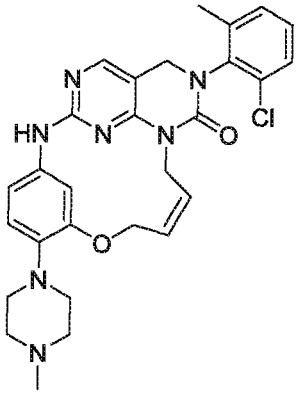

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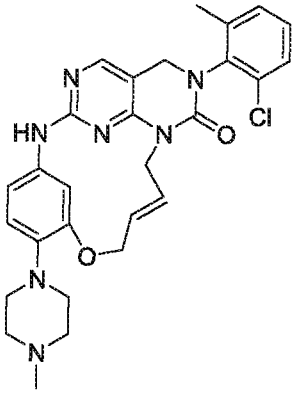

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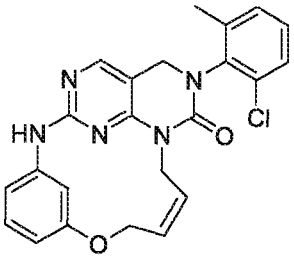

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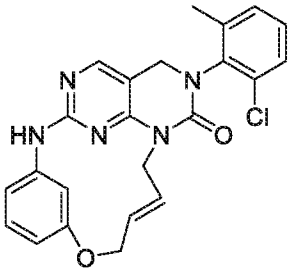

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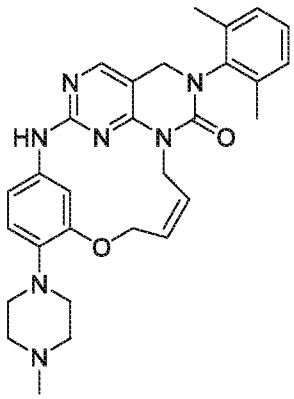

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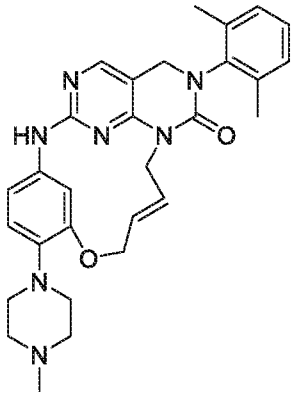

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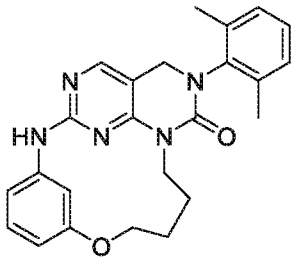
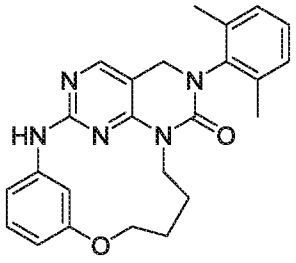


(YKL-05-205),

or a pharmaceutically acceptable salt thereof.

102. The method, pharmaceutical composition, or kit of claim 100, wherein the inhibitor of SIK is of the formula:



(YKL-05-205),

or a pharmaceutically acceptable salt thereof.

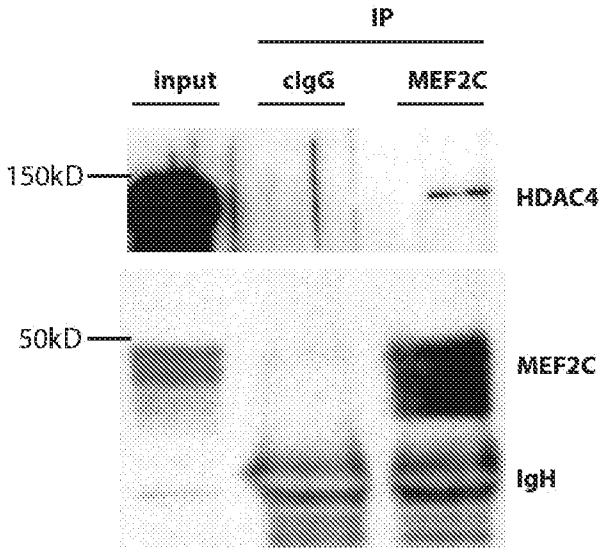


Figure 1A

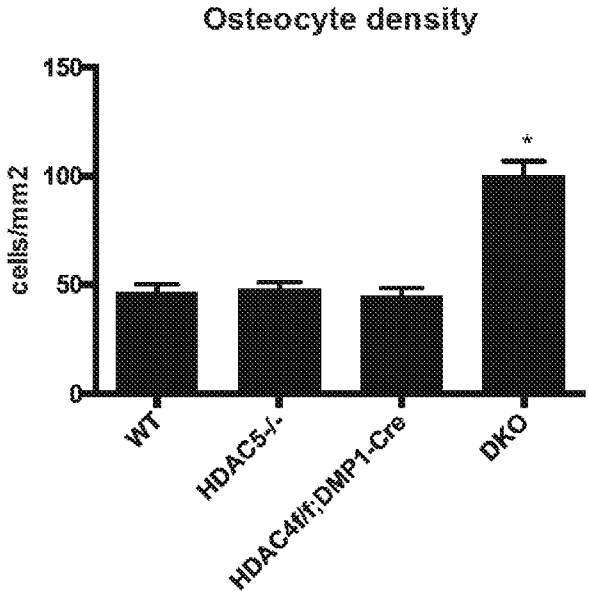


Figure 1B

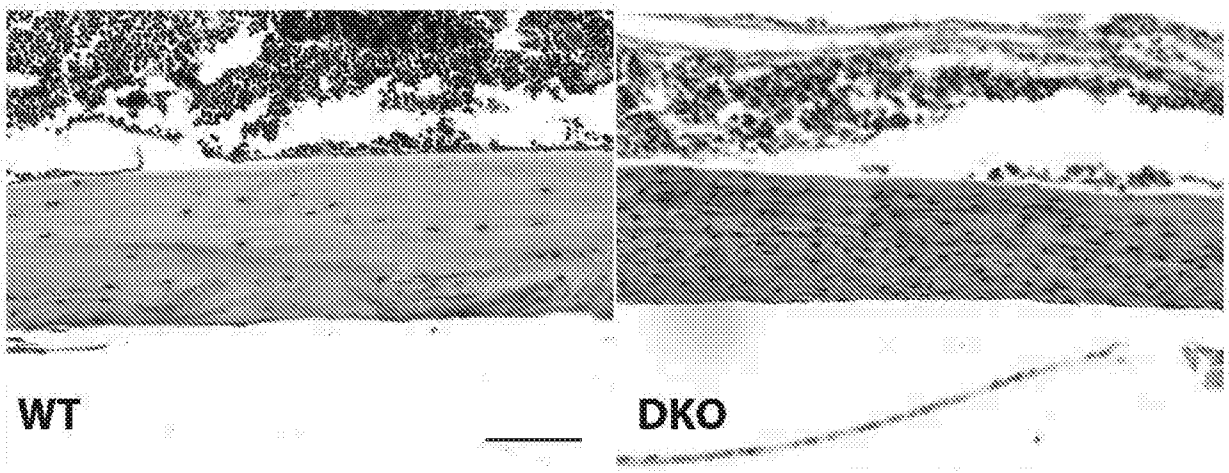


Figure 1C

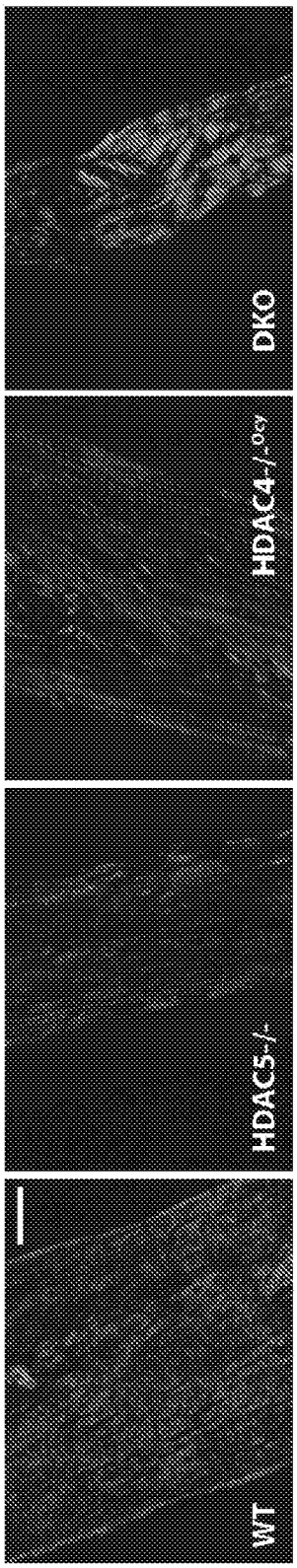


Figure 1D

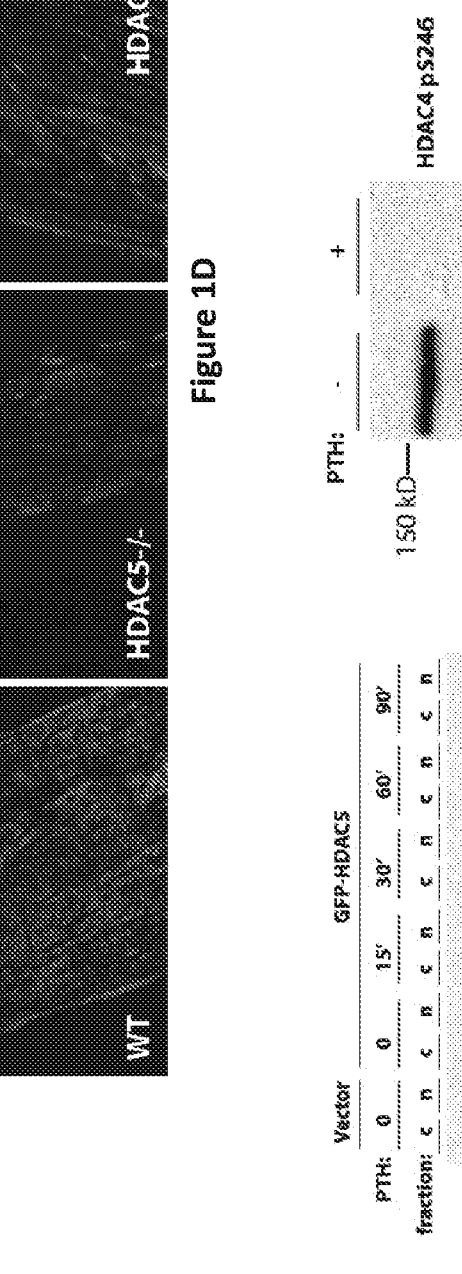


Figure 2A

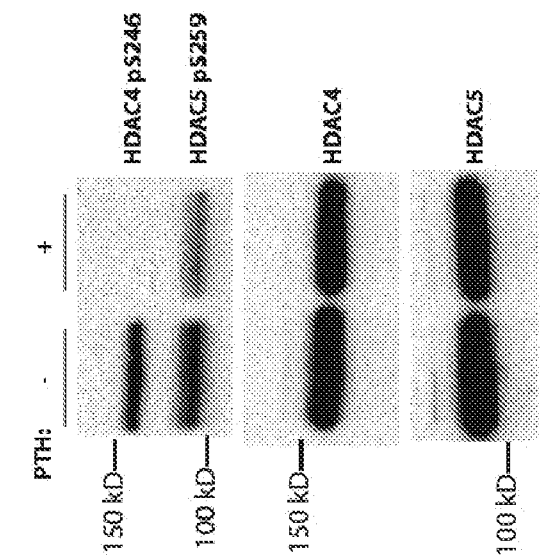
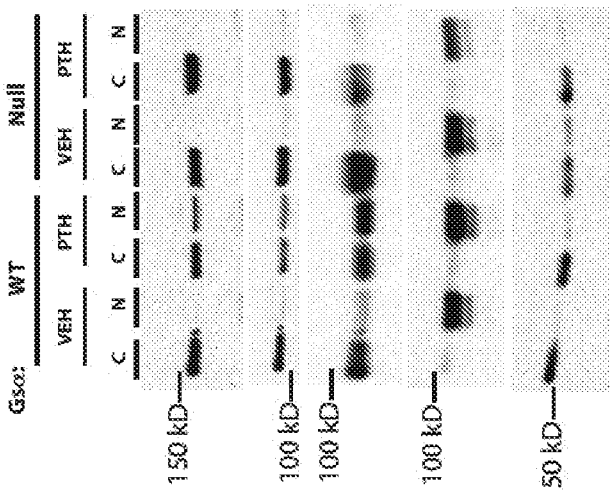


Figure 2B



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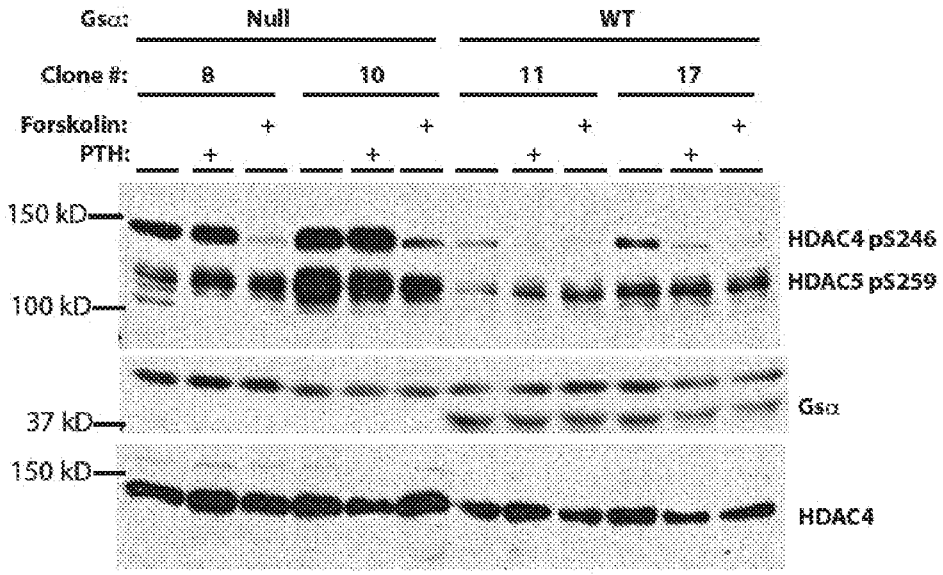

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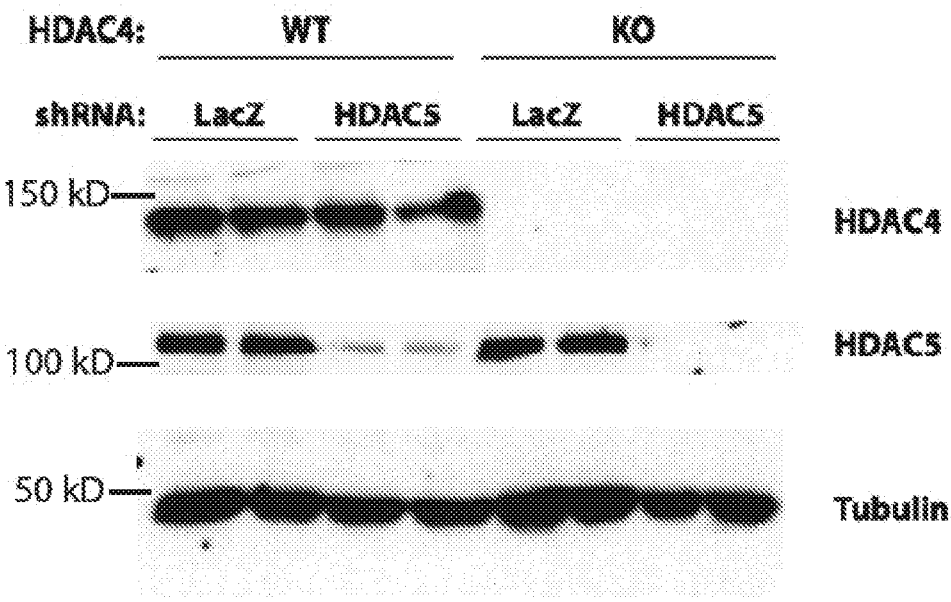

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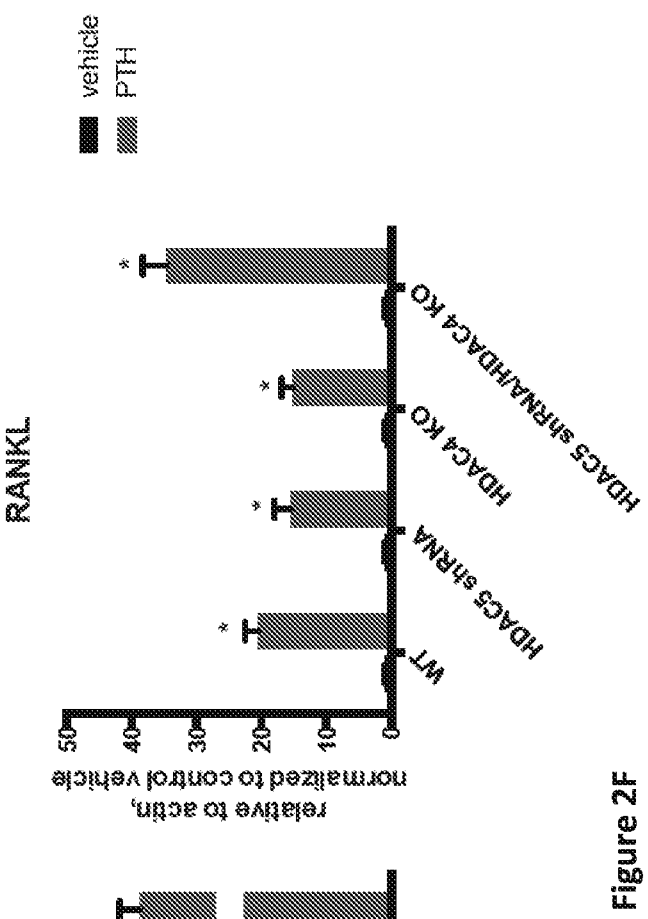

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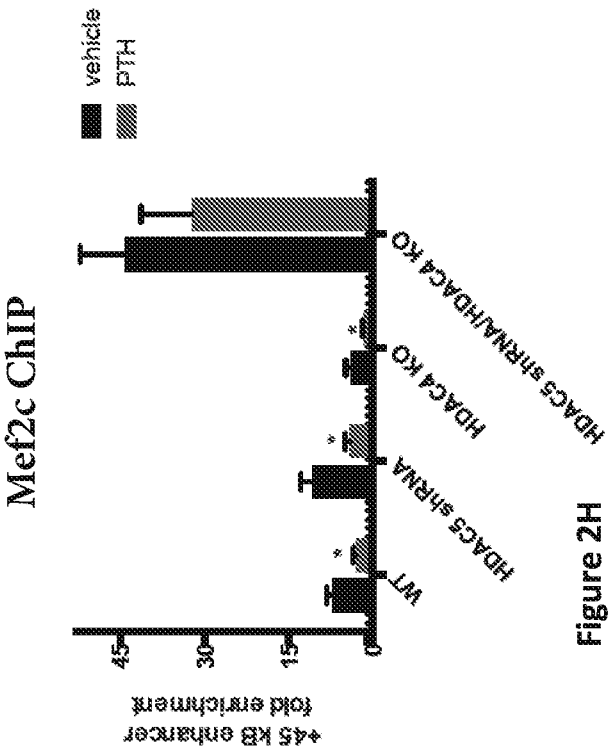


Figure 2H

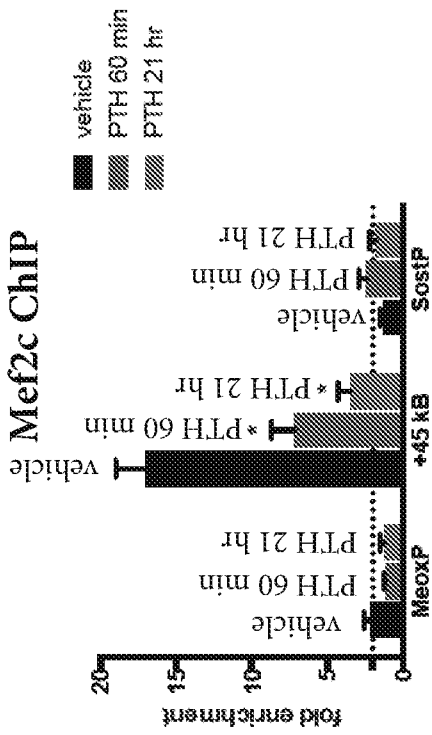


Figure 2G

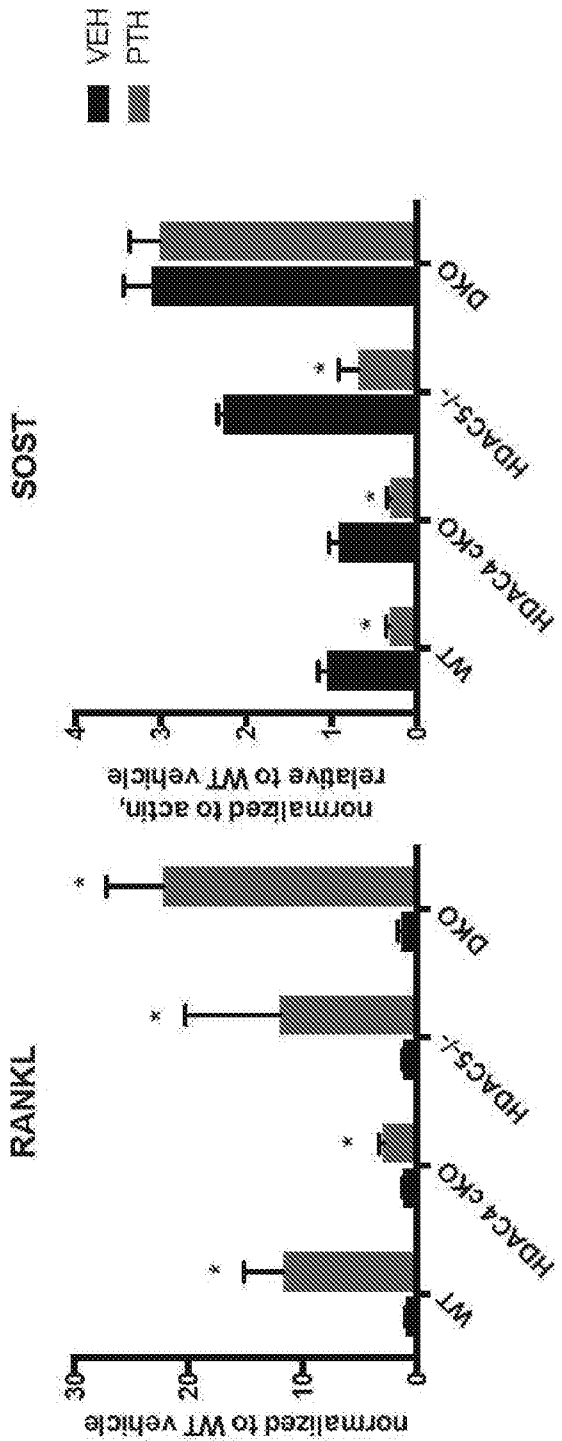


Figure 3A

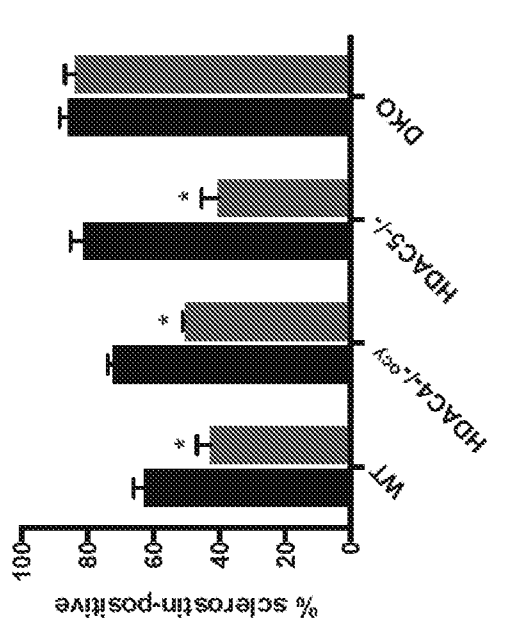
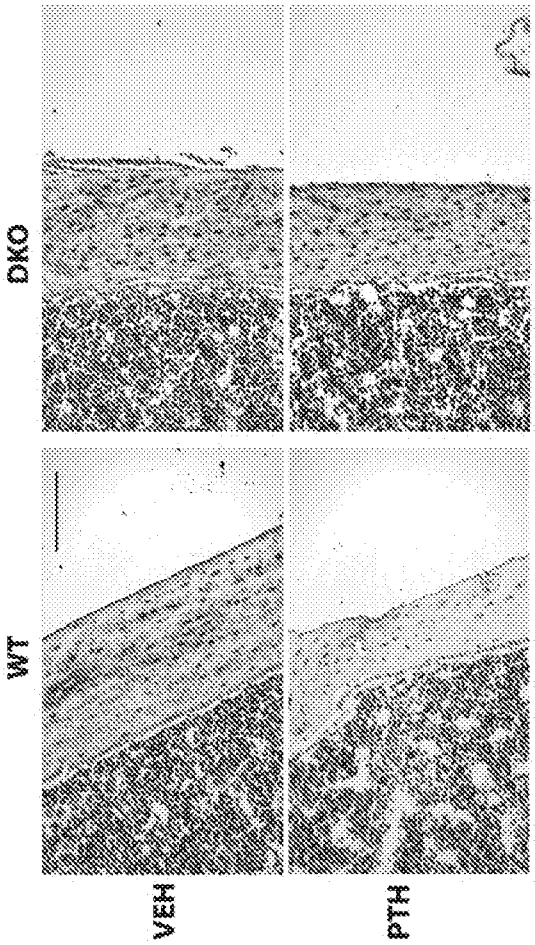


Figure 3B

Figure 3D



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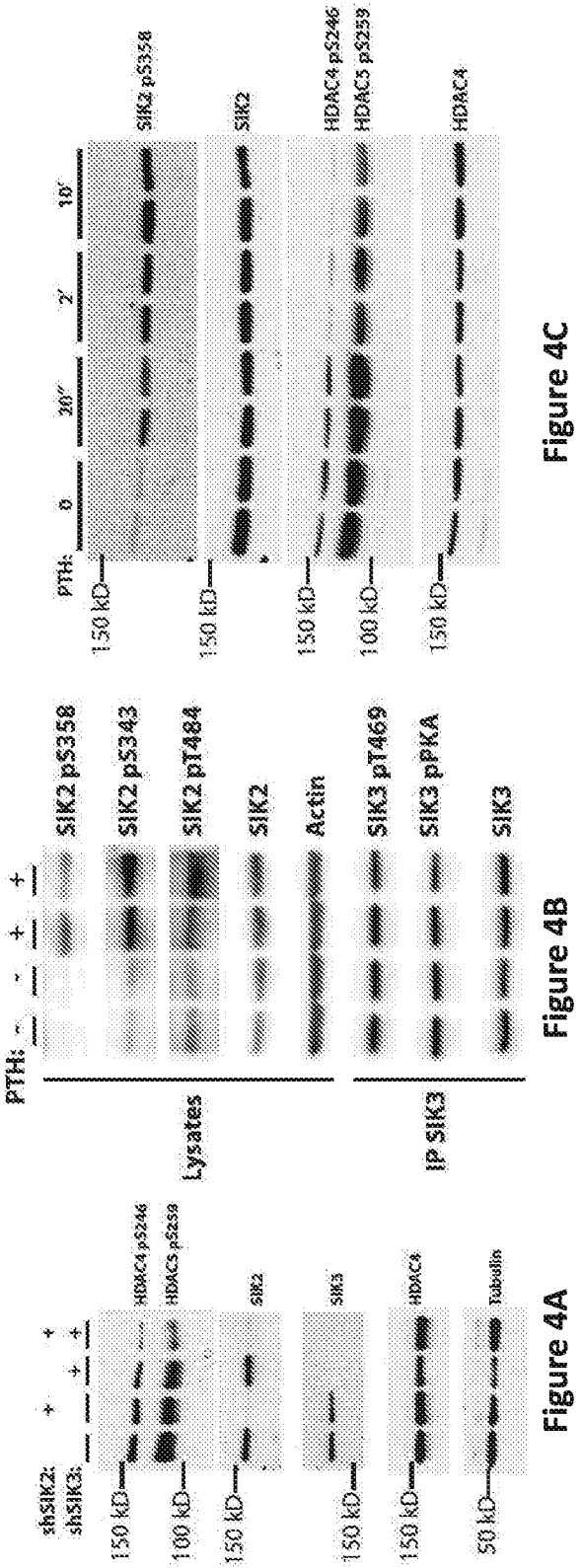


Figure 4A

Figure 4B

Figure 4C

Figure 4E

Figure 4D

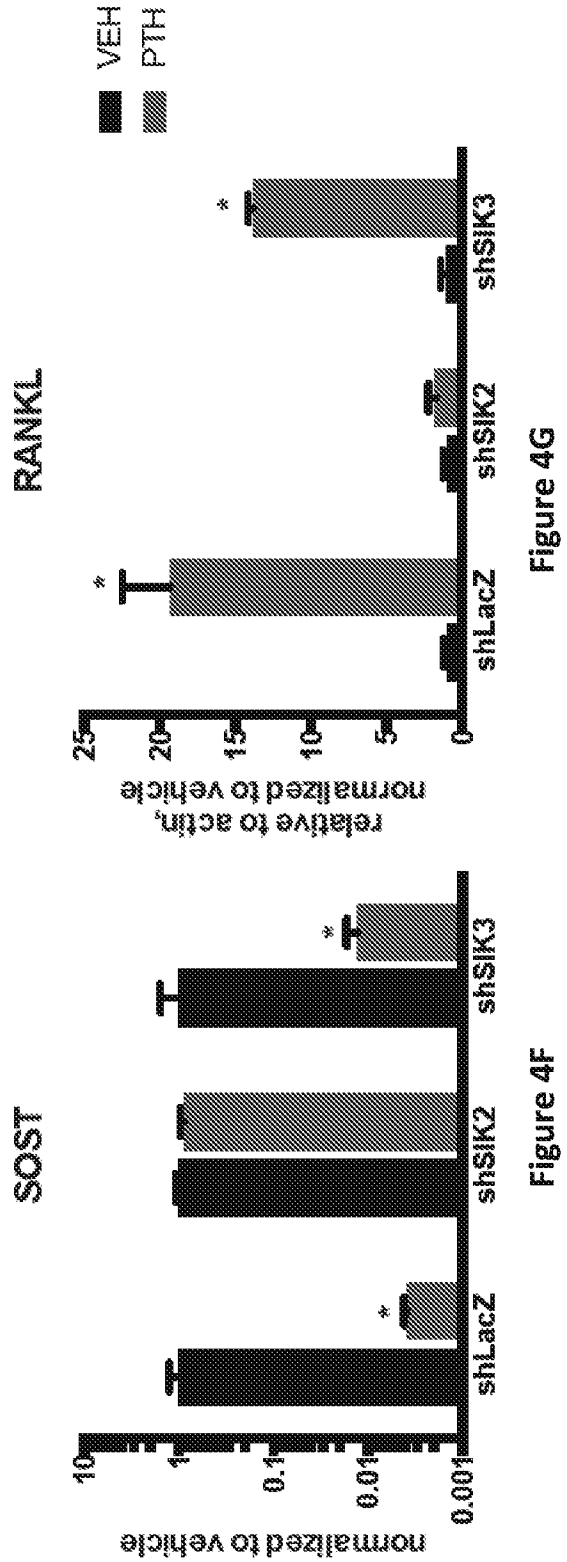


Figure 4F

Figure 4G

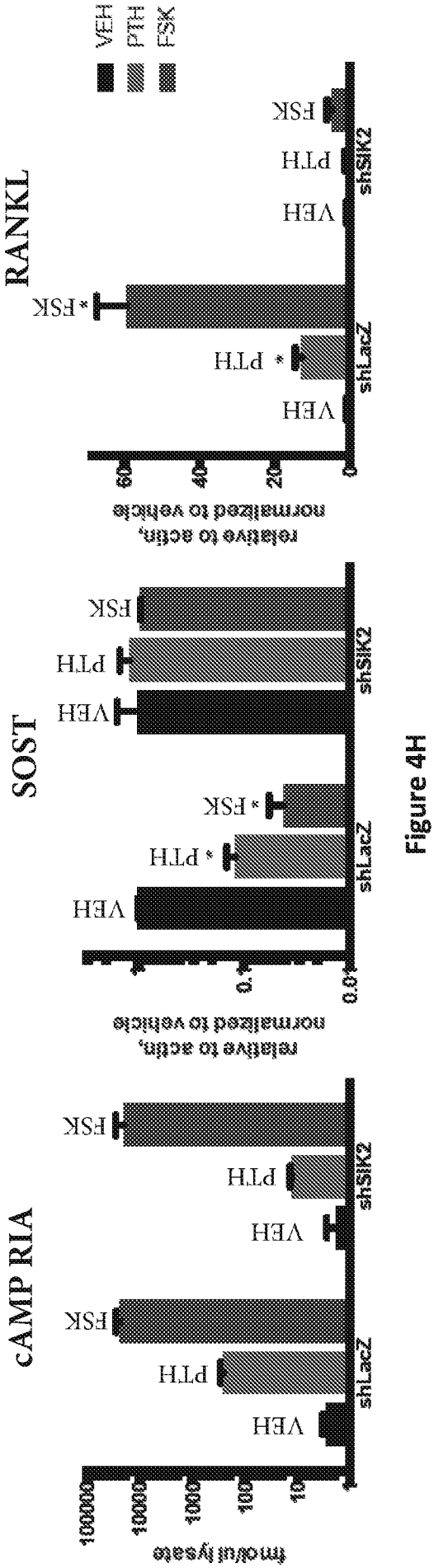


Figure 4H

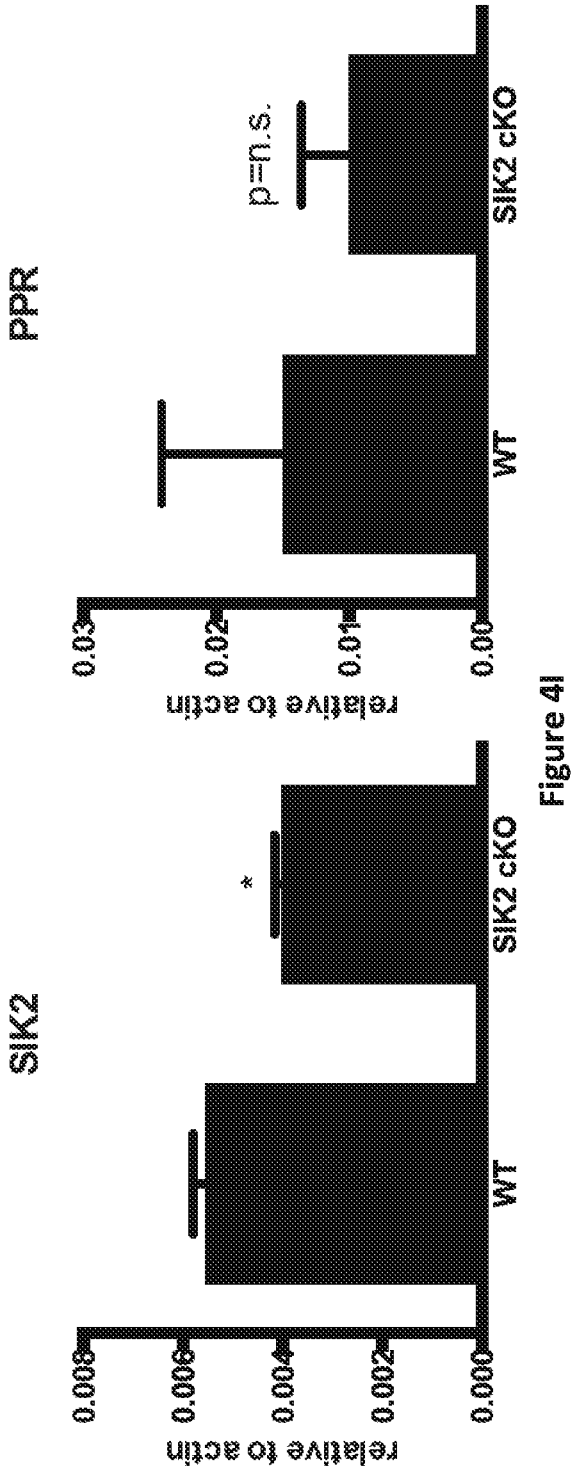


Figure 4I

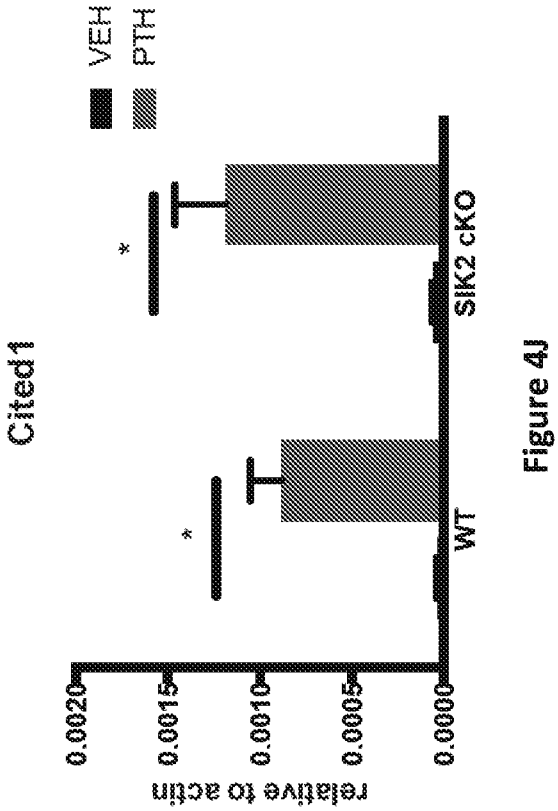


Figure 4J

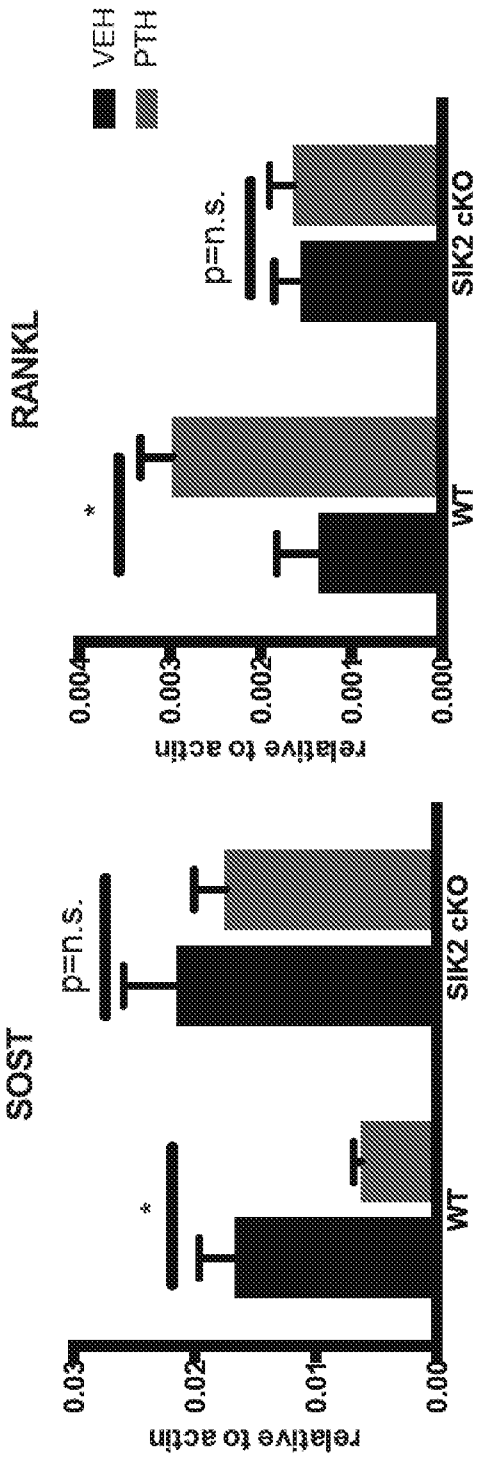
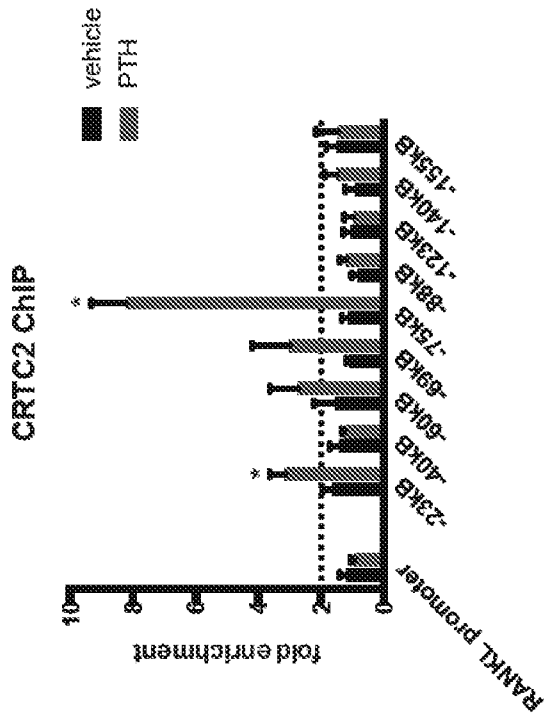


Figure 4K



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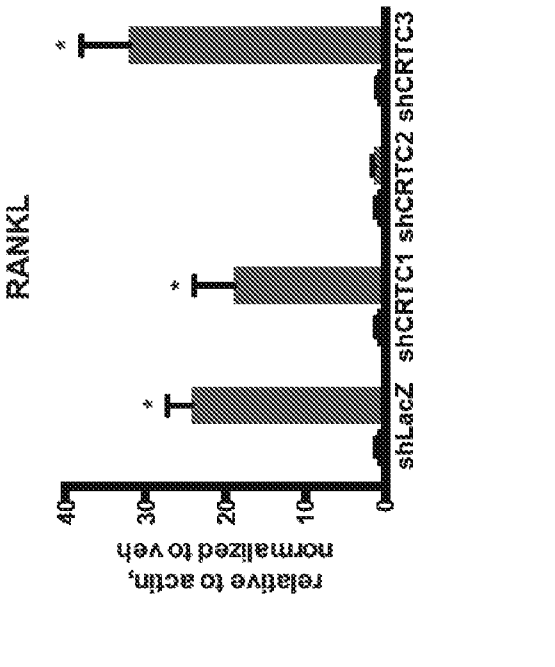
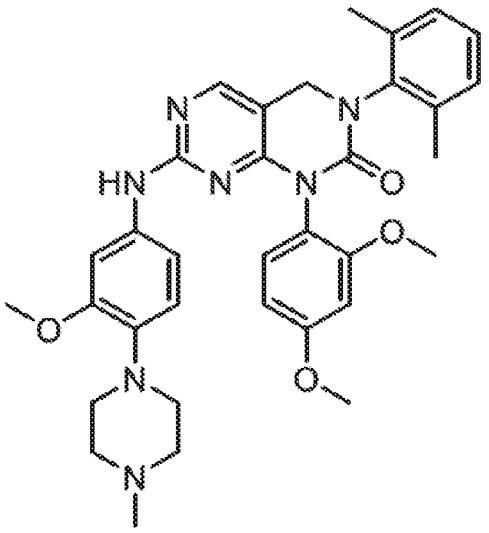
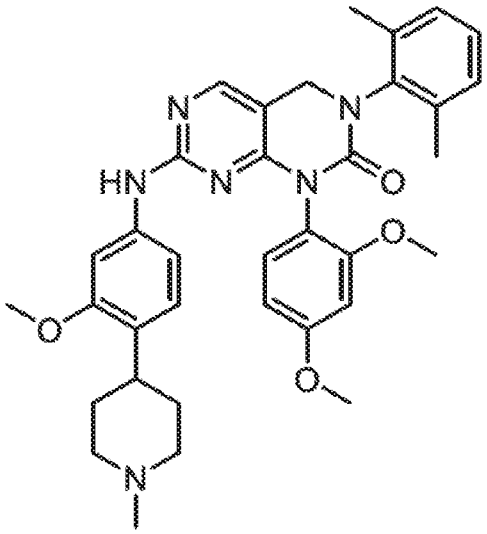


Figure 4L



YKL-04-114



YKL-05-093

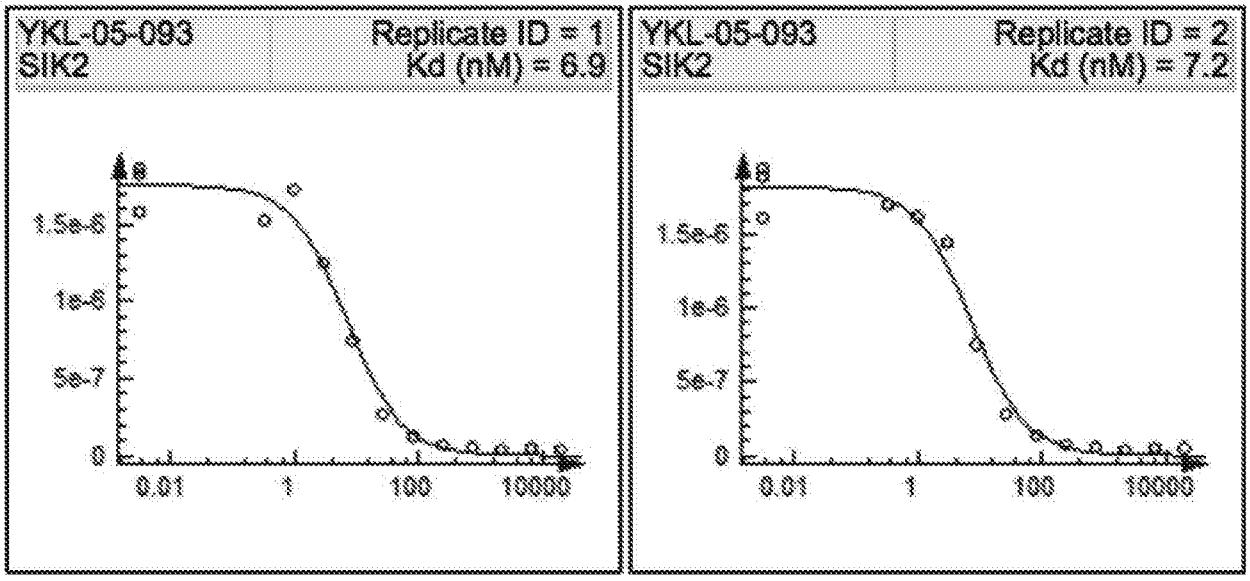


Figure 5A

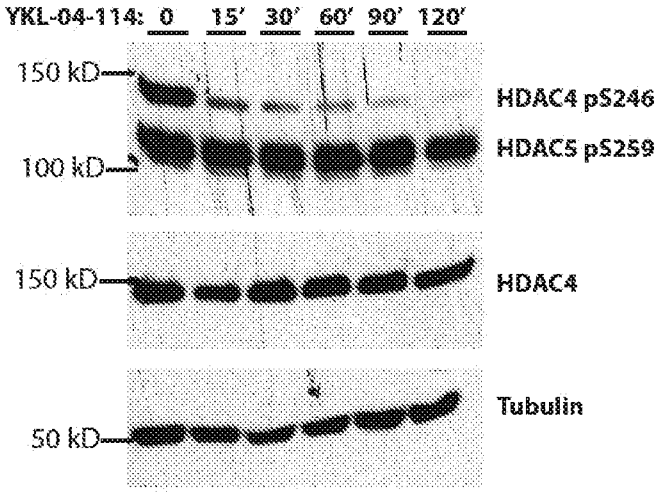


Figure 5B

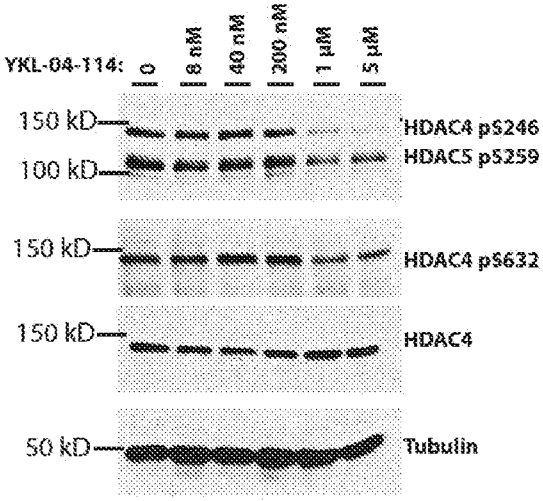


Figure 5C

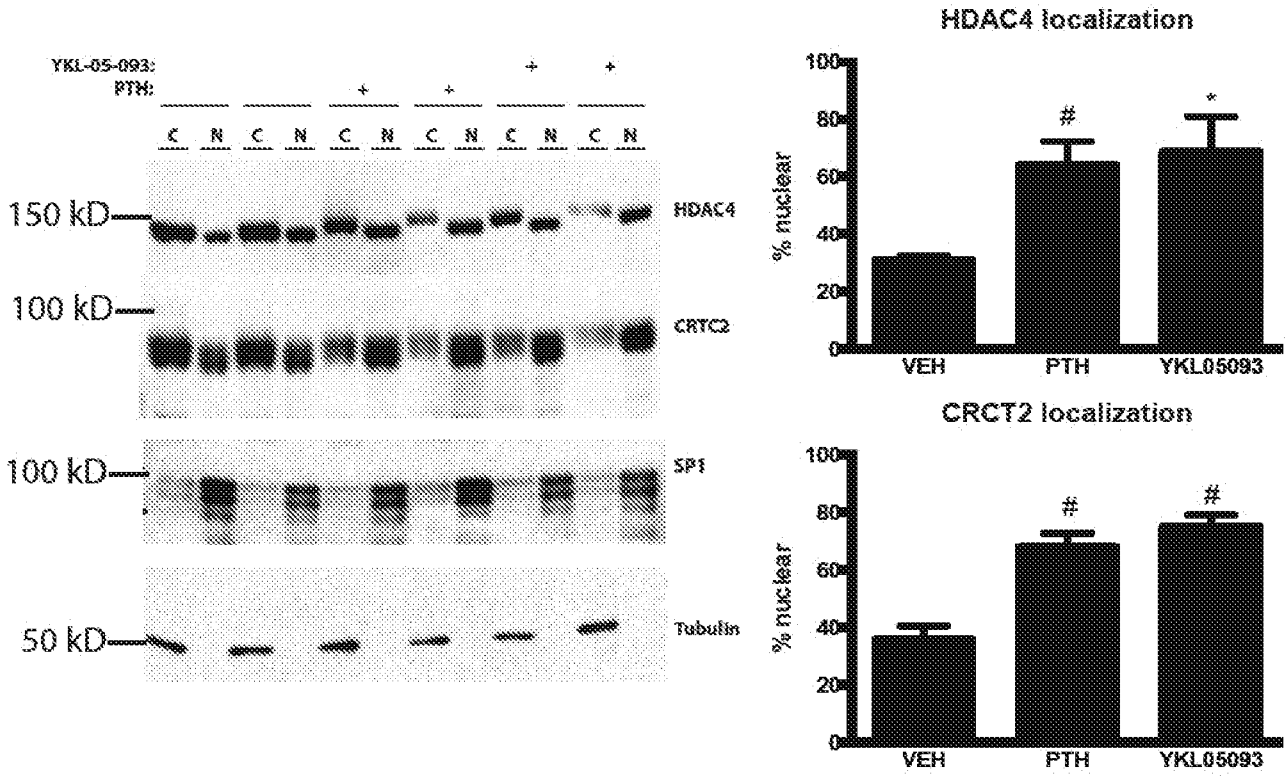


Figure 5D

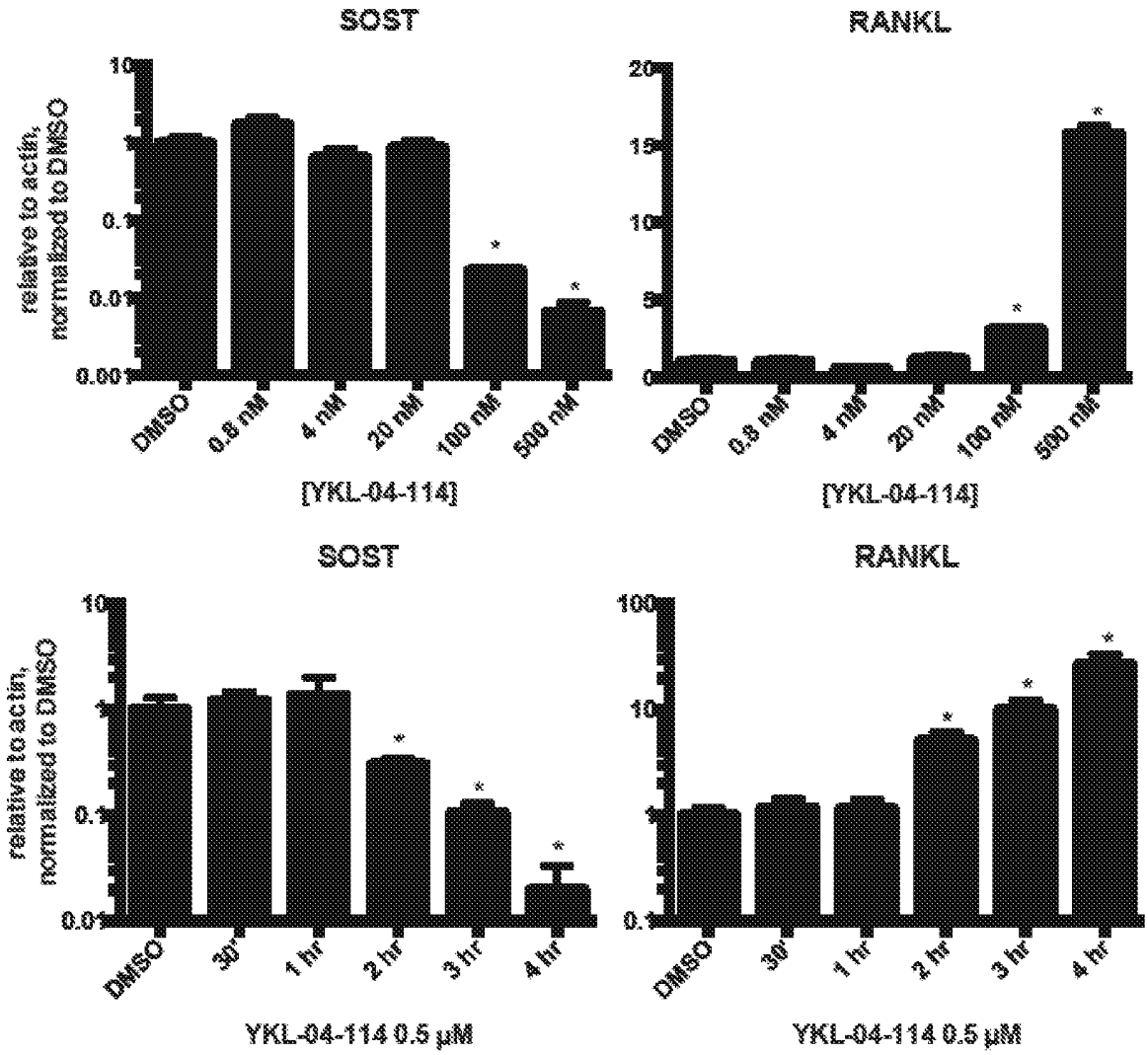


Figure 5E

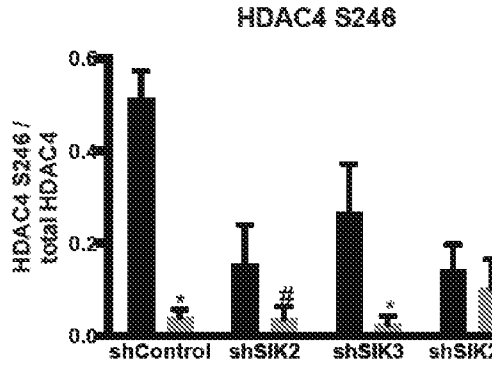


Figure 5F

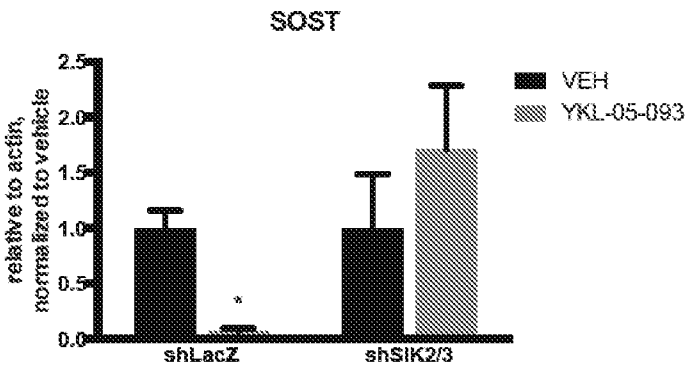


Figure 5G

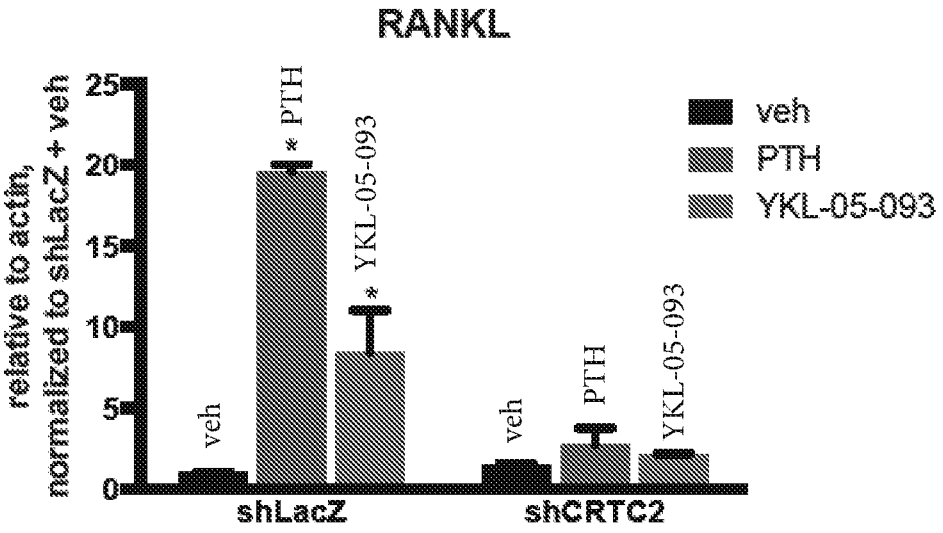


Figure 5H

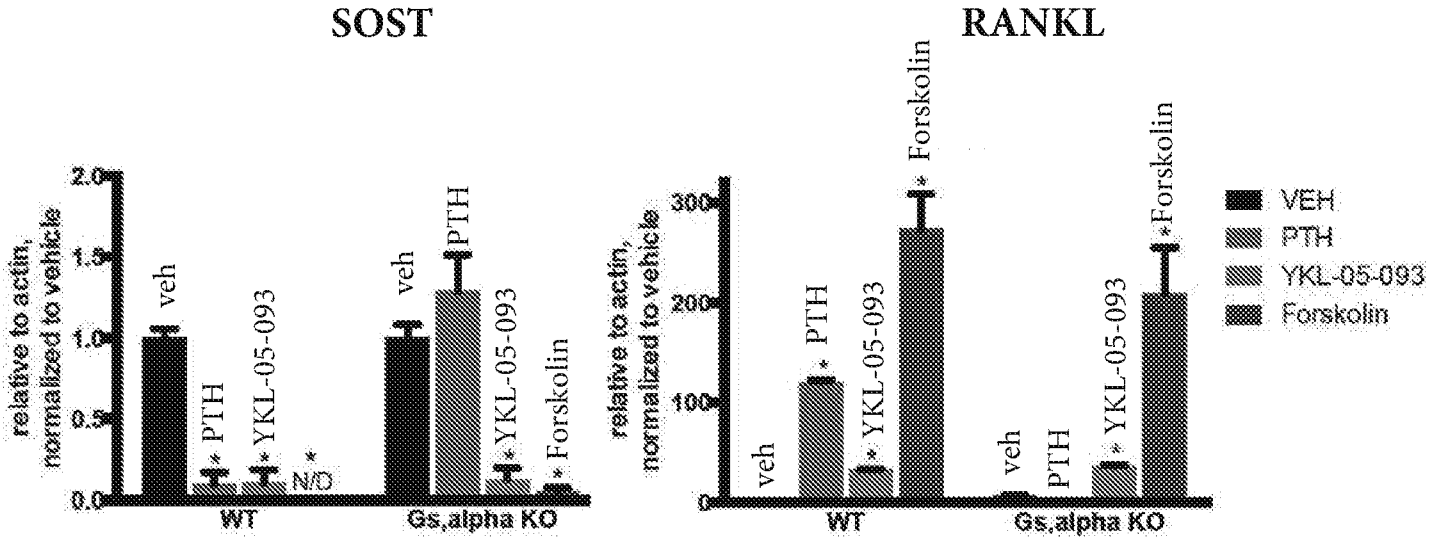
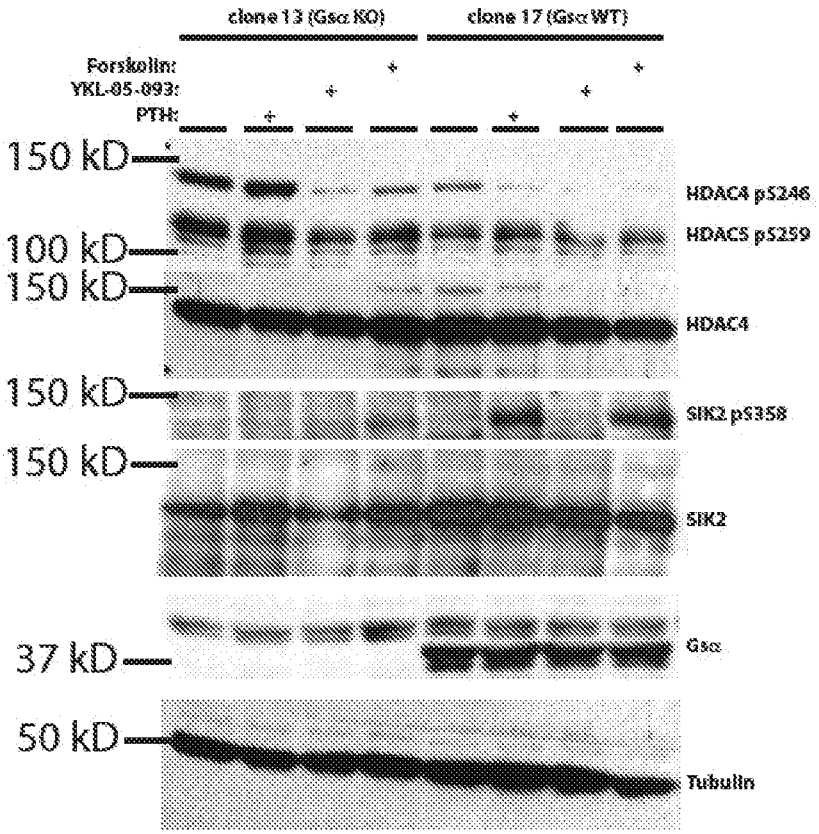


Figure 5I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clone 17 (Gsα WT)
Forskolin:
YKL-05-093:
PTH:
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HDAC4 pS246
100 kD
HDAC5 pS259
150 kD
HDAC4
150 kD
SIK2 pS358
150 kD
SIK2
37 kD
Gsα
50 kD
Tubulin

Figure 5J

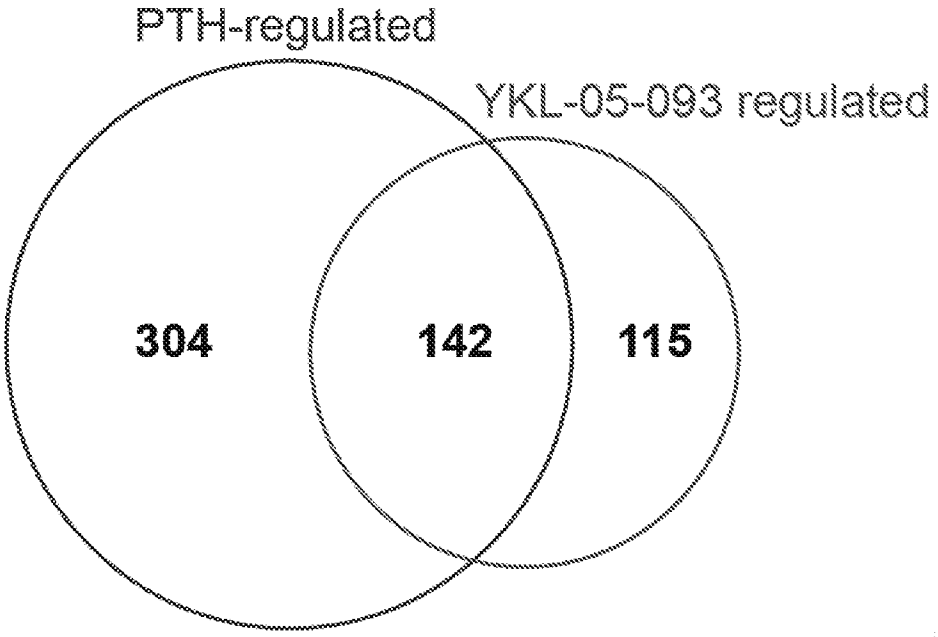


Figure 6A

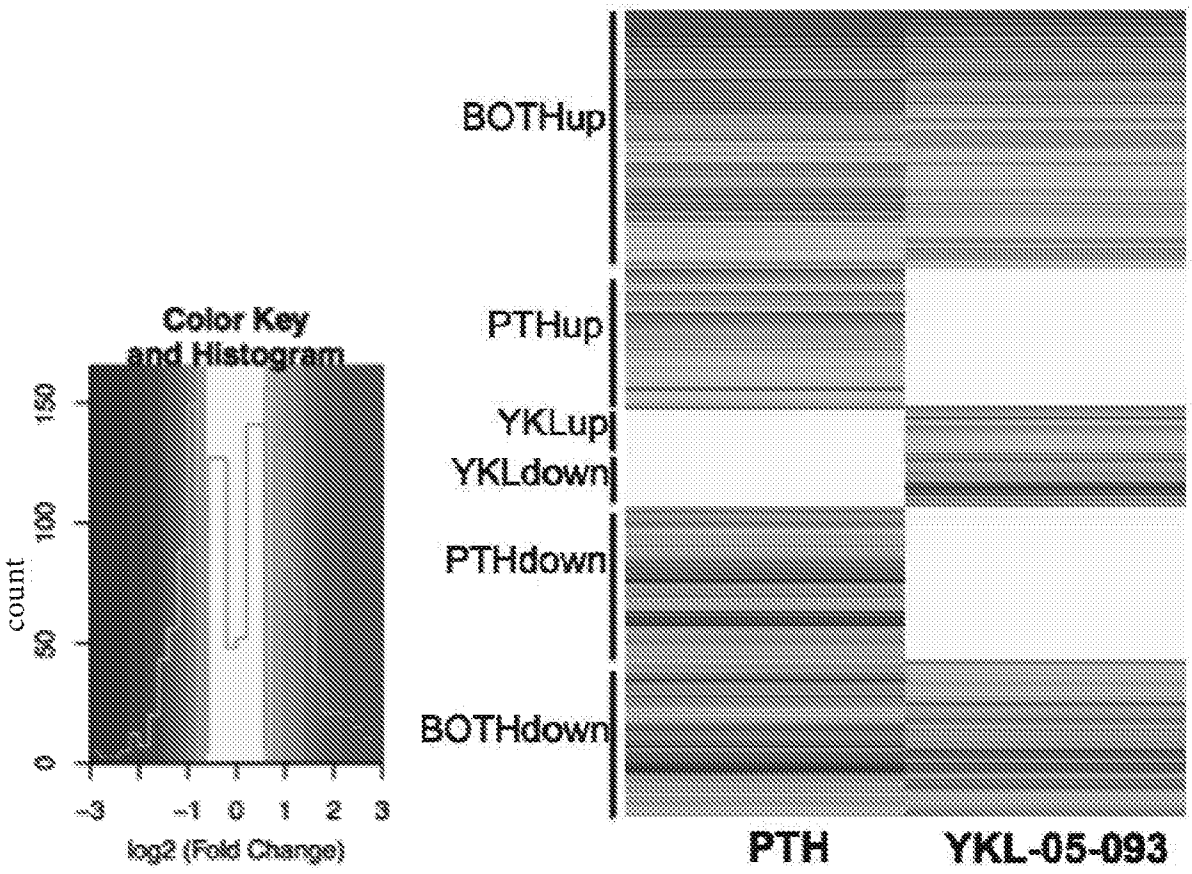


Figure 6B

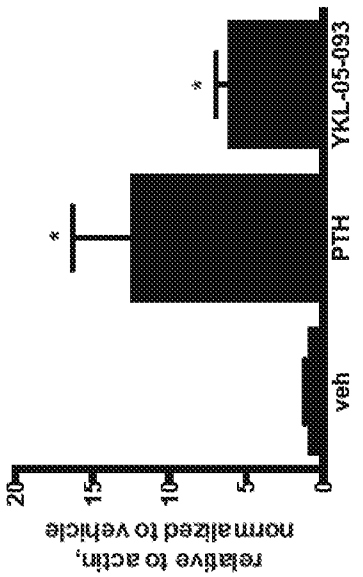


Figure 6E

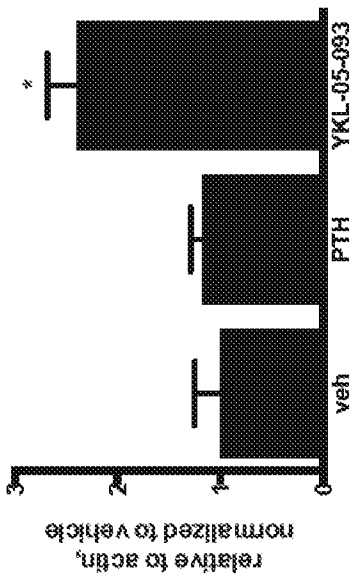


Figure 6D

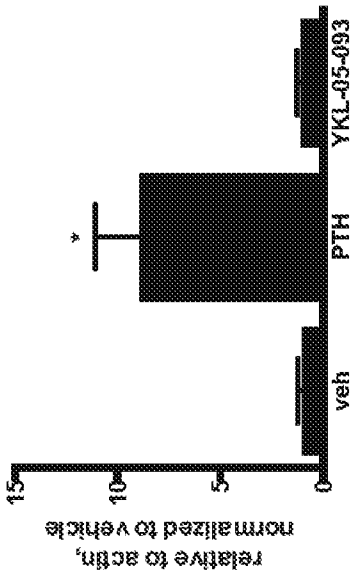


Figure 6C

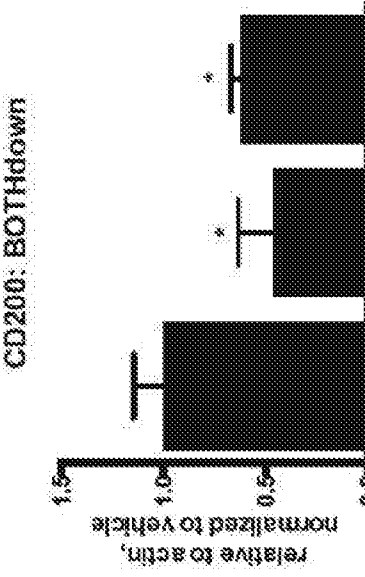


Figure 6H

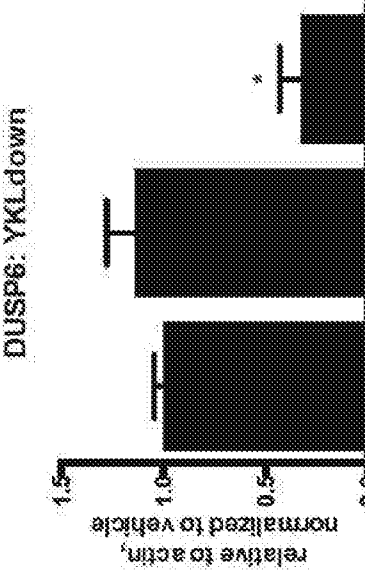


Figure 6G

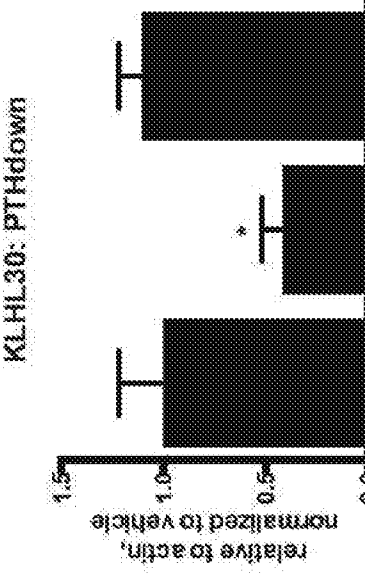


Figure 6F

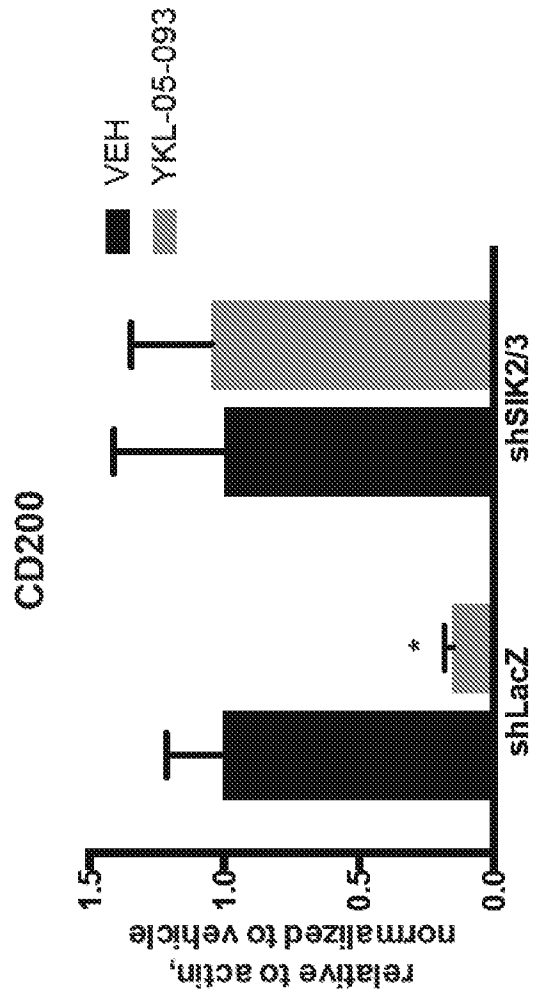


Figure 6J

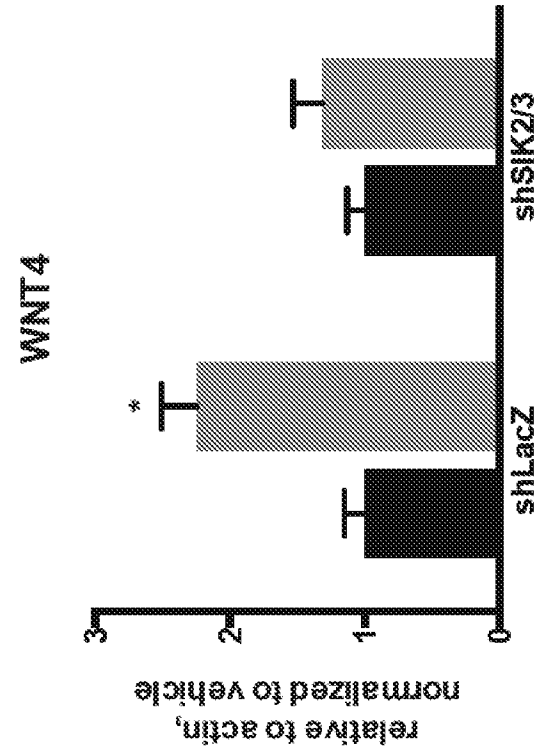


Figure 6I

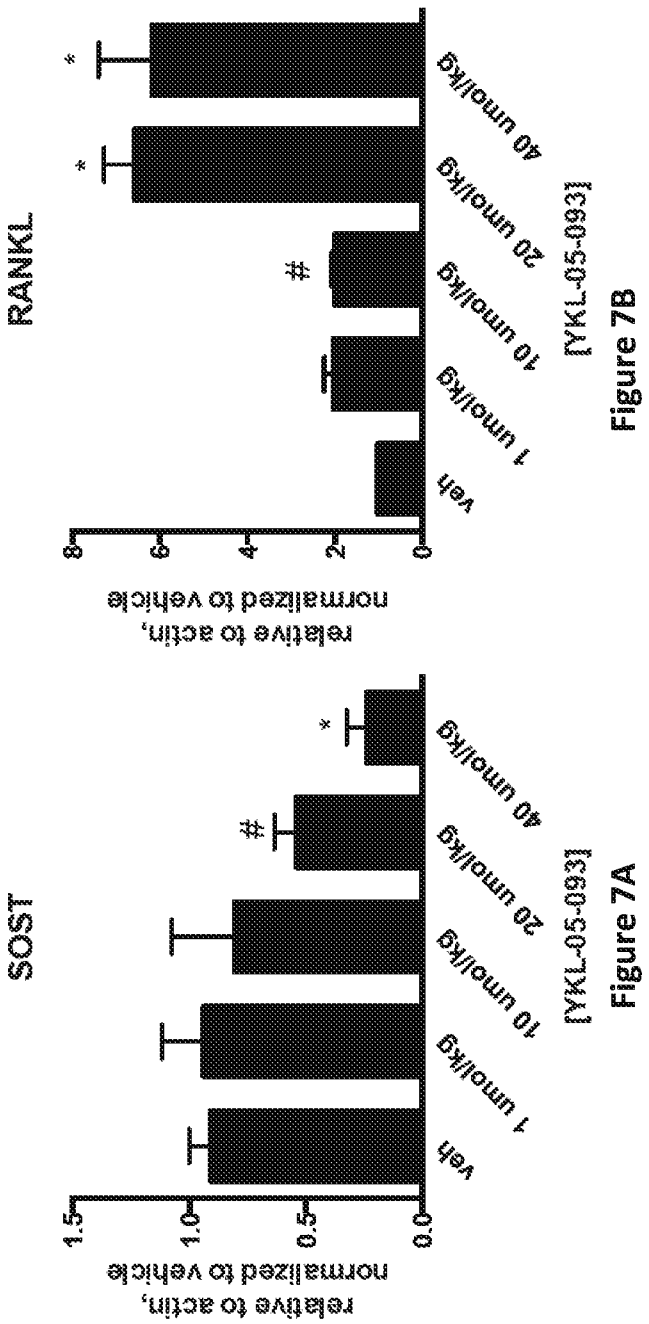
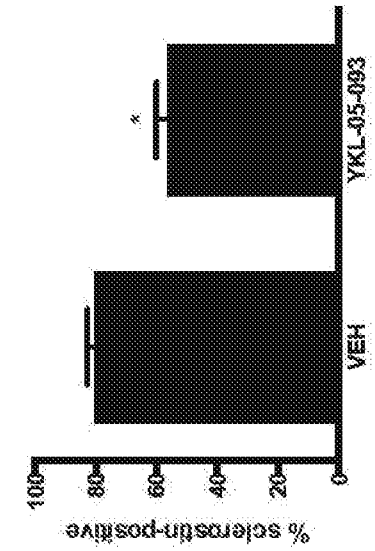


Figure 7A [YKL-05-093]

Figure 7B [YKL-05-093]



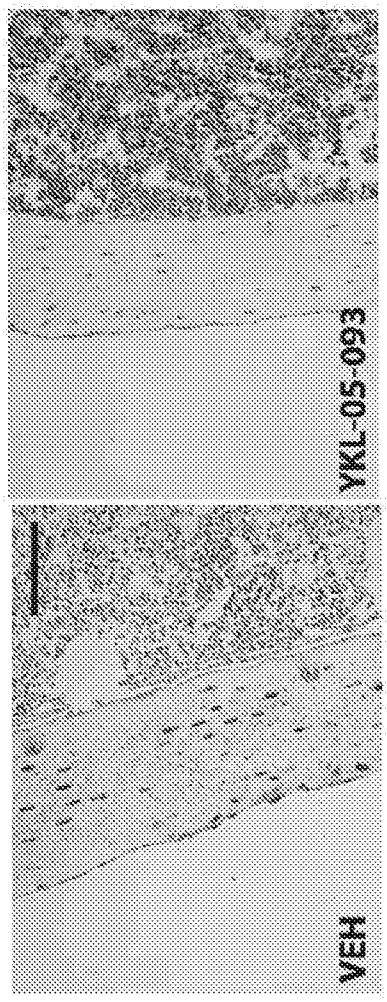


Figure 7C

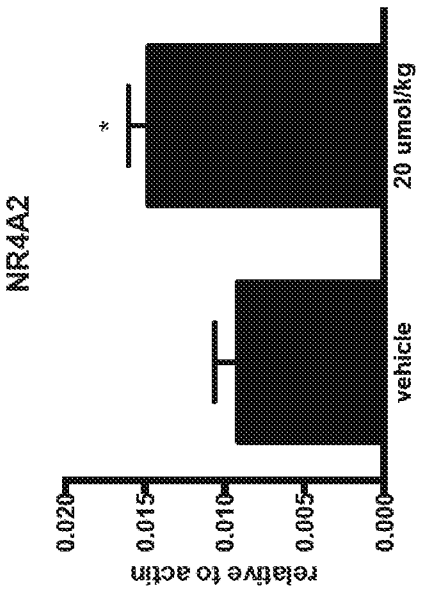


Figure 7D

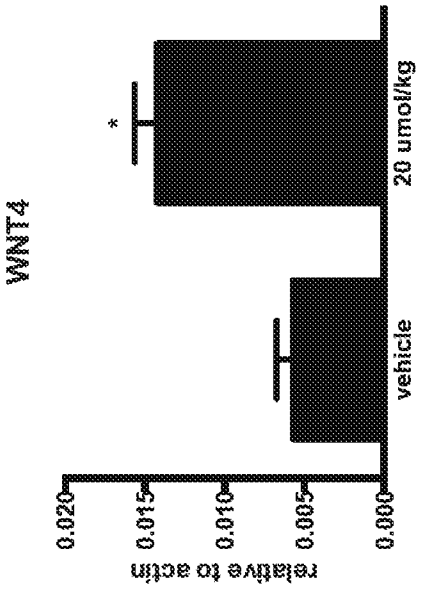


Figure 7E

Figure 7F

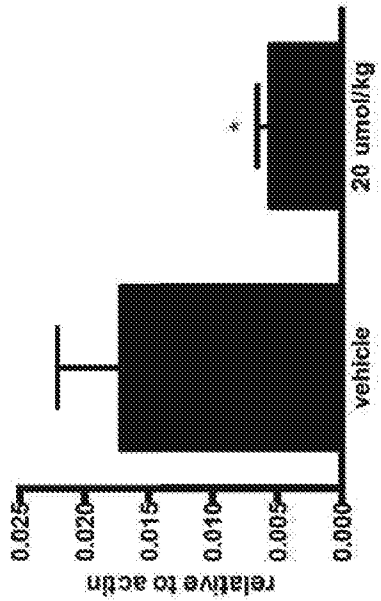


Figure 7G

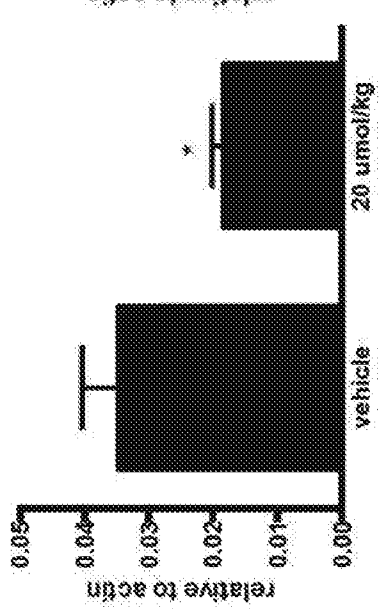


Figure 7H

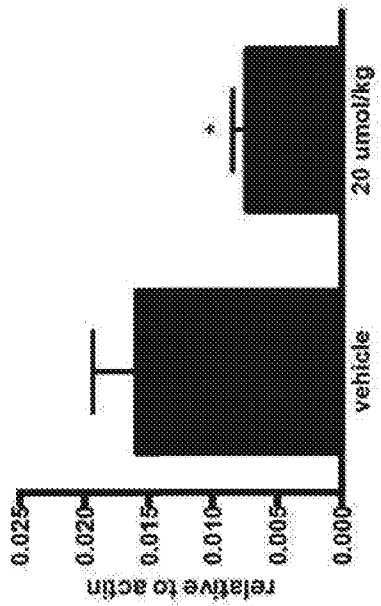


Figure 7I

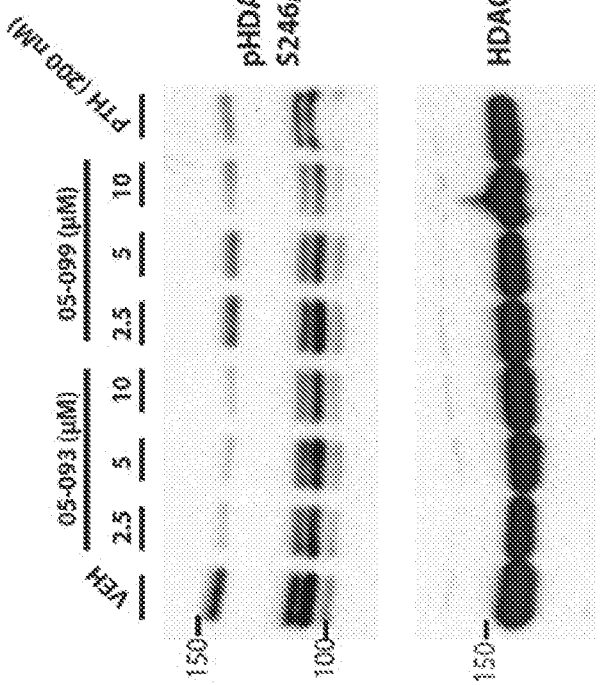


Figure 8A

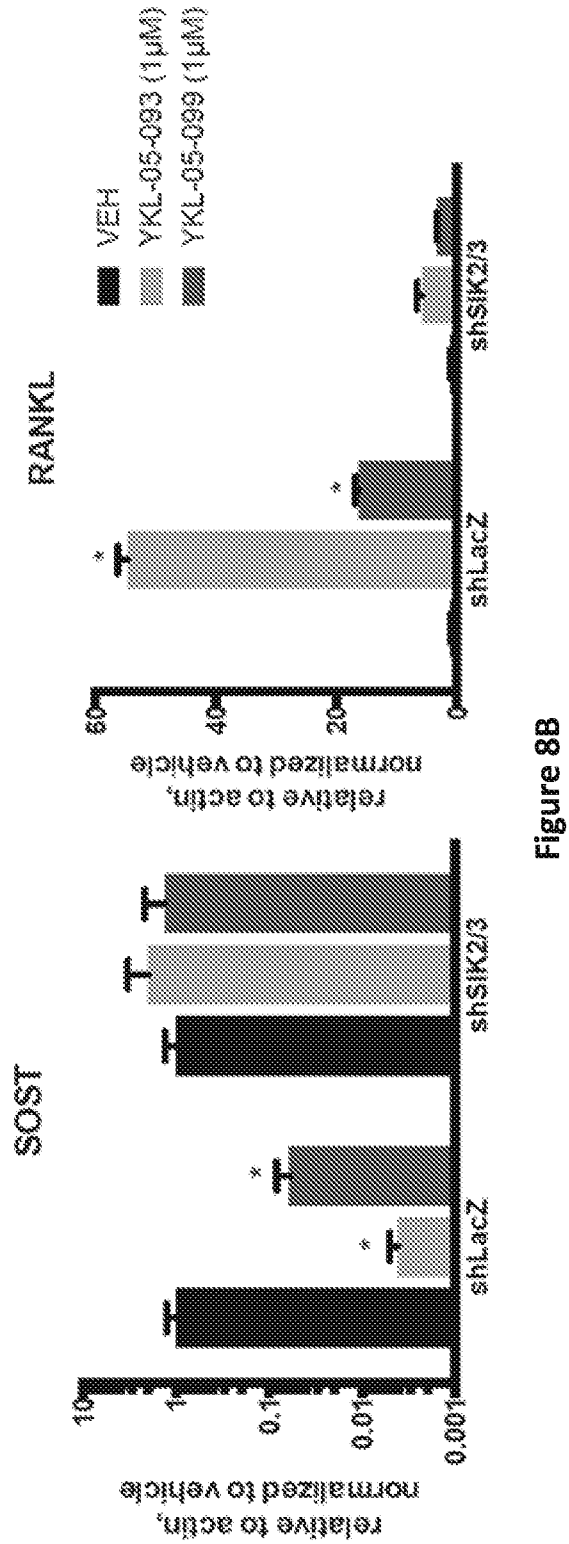


Figure 8B

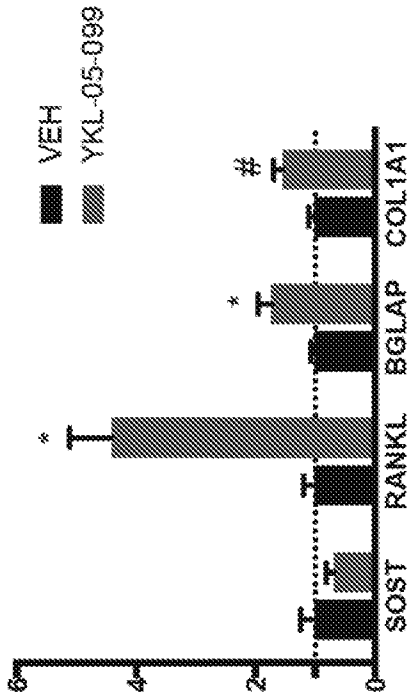


Figure 8D

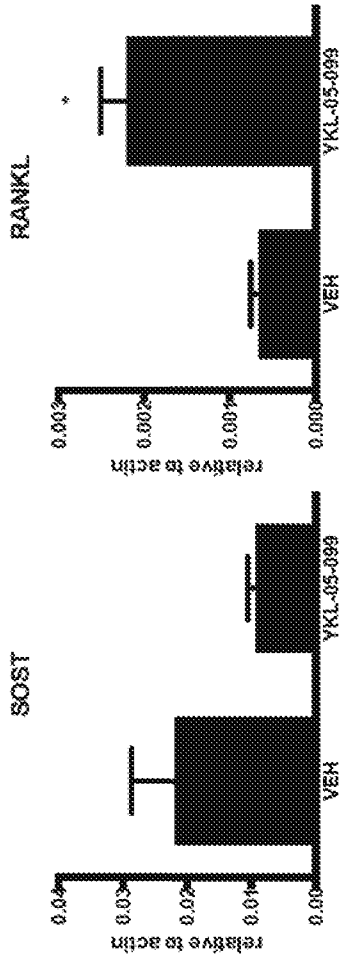


Figure 8C

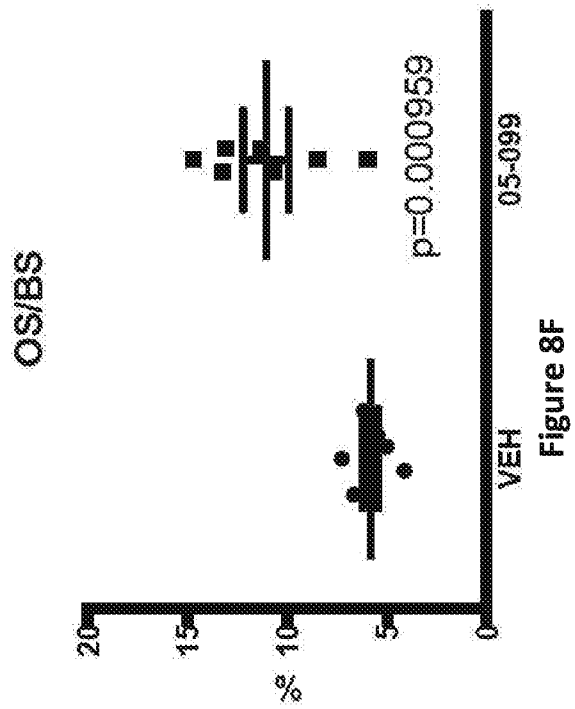


Figure 8F

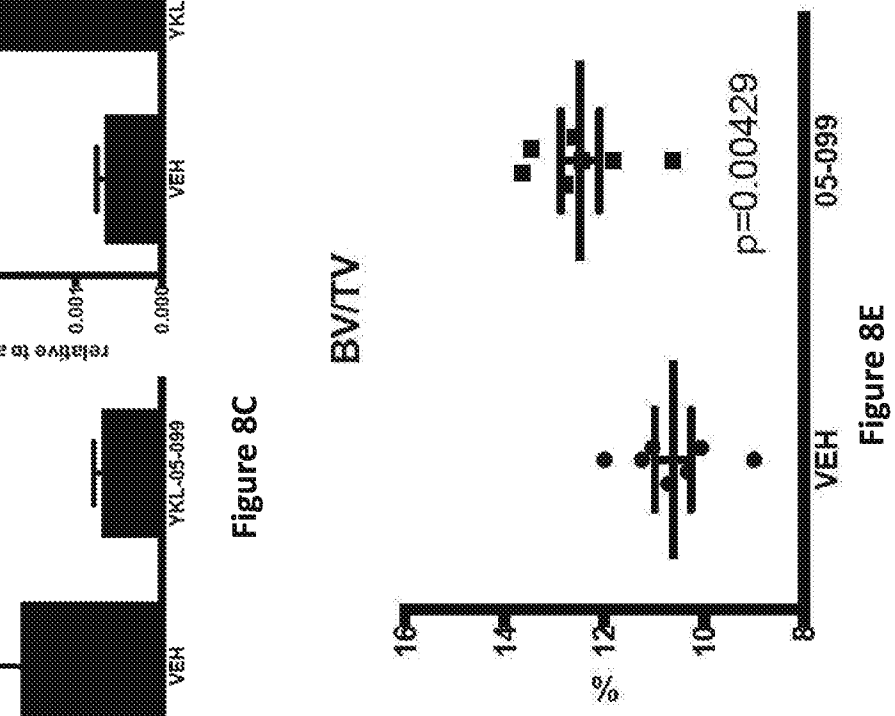


Figure 8E

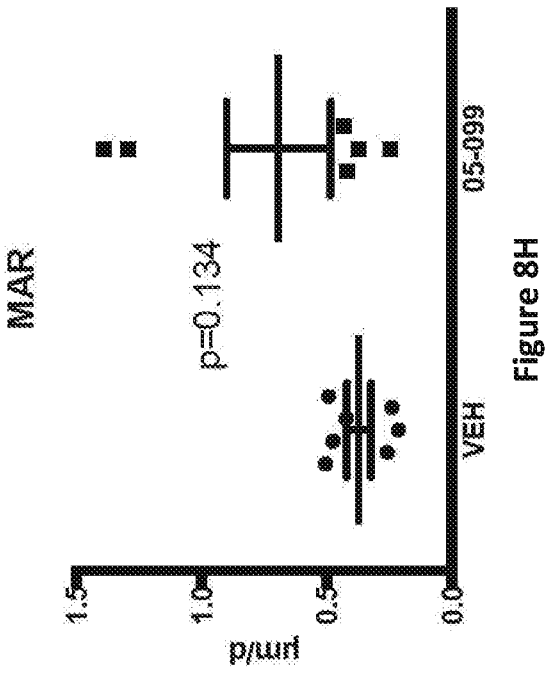


Figure 8H

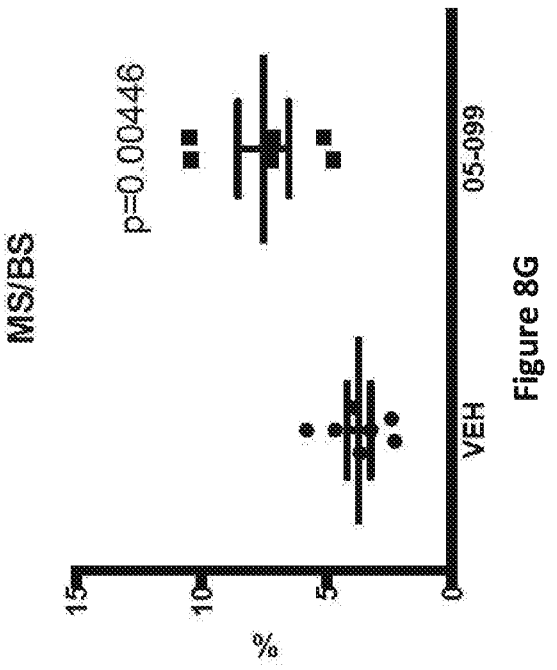


Figure 8G

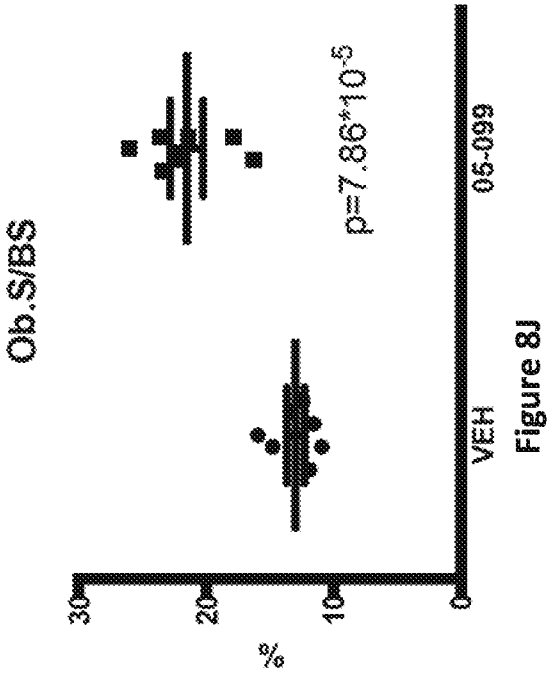


Figure 8J

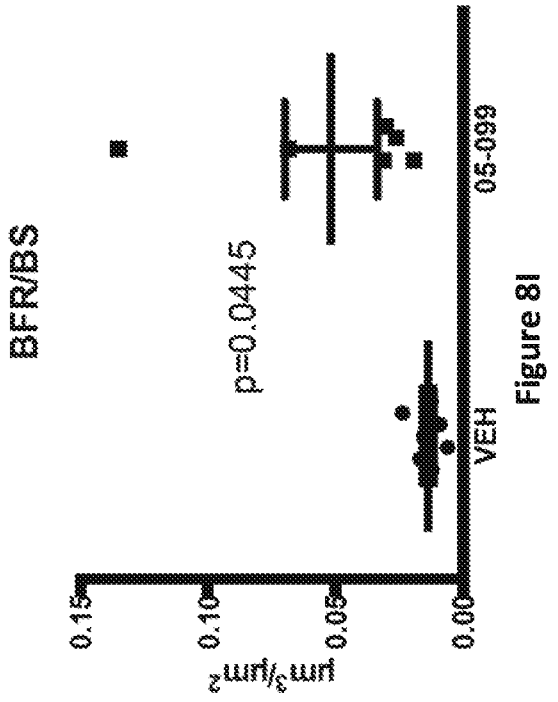


Figure 8I

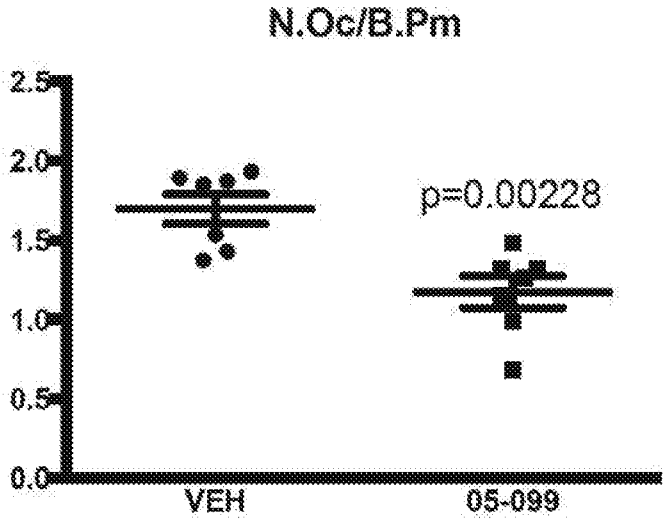


Figure 8K

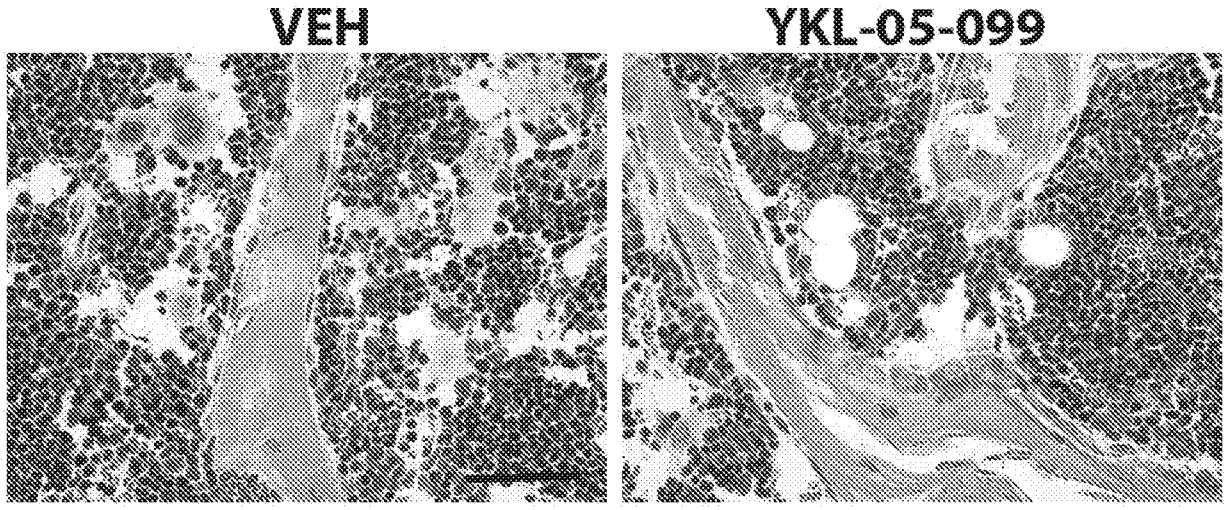


Figure 8L

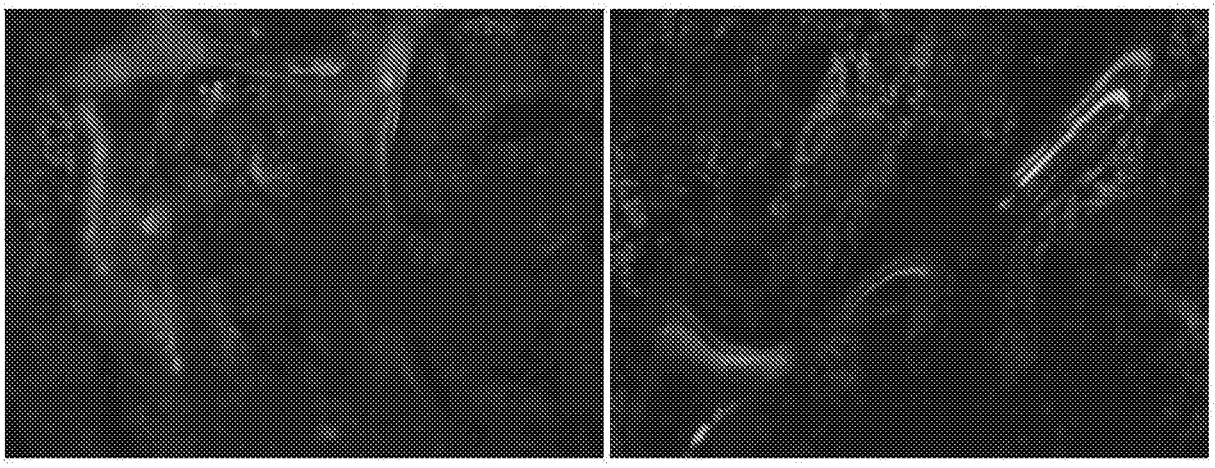


Figure 8M

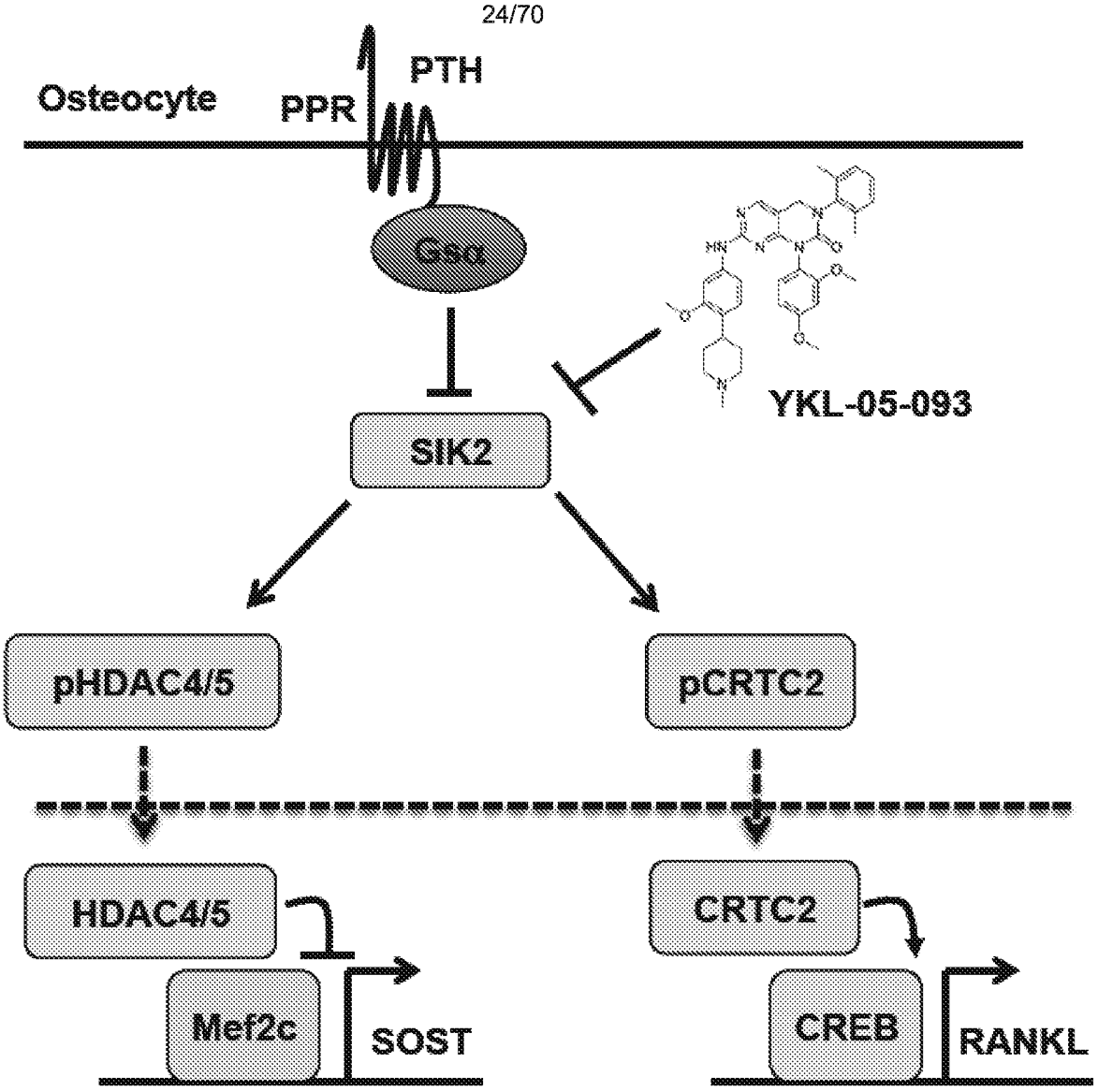

Osteocyte
PPR
PTH
Gsα
YKL-05-093
SIK2
pHDAC4/5
pCRTC2
HDAC4/5
Mef2c
SOST
CRTC2
CREB
RANKL

Figure 9

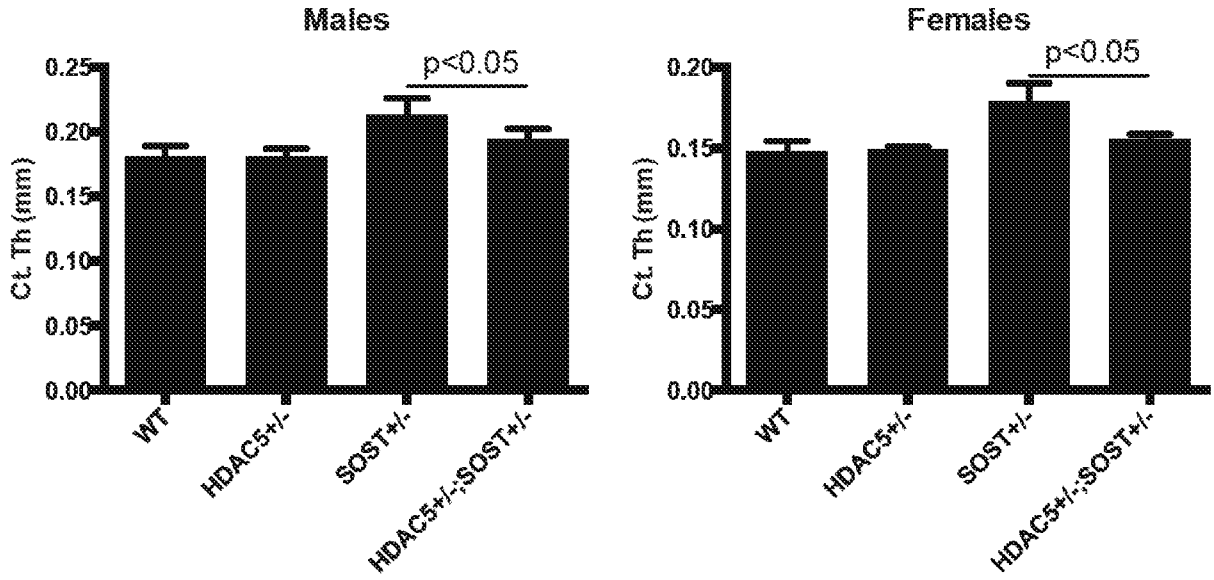


Figure 10A

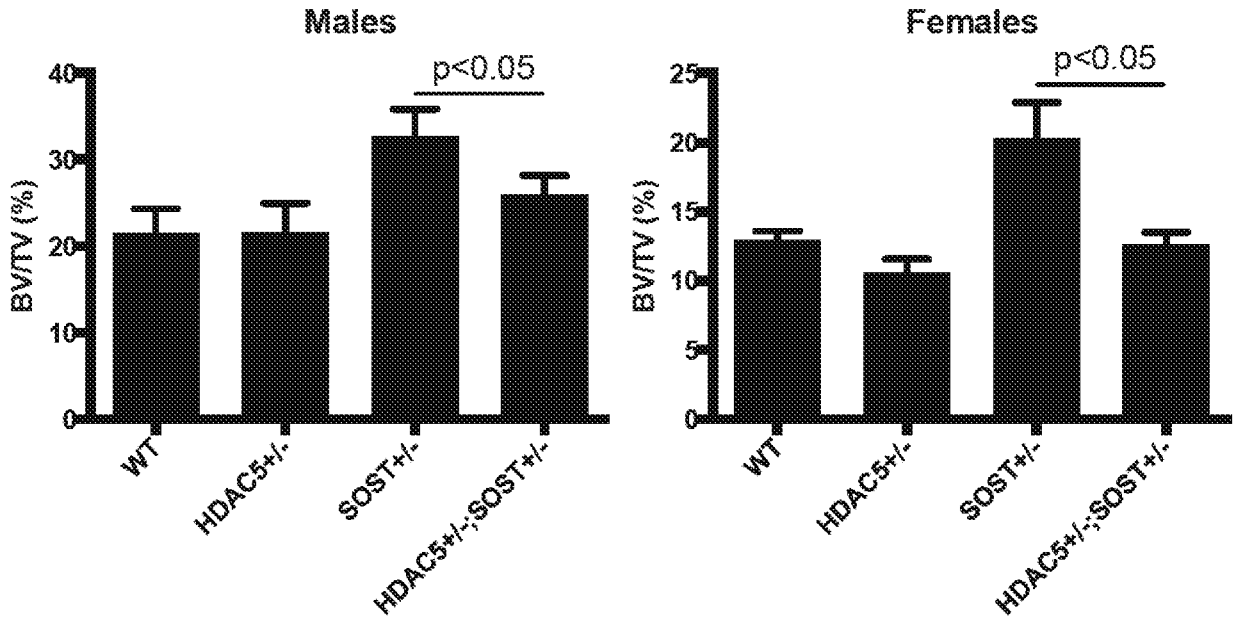


Figure 10B

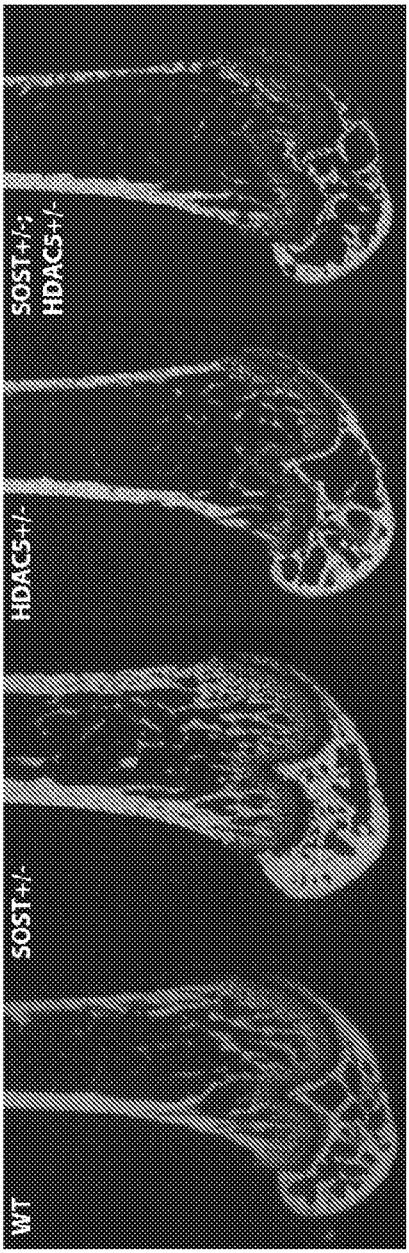


Figure 10C

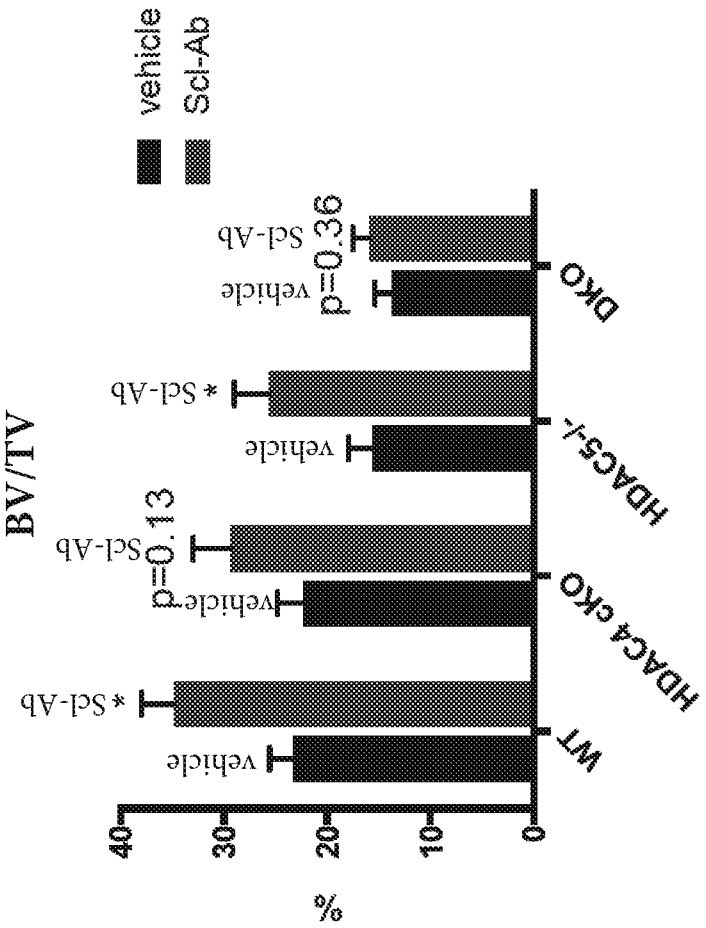


Figure 10D

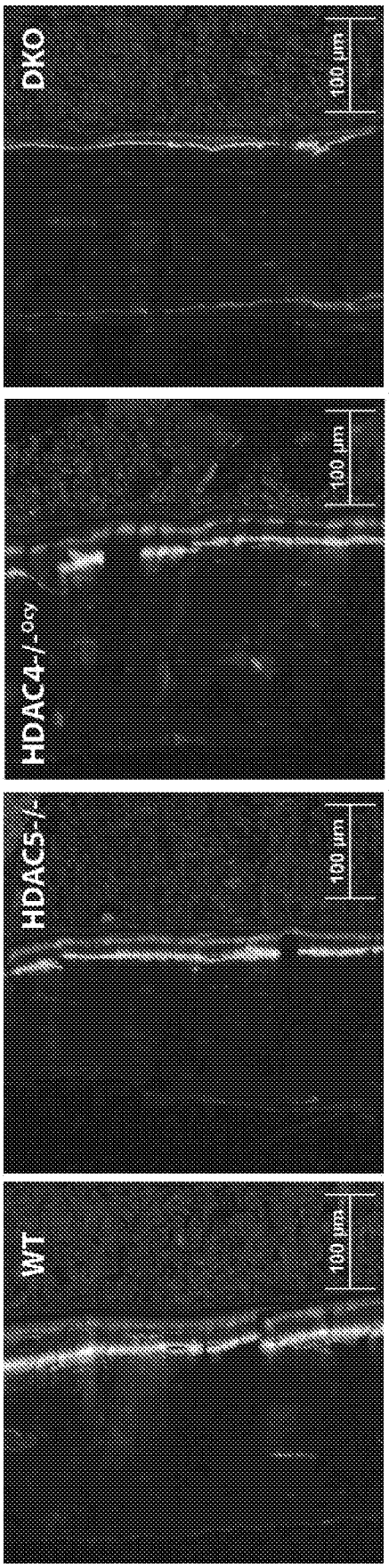


Figure 10E

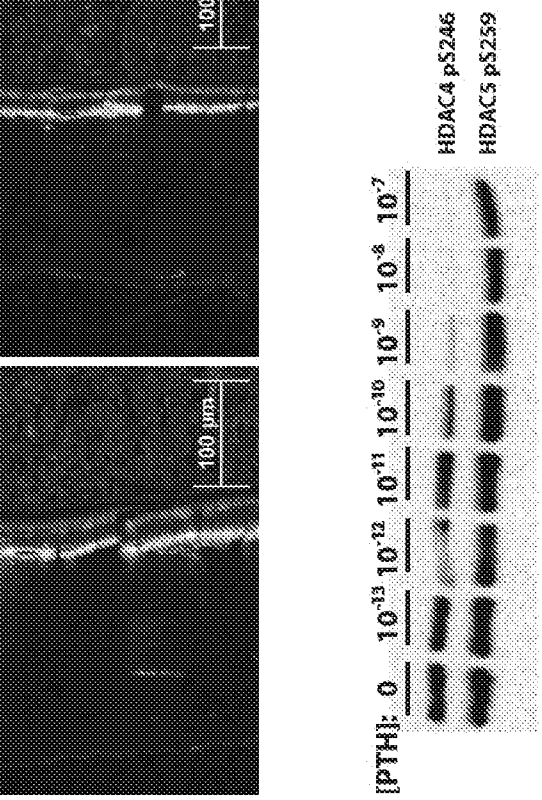


Figure 11A

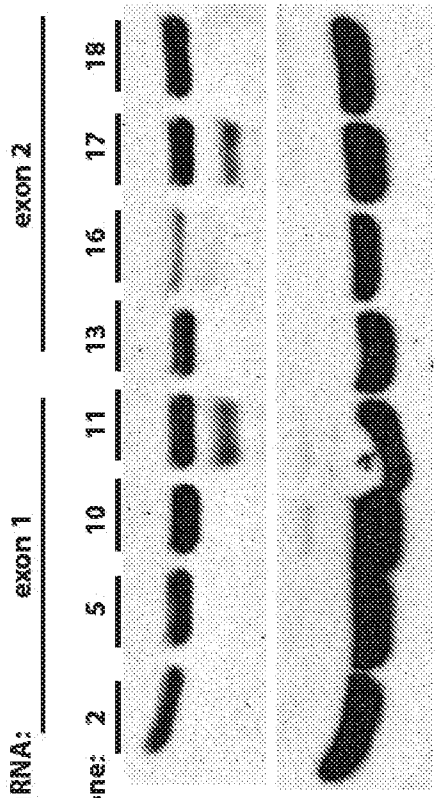


Figure 11B

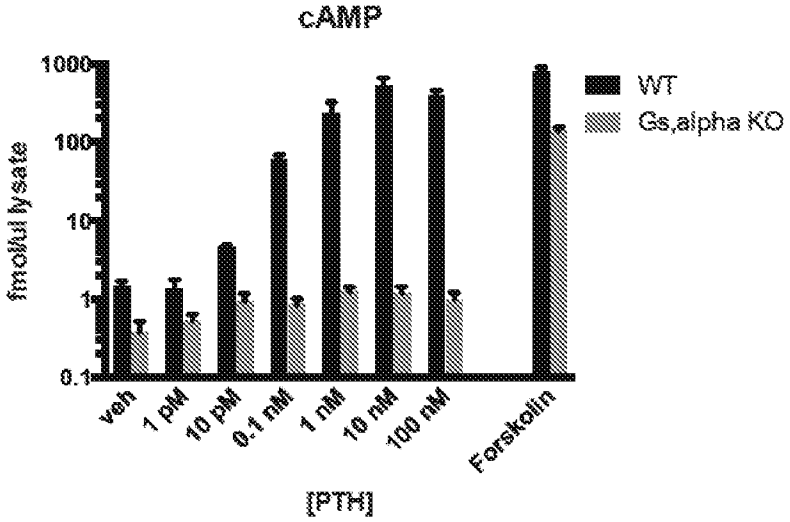


Figure 11C

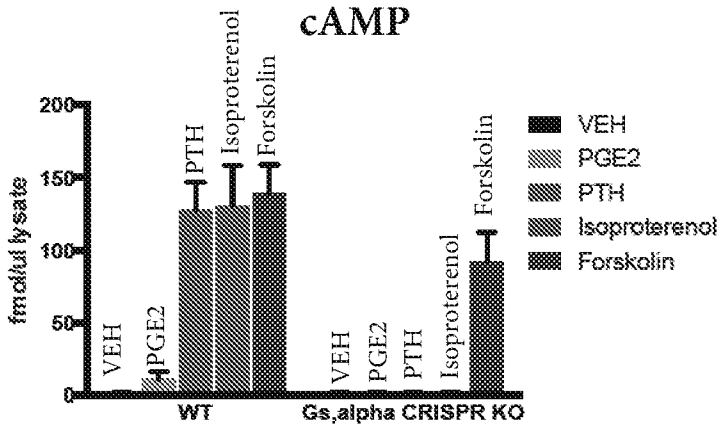


Figure 11D

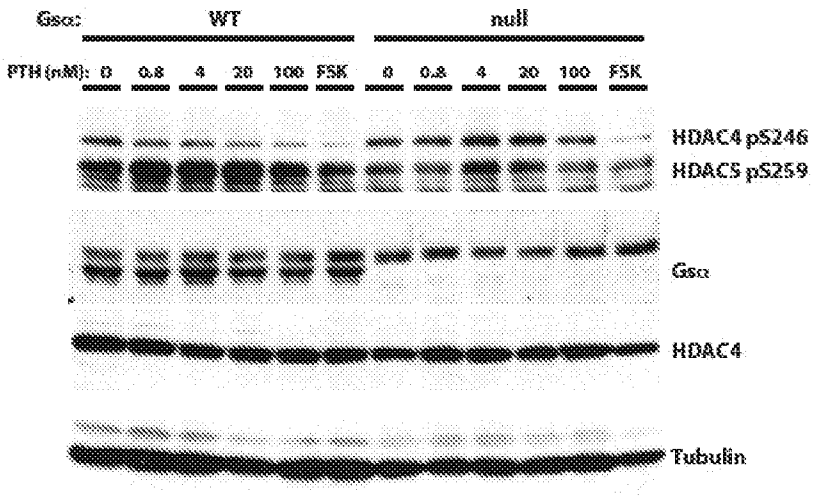


Figure 11E

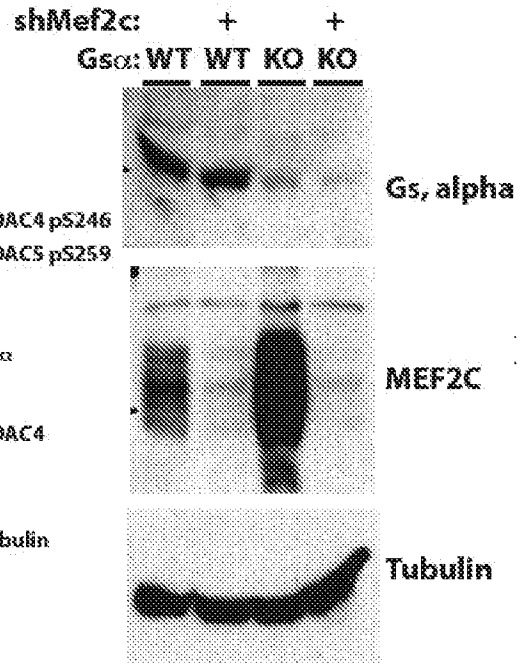


Figure 11F

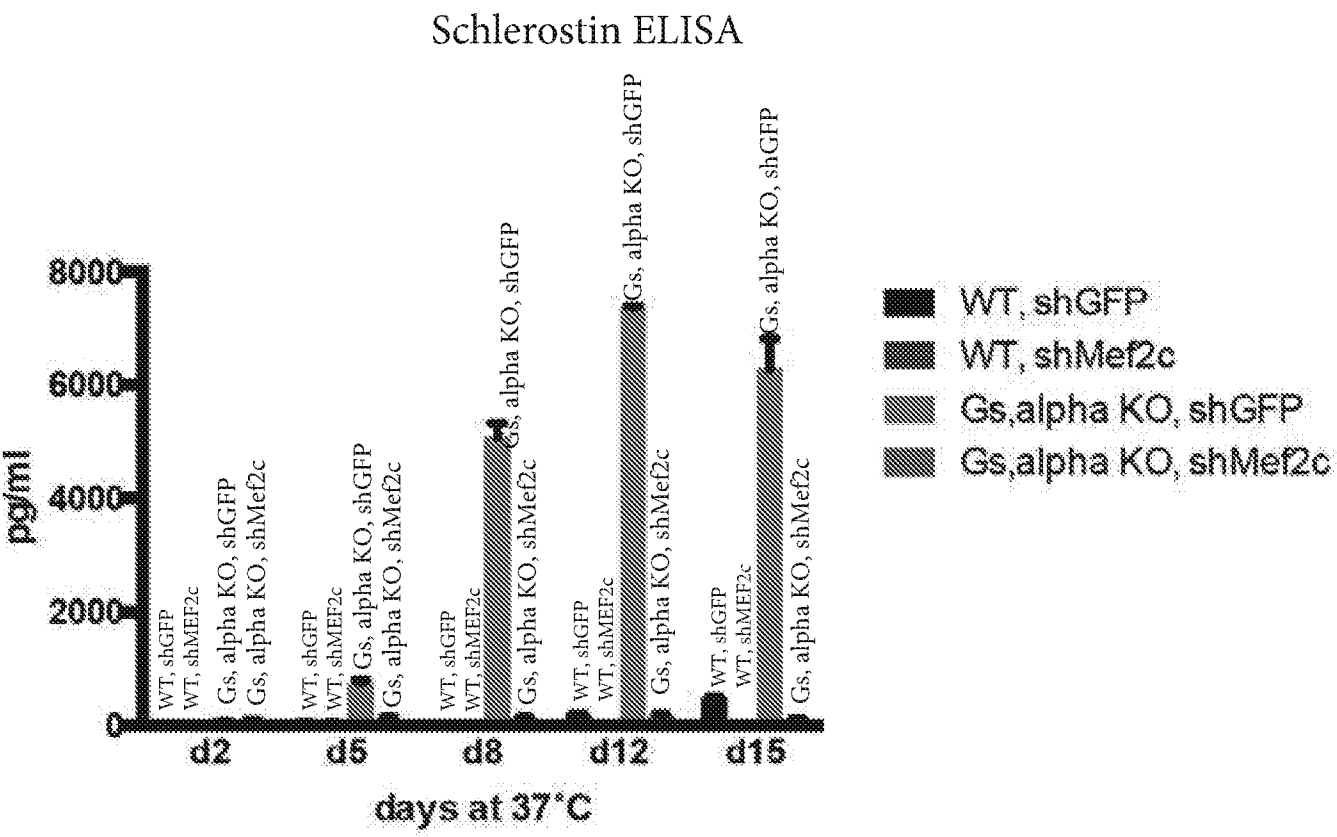


Figure 11G

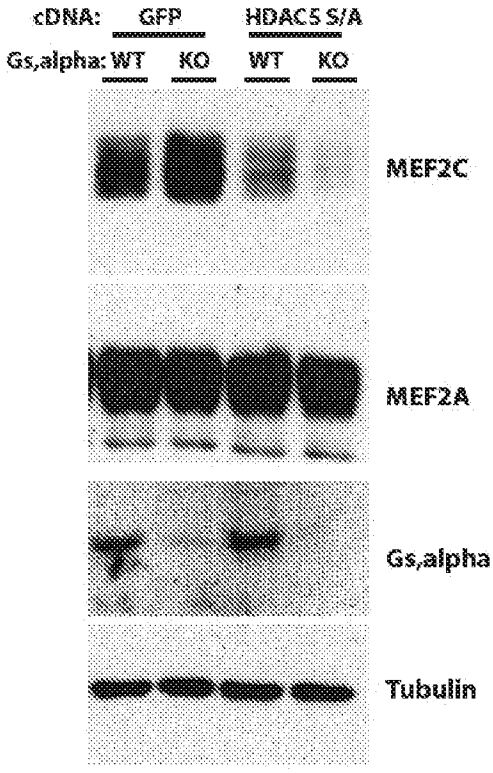


Figure 11H

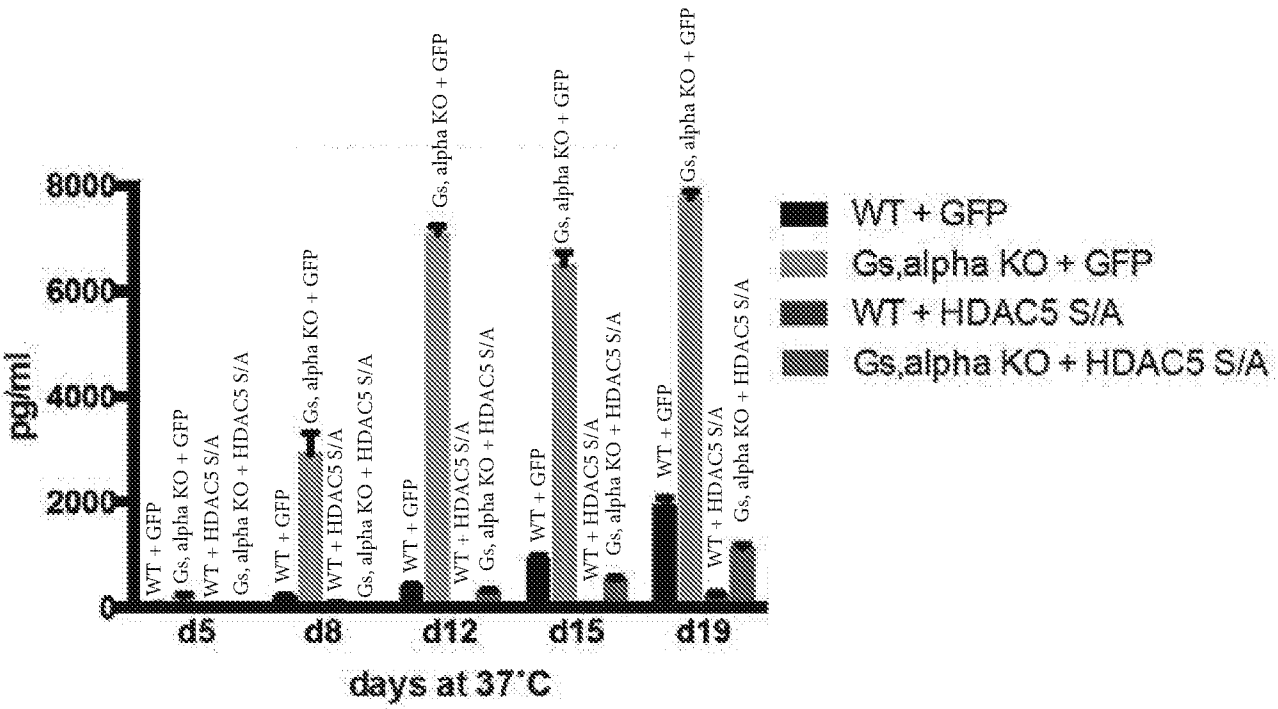

Schelorostin ELISA
pg/ml
8000
6000
4000
2000
0
WT + GFP
Gs, alpha KO + GFP
WT + HDAC5 S/A
Gs, alpha KO + HDAC5 S/A
d5
d8
d12
d15
d19
days at 37˚C
WT + GFP
Gs,alpha KO + GFP
WT + HDAC5 S/A
Gs,alpha KO + HDAC5 S/A

Figure 11I

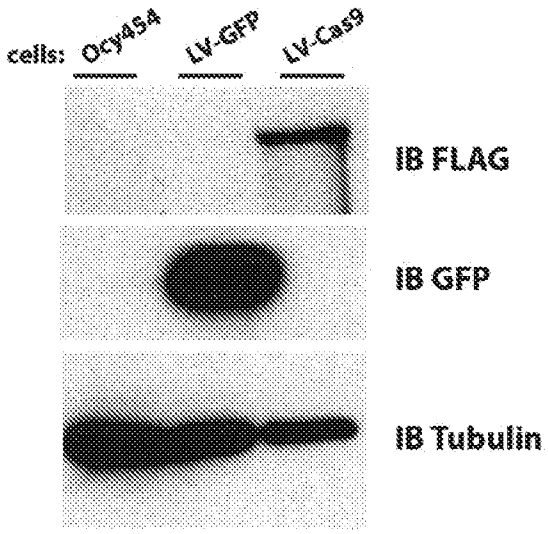


Figure 12A

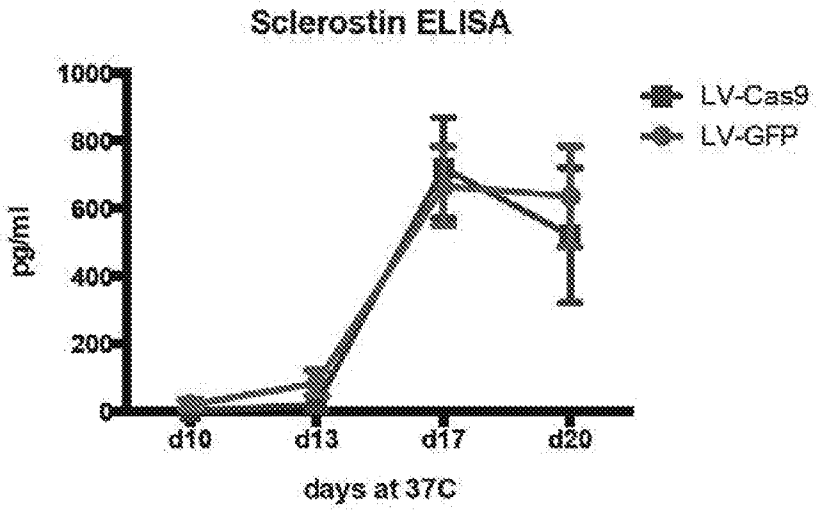


Figure 12B

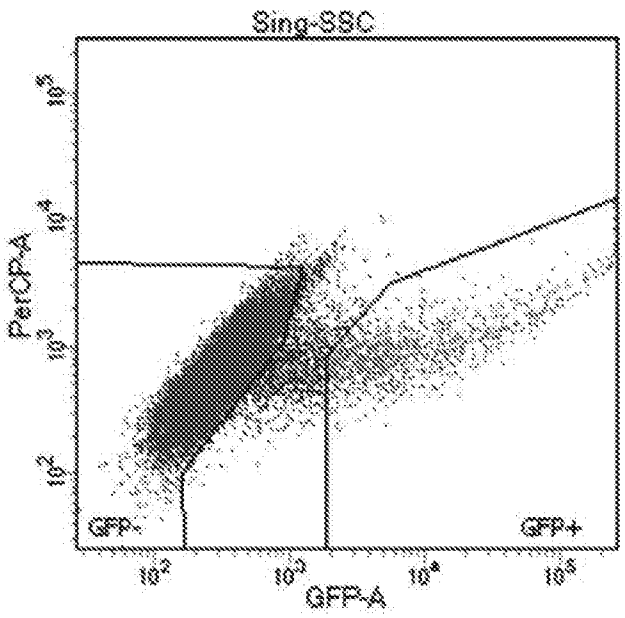


Figure 12C

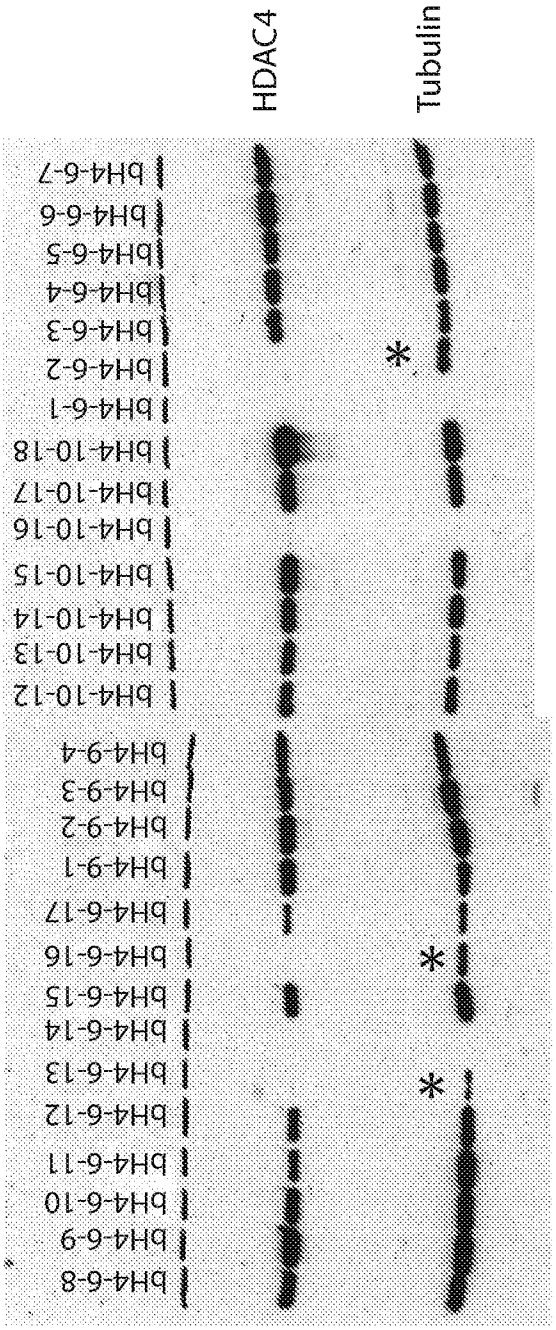


Figure 12D

Figure 12E

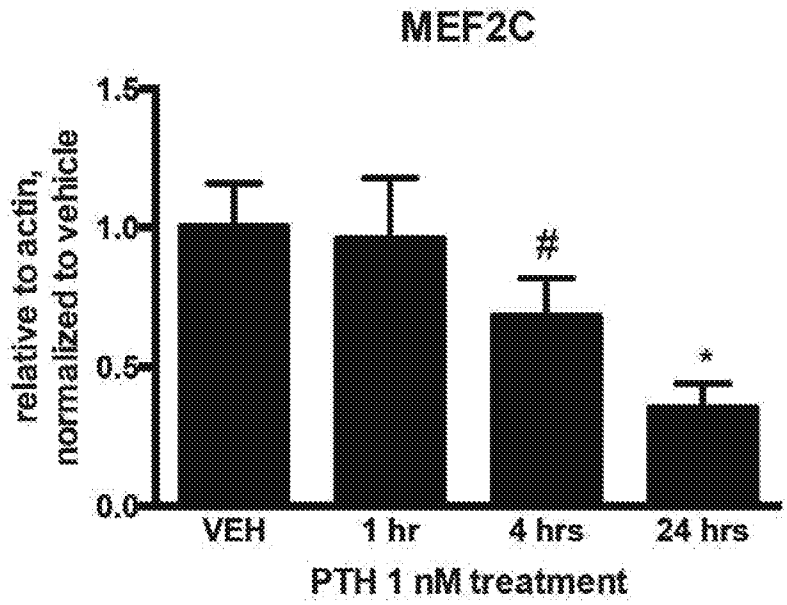


Figure 12F

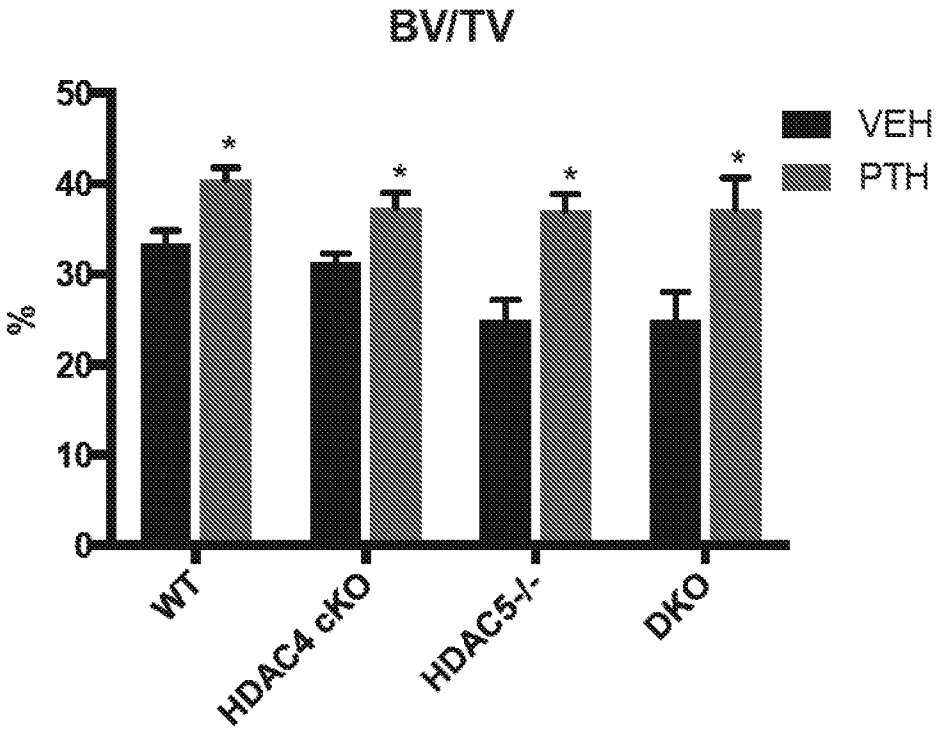


Figure 13A

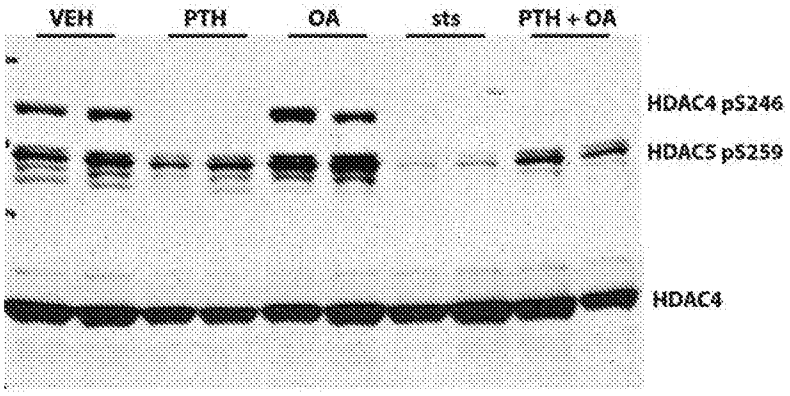


Figure 13B

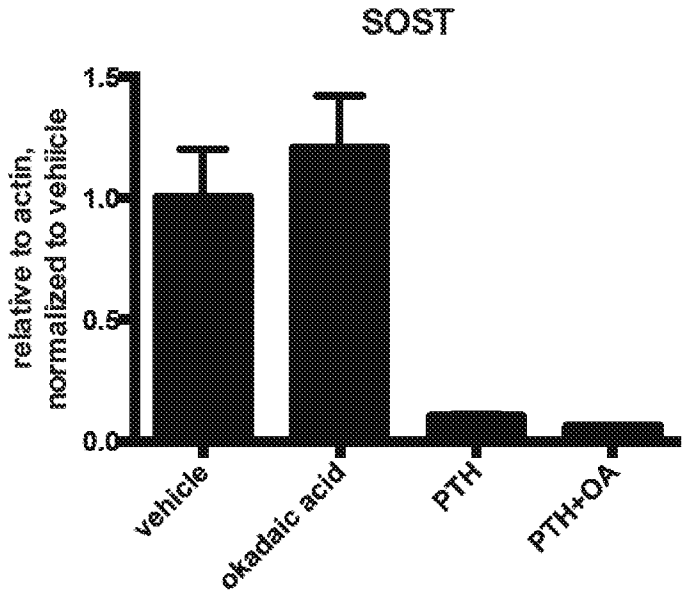


Figure 13C

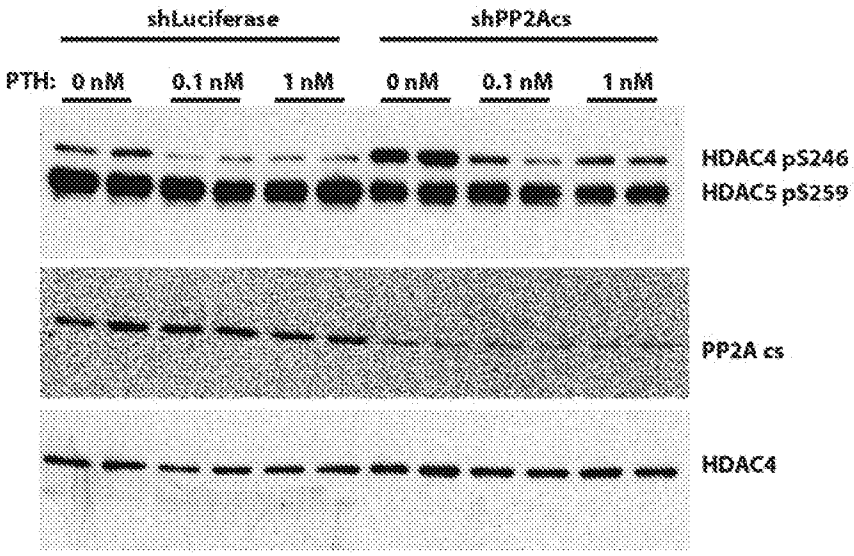


Figure 13D

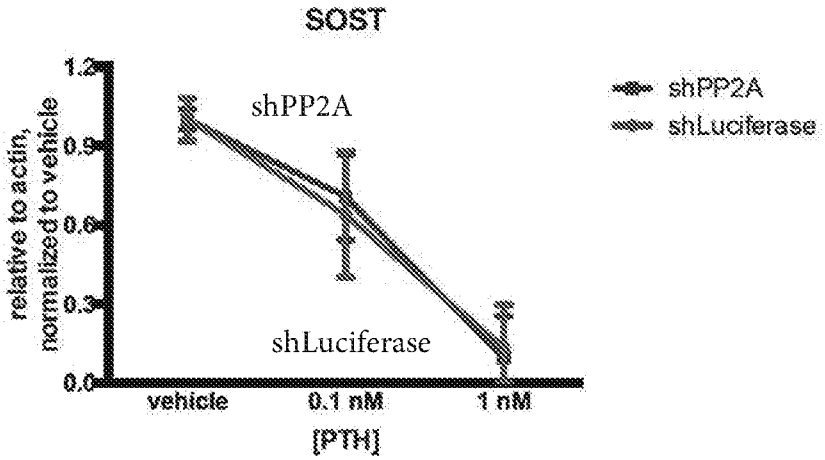


Figure 13E

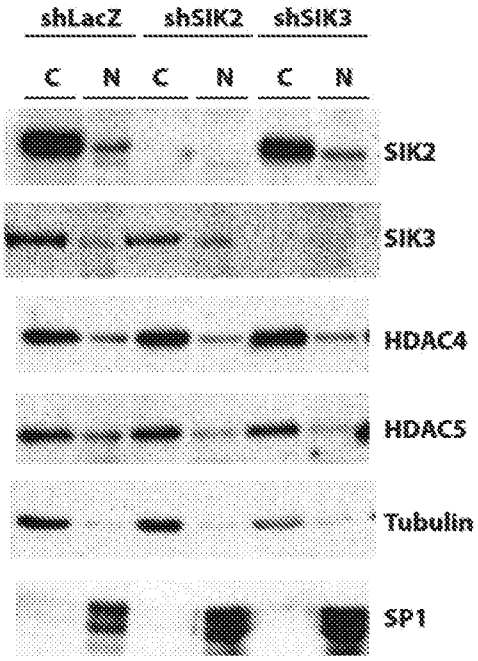


Figure 13F

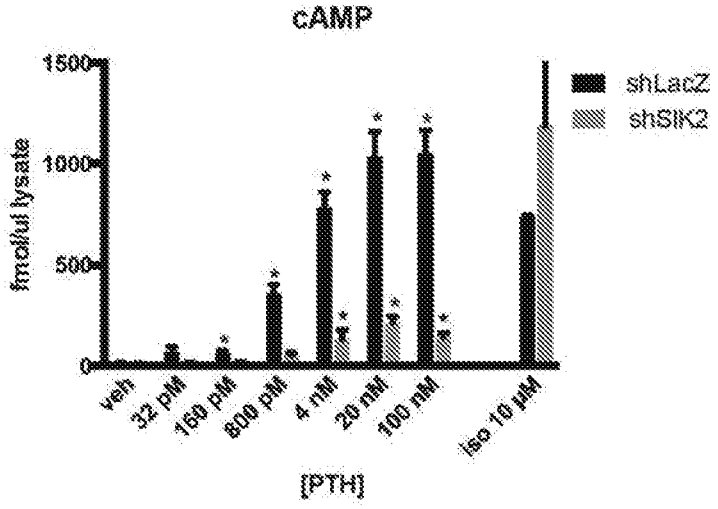


Figure 13G

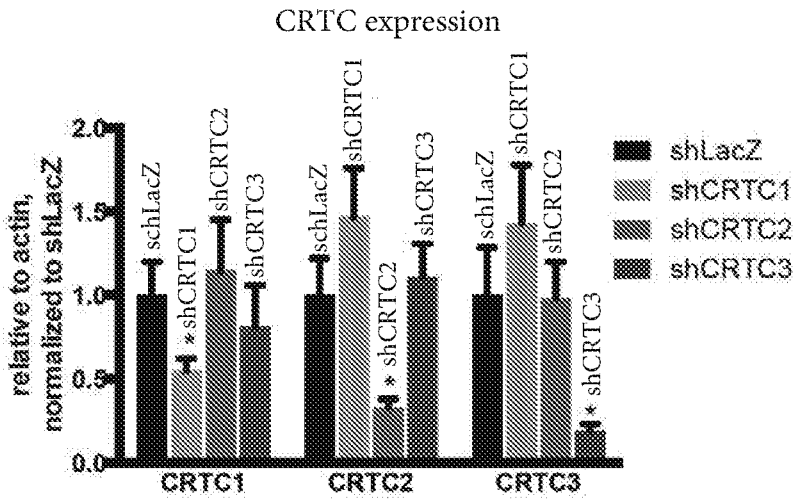


Figure 13H

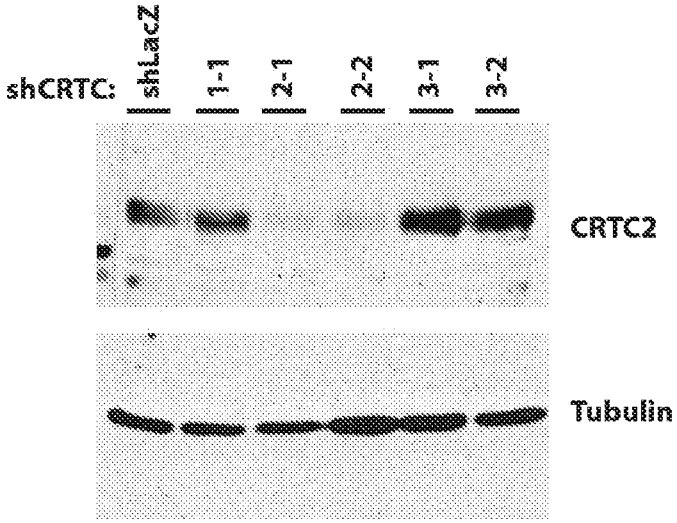


Figure 13I

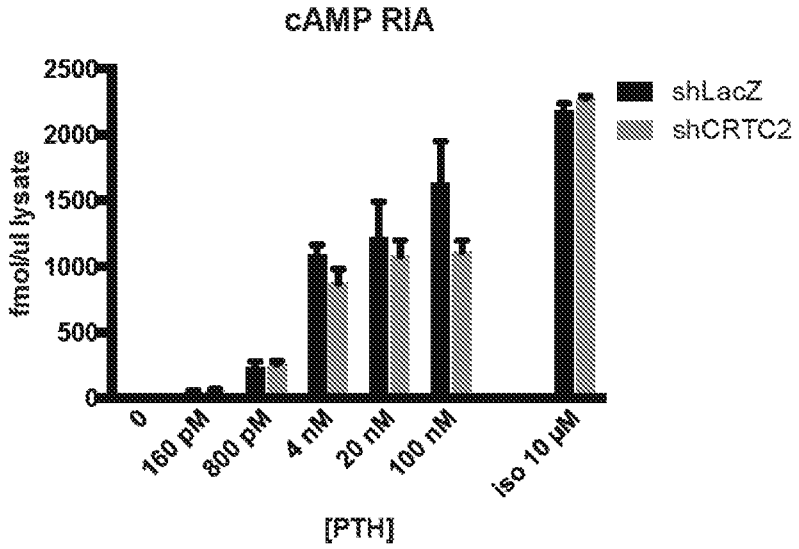


Figure 13J

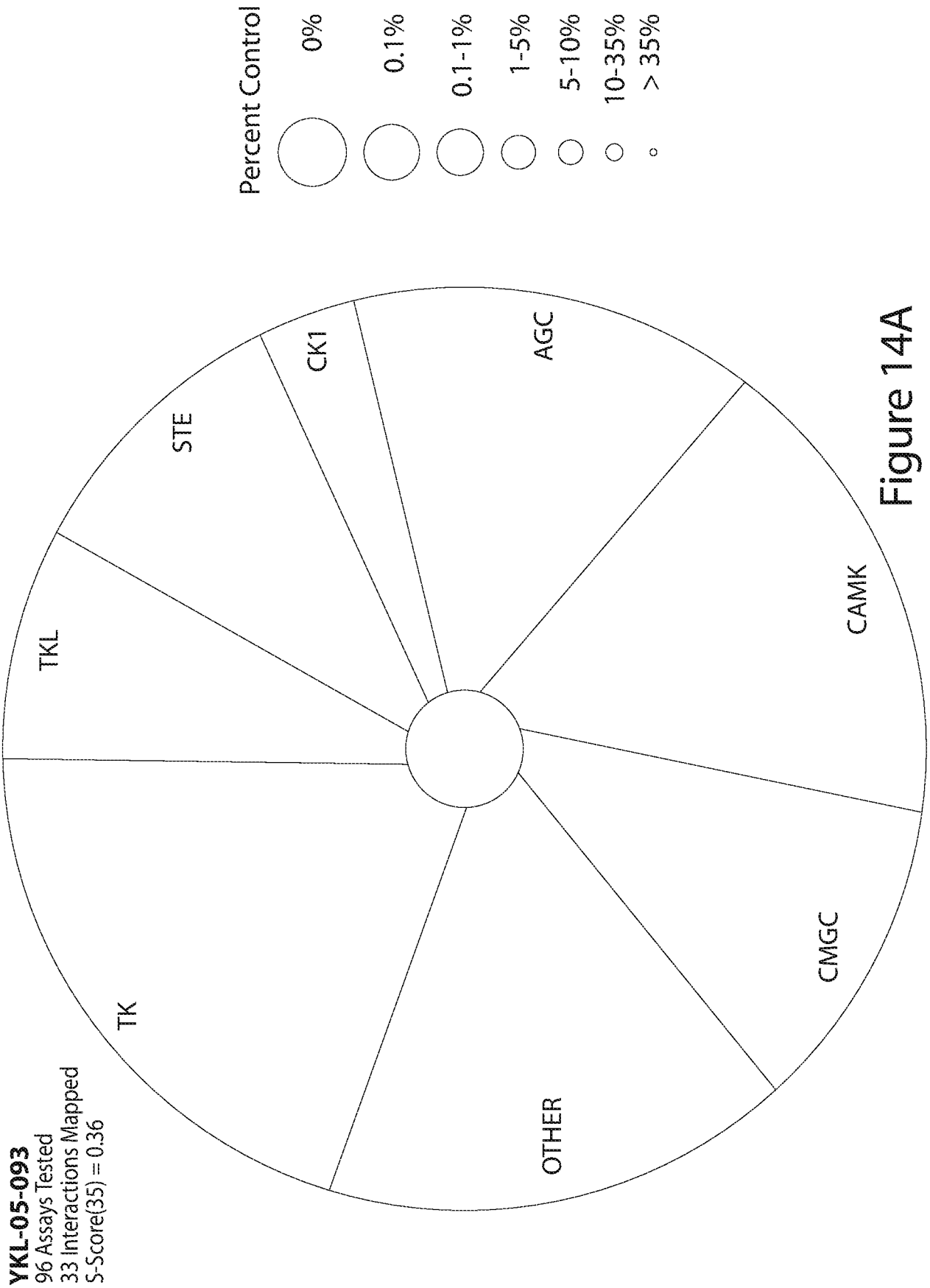

Percent Control
0%
0.1%
0.1-1%
1-5%
5-10%
10-35%
> 35%
AGC
CAMK
CMGC
OTHER
TK
TKL
STE
CK1
YKL-05-093
96 Assays Tested
33 Interactions Mapped
S-Score(35) = 0.36

Figure 14A

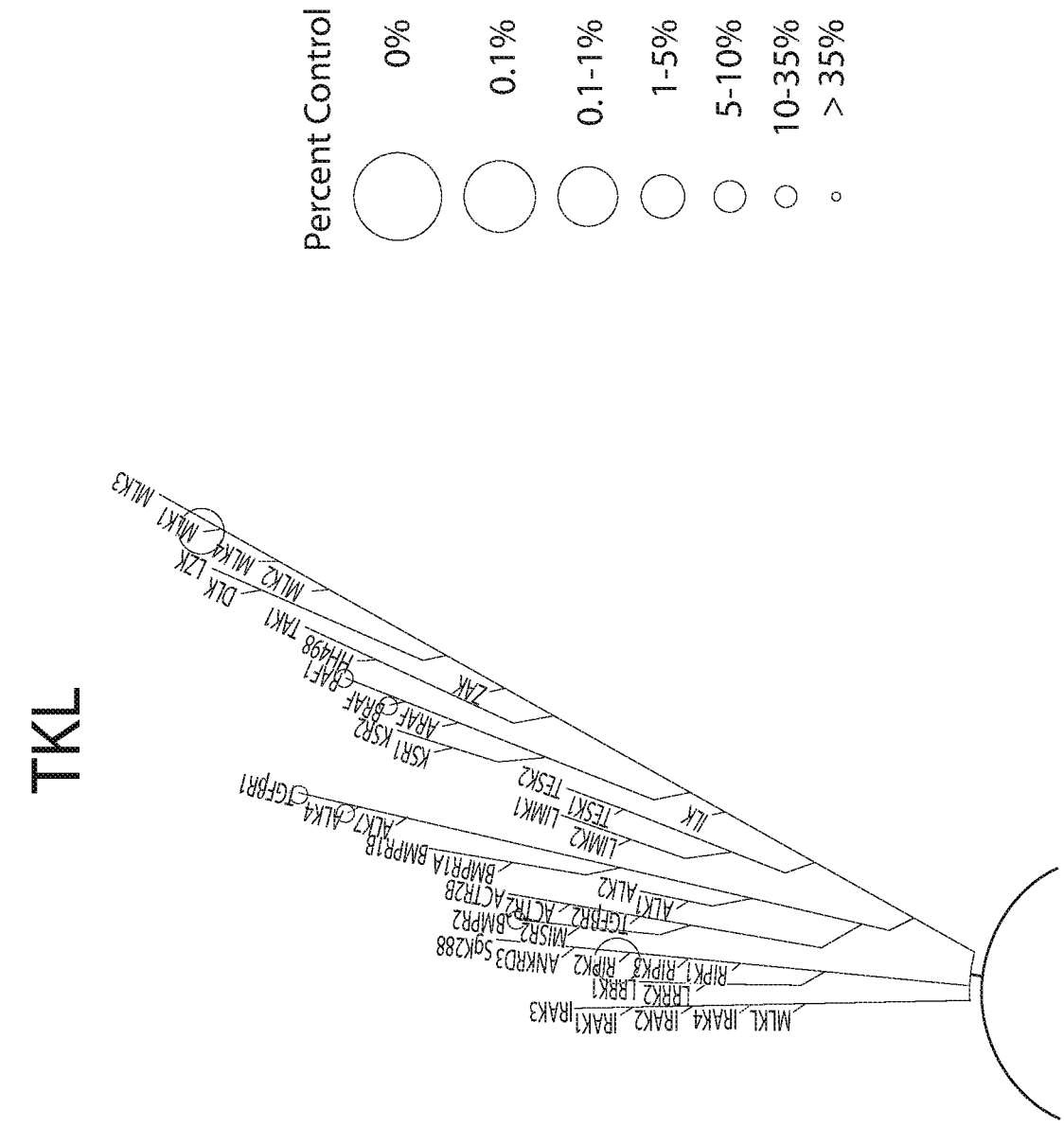


Figure 14A (continued)

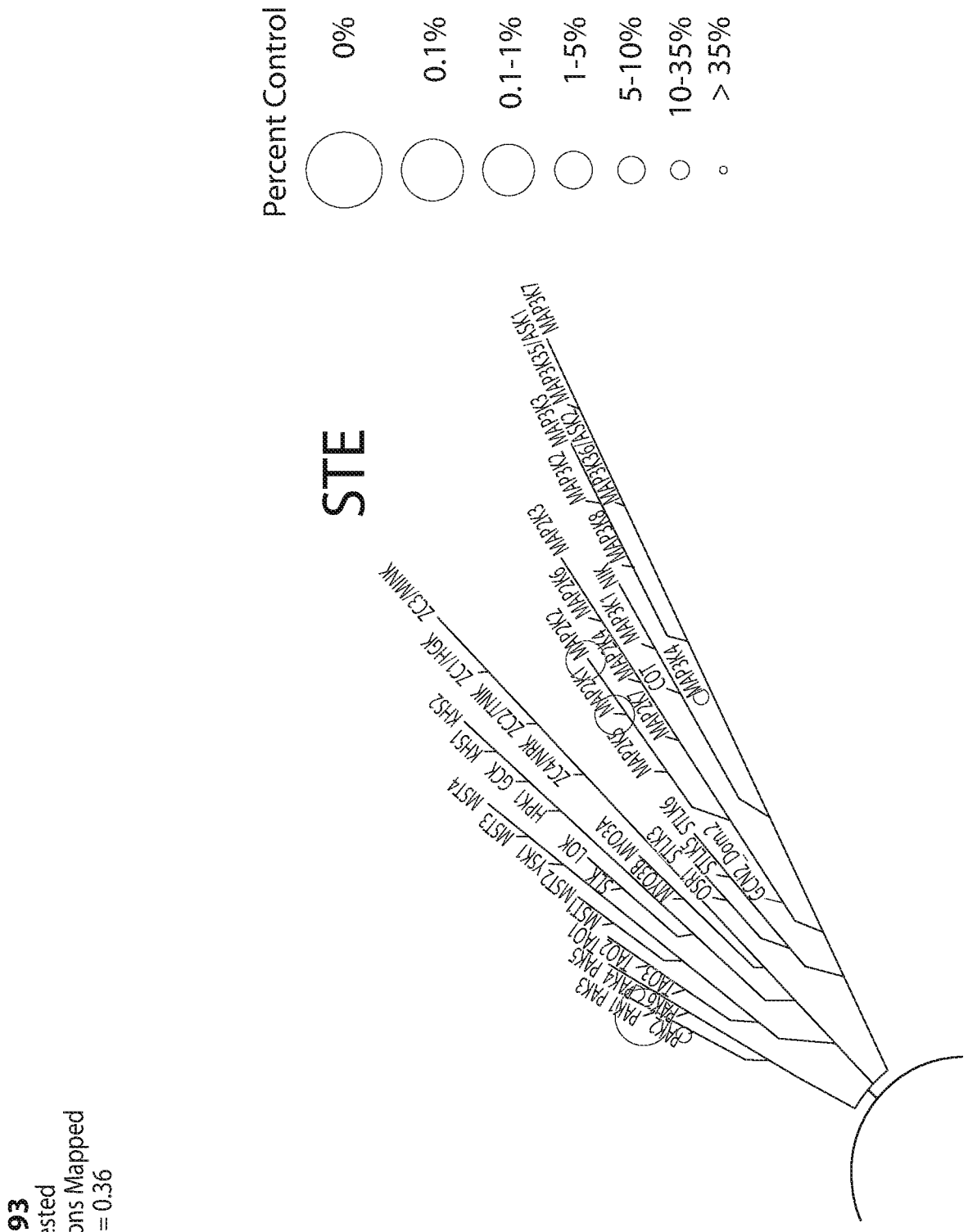


Figure 14A (continued)

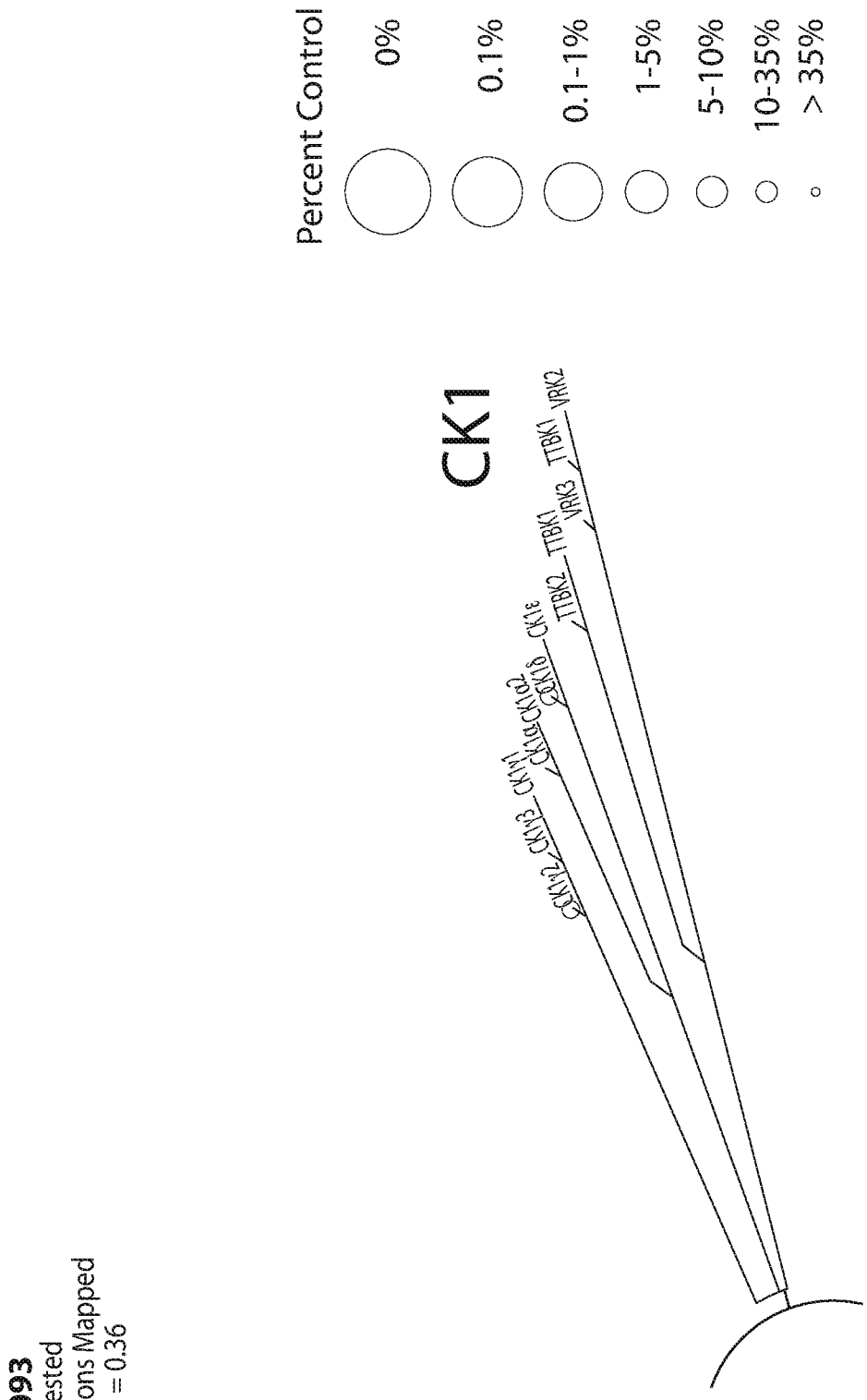


Figure 14A (continued)

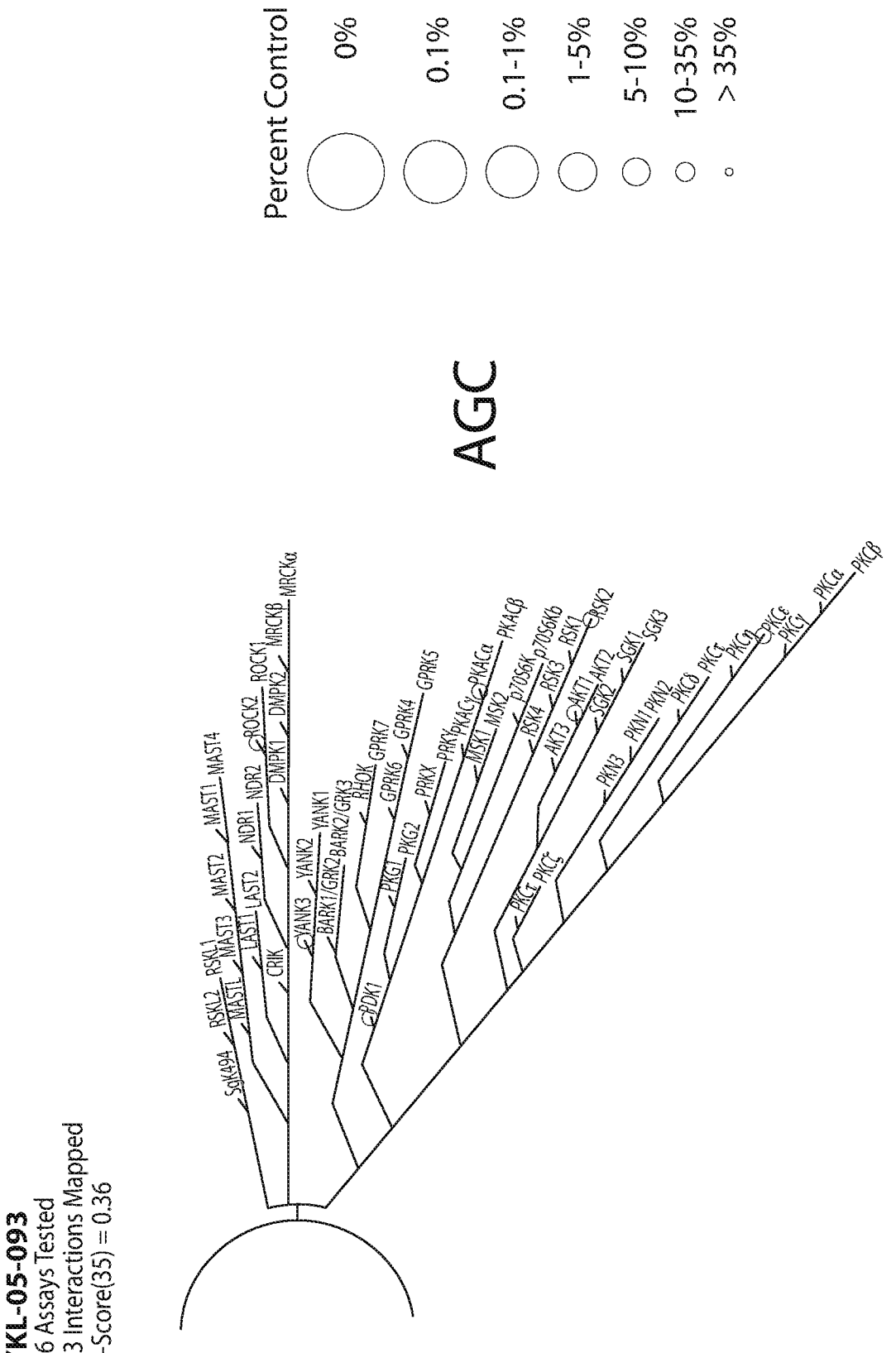


Figure 14A (continued)

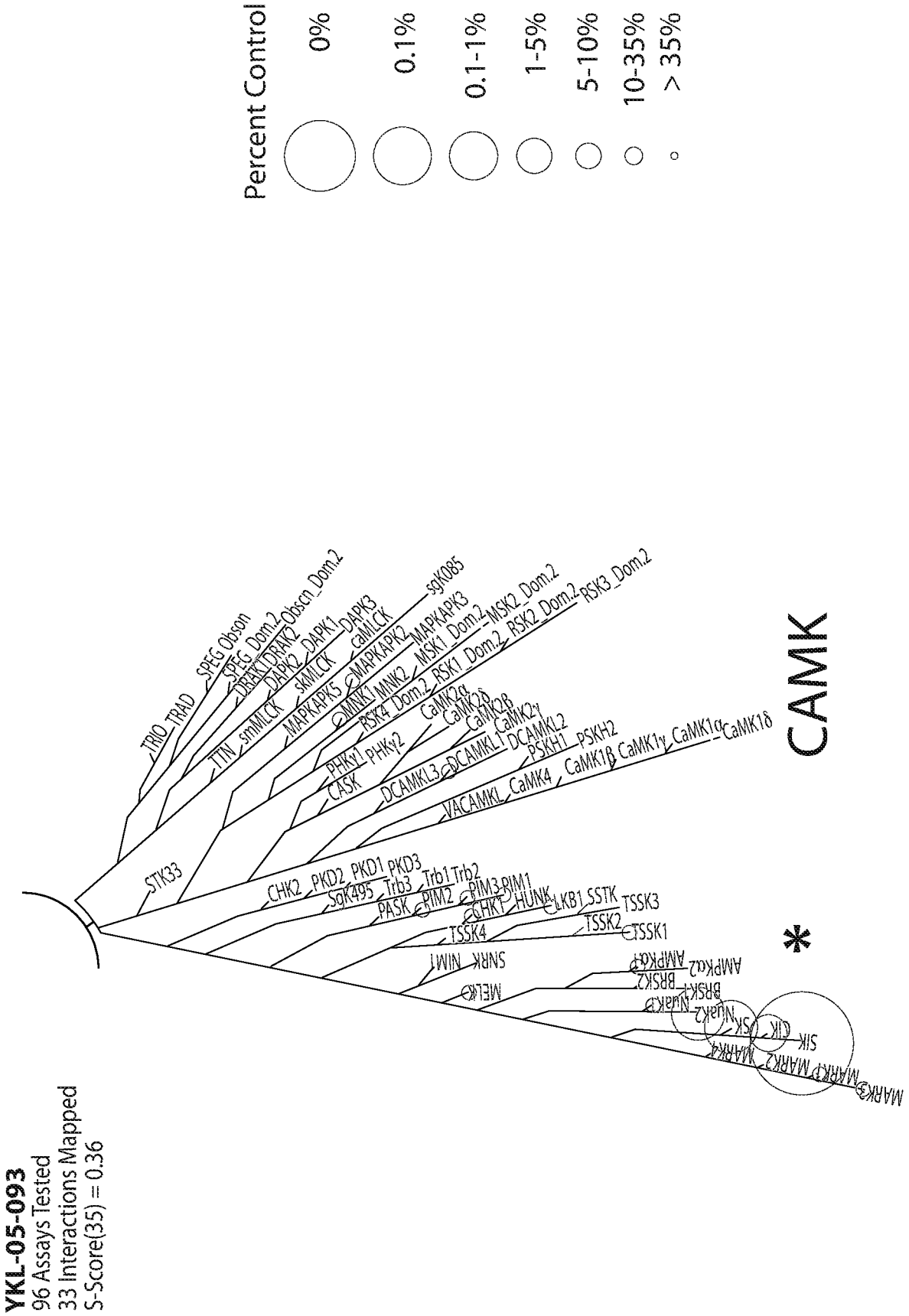


Figure 14A (continued)

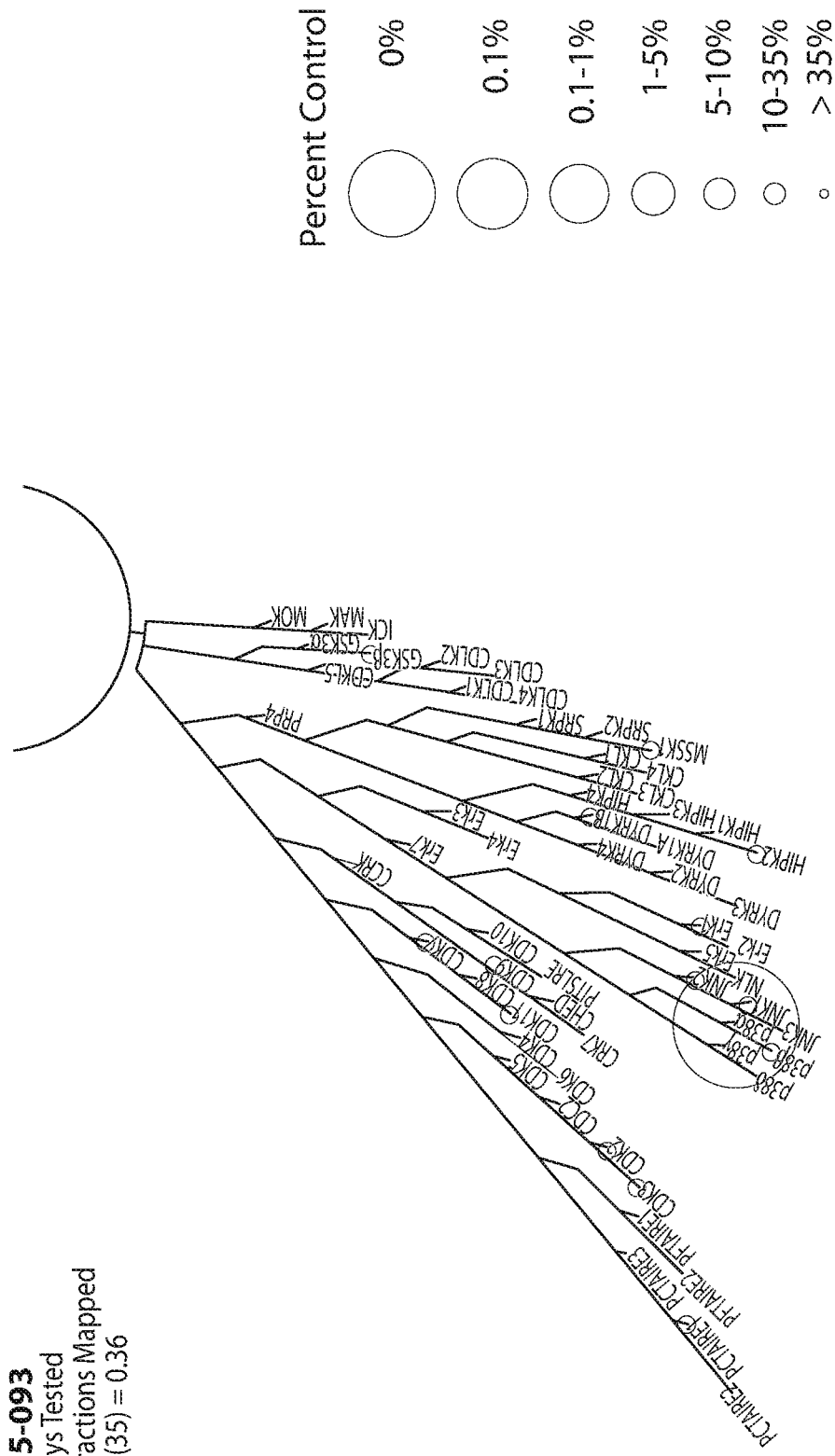


Figure 14A (continued)

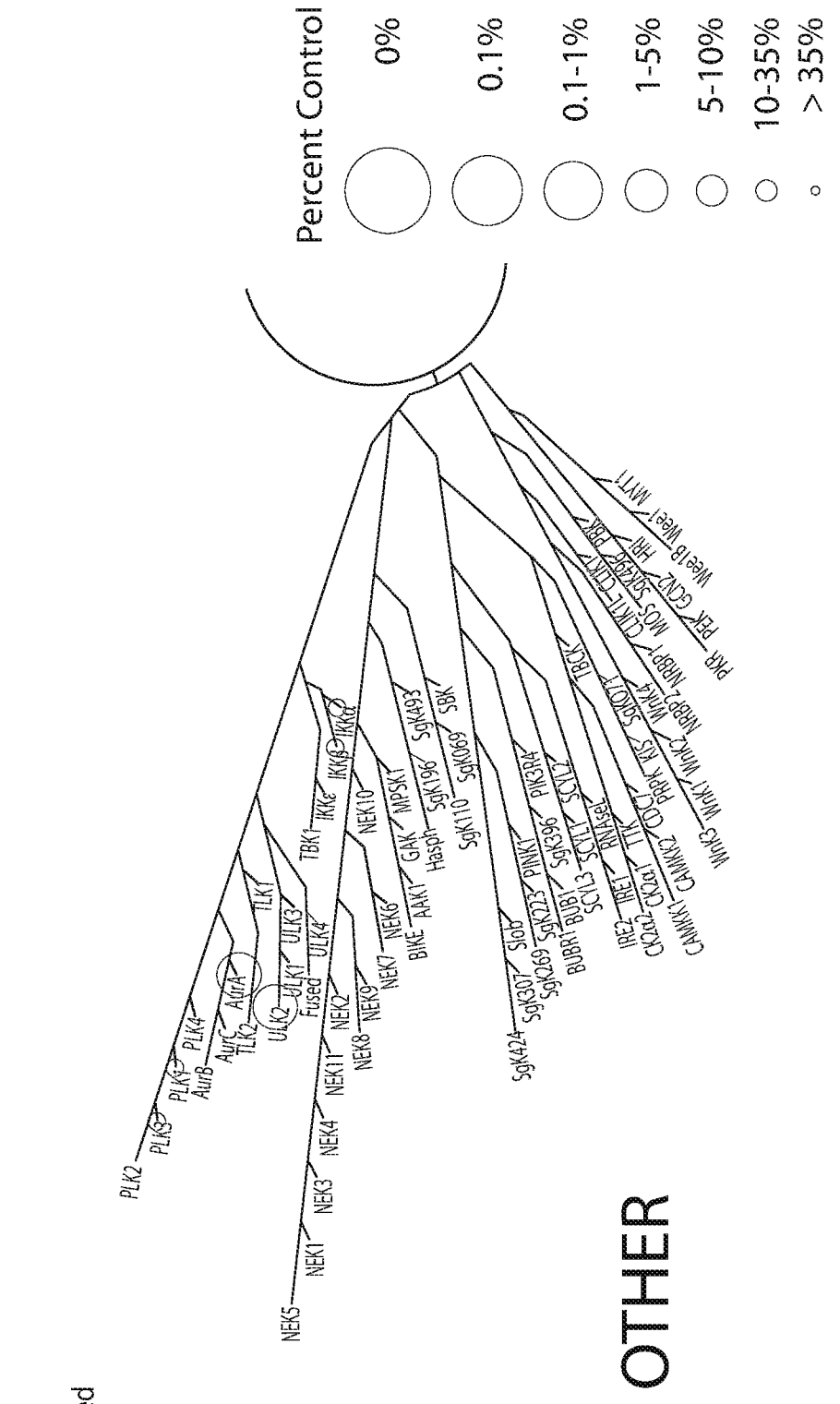


Figure 14A (continued)

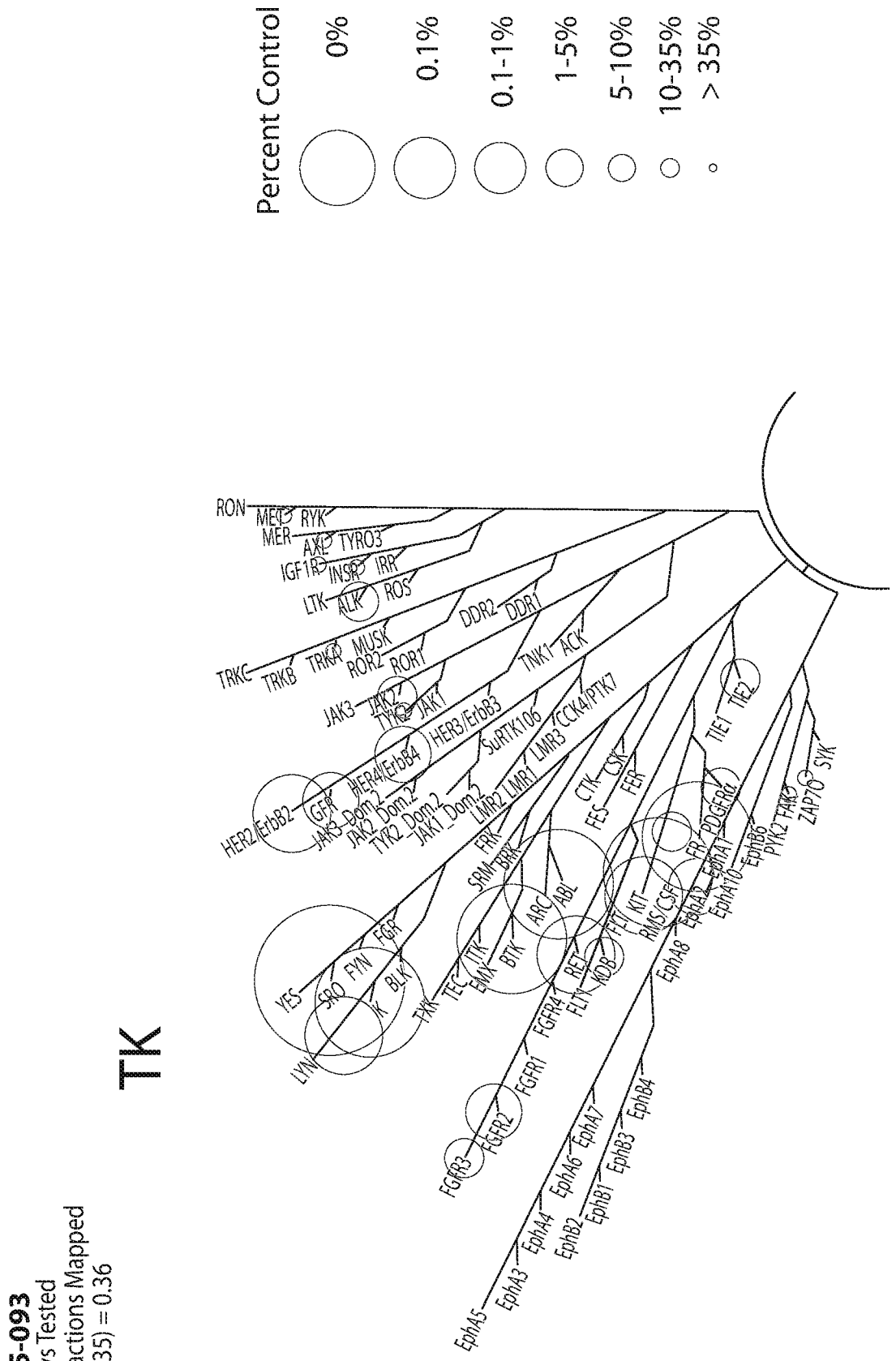


Figure 14A (continued)

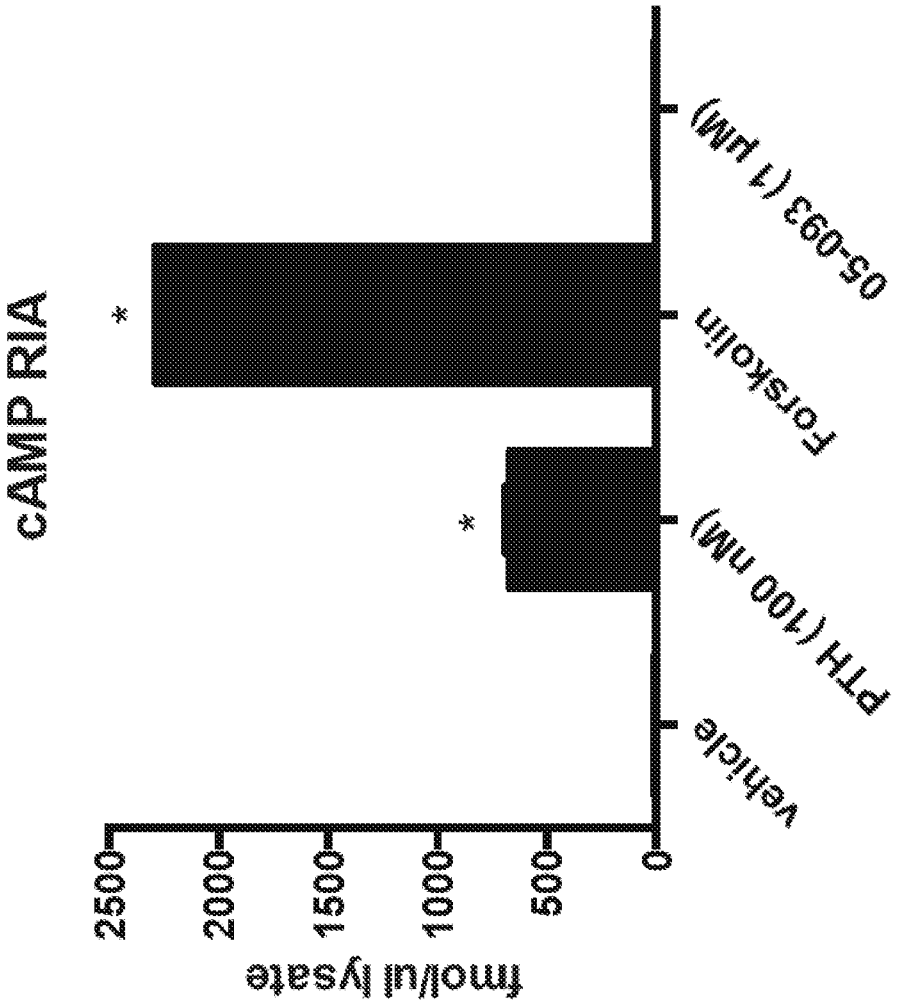

cAMP RIA
fmol/ul lysate
2500
2000
1500
1000
500
0
Vehicle
PTH (100 nM)
Forskolin
05-093 (1 uM)
*
*

Figure 14B

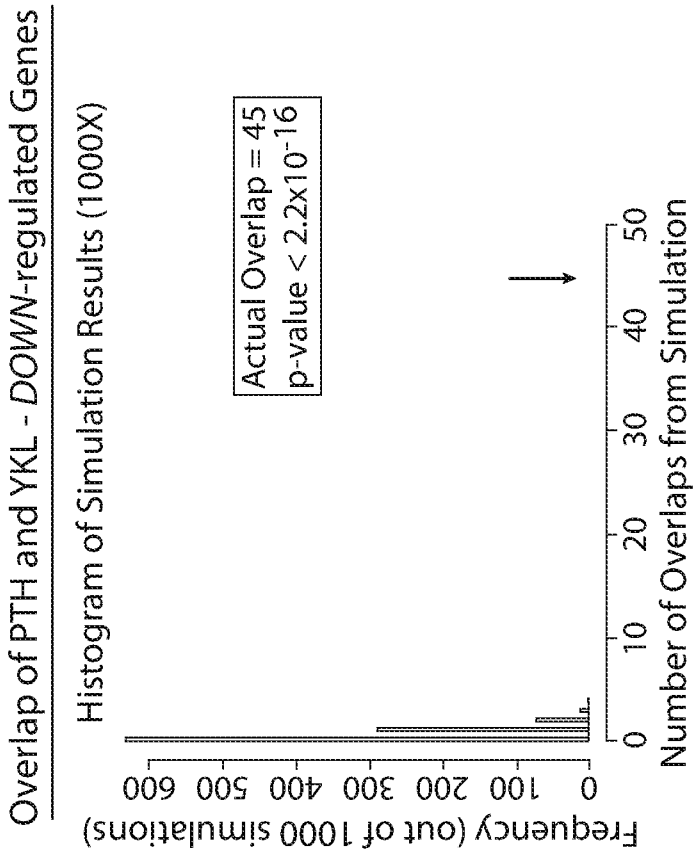


Figure 15B

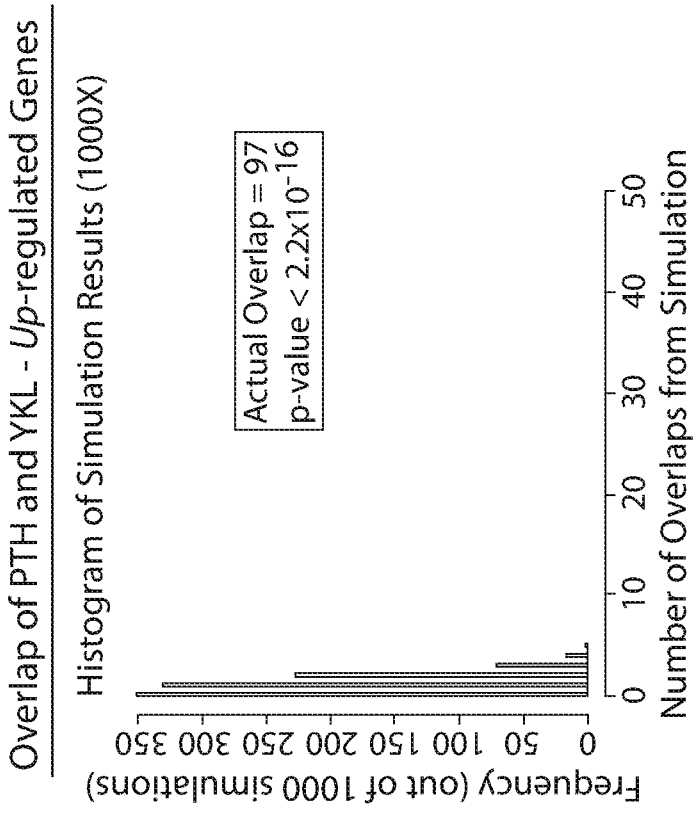


Figure 15A

GO Term	FDR value (coverage)
Cell chemotaxis	2.04e-5 (10/174)
Blood vessel morphogenesis	2.04e-5 (12/278)
Ossification	8.99e-5 (11/275)
Muscle organ development	1.54e-4 (11/298)
Relaxation of cardiac muscle	2.1e-4 (4/10)

Figure 15C

GO Term	FDR value (coverage)
Skeletal muscle tissue development	6.052e-6 (9/166)
Blood vessel morphogenesis	1.69e-5 (10/278)
Muscle organ development	2.2e-5 (10/298)
Skeletal muscle cell differentiation	2.35e-3 (5/61)
Regulation of muscle tissue development	2.78e-2 (5/113)

Figure 15D

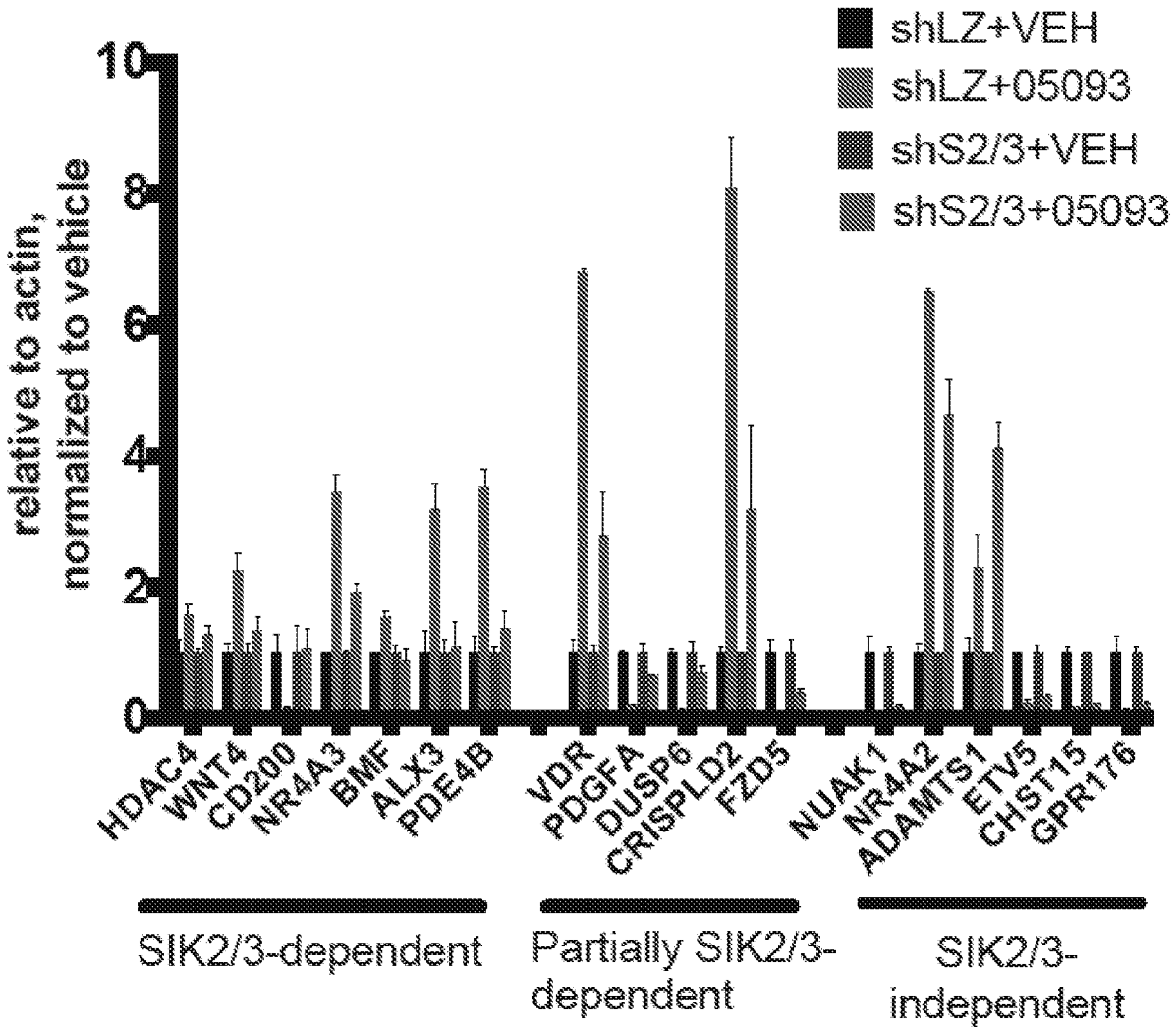


Figure 15E

Half life in 1 mg/ml hepatic microsomes

Compound ID	Mouse
YKL-04-114	13.8
YKL-05-093	22.7
HG-9-91-01	13.0

Figure 16

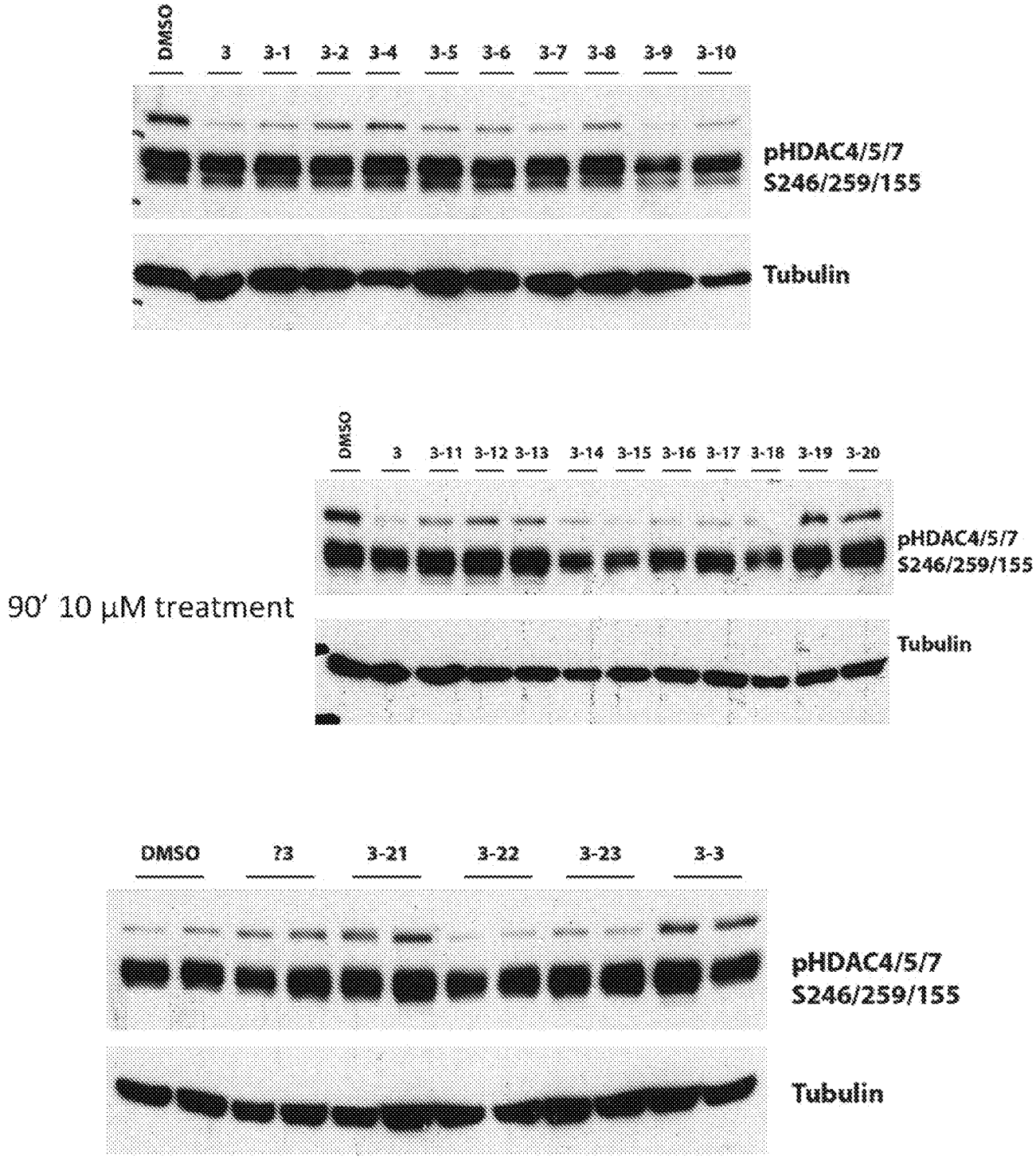

DMSO
3
3-1
3-2
3-4
3-5
3-6
3-7
3-8
3-9
3-10
pHDAC4/5/7
S246/259/155
Tubulin
90' 10 µM treatment
DMSO
3
3-11
3-12
3-13
3-14
3-15
3-16
3-17
3-18
3-19
3-20
pHDAC4/5/7
S246/259/155
Tubulin
DMSO
?3
3-21
3-22
3-23
3-3
pHDAC4/5/7
S246/259/155
Tubulin

Figure 17

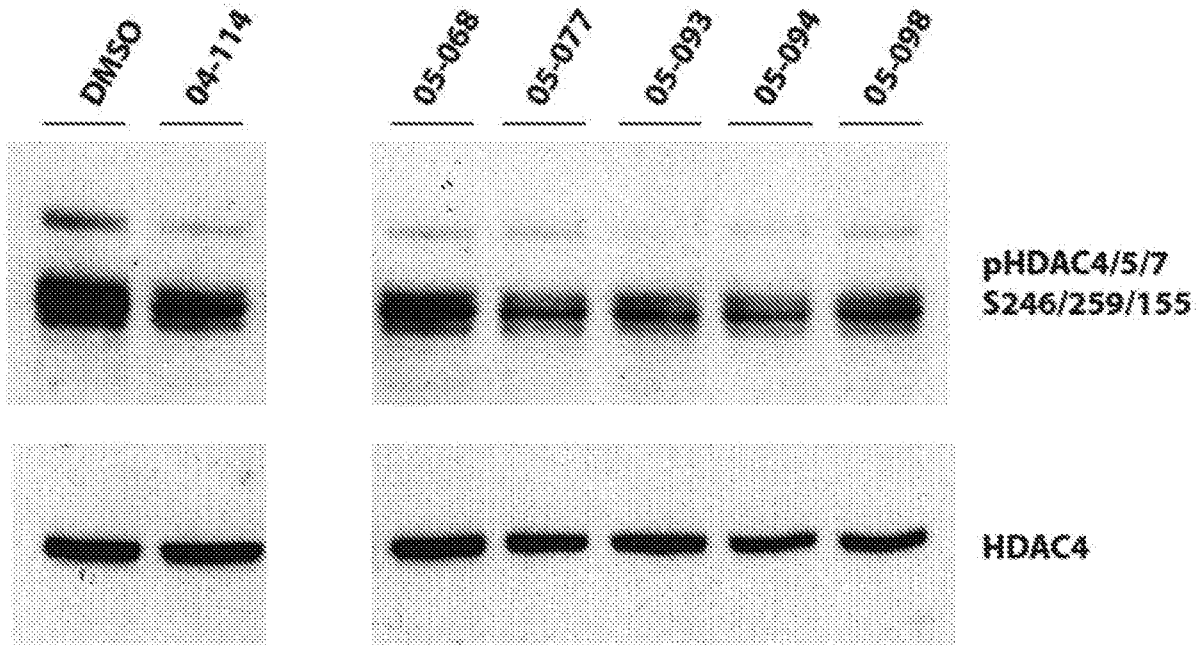

DMSO
04-114
05-068
05-077
05-093
05-094
05-098
pHDAC4/5/7
S246/259/155
HDAC4
6-9 cells, 7 days at 37˚C, 90' cmpd treatment at 10 µM

Figure 18

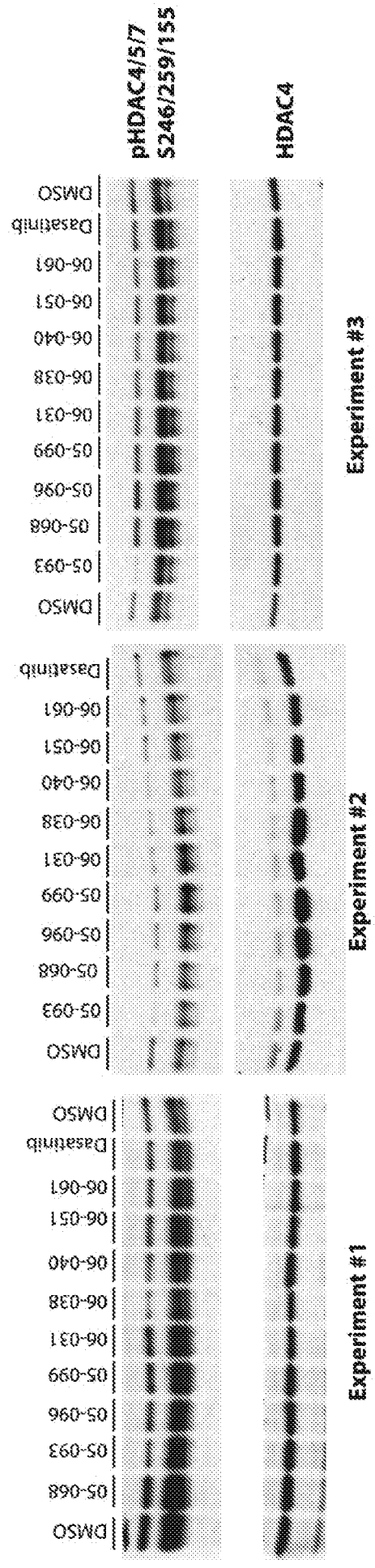

pHDAC4/5/7
S246/259/155
HDAC4
DMSO
05-093
05-068
05-096
05-099
06-031
06-038
06-040
06-051
06-061
Dasatinib
Experiment #3
Experiment #2
Experiment #1
[cmpd] = 10 µM, 75 minute treatment

Figure 19

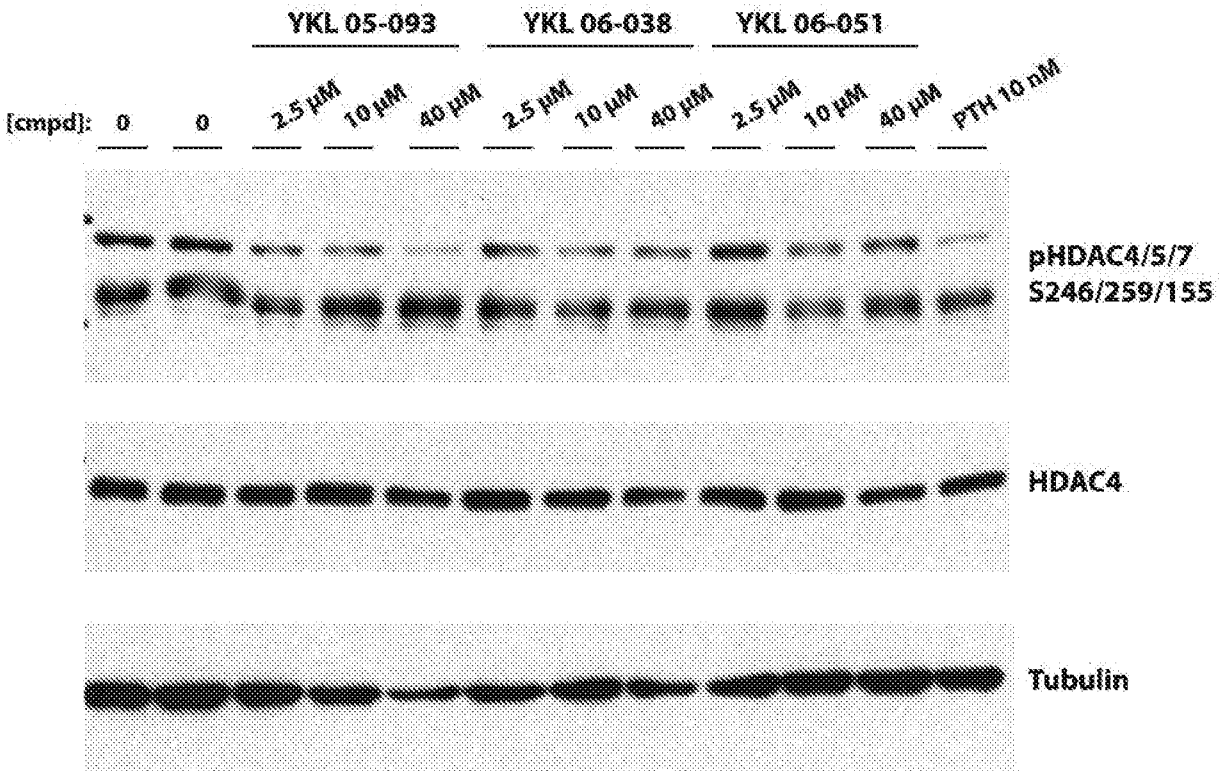
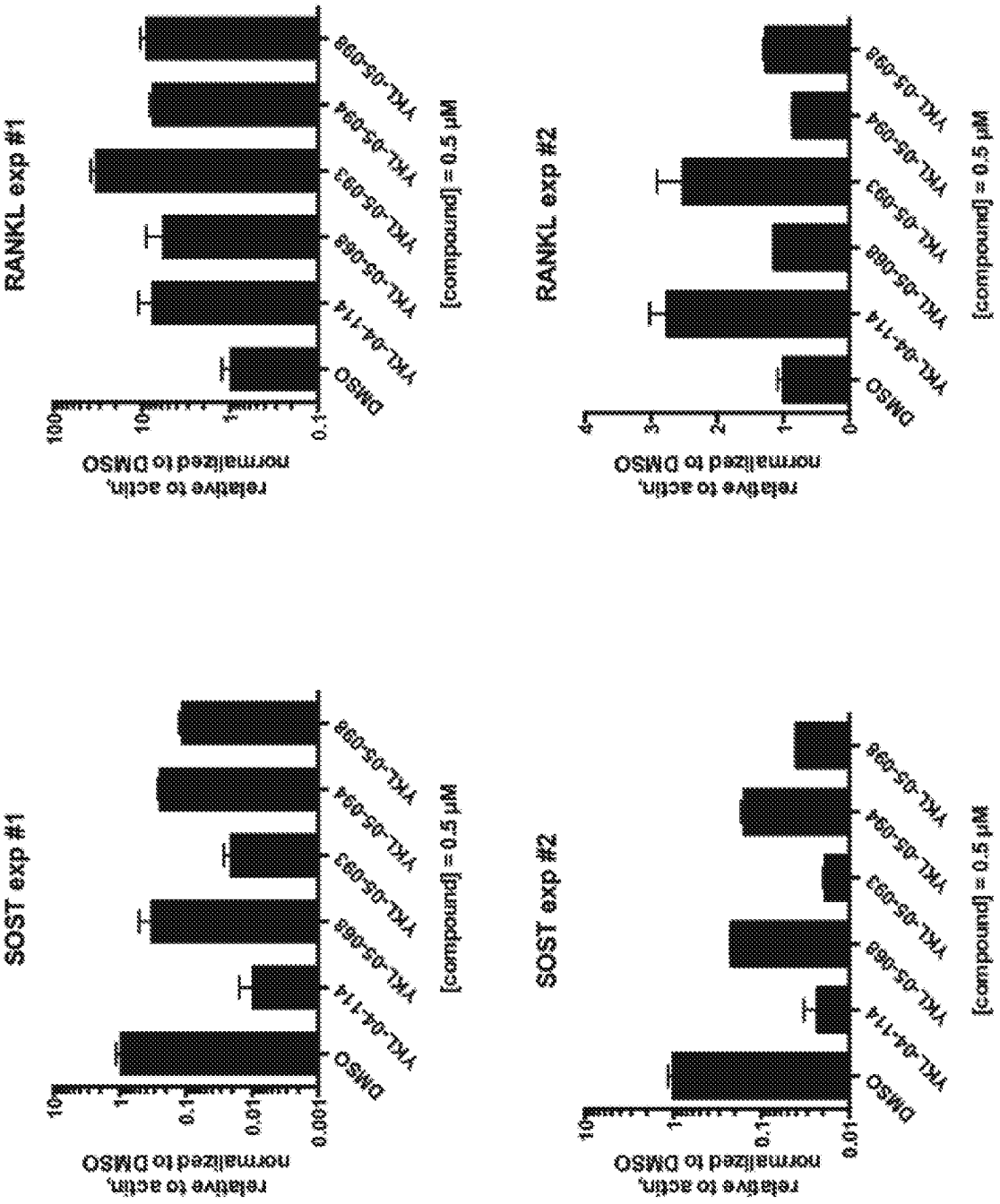

YKL 05-093
YKL 06-038
YKL 06-051
[cmpd]:
0
0
2.5 μM
10 μM
40 μM
2.5 μM
10 μM
40 μM
2.5 μM
10 μM
40 μM
PTH 10 nM
pHDAC4/5/7
S246/259/155
HDAC4
Tubulin
90 minute compound treatment

Figure 20



6-9 cells, 14 days at 37°C, 3.5 hr treatment

Figure 21

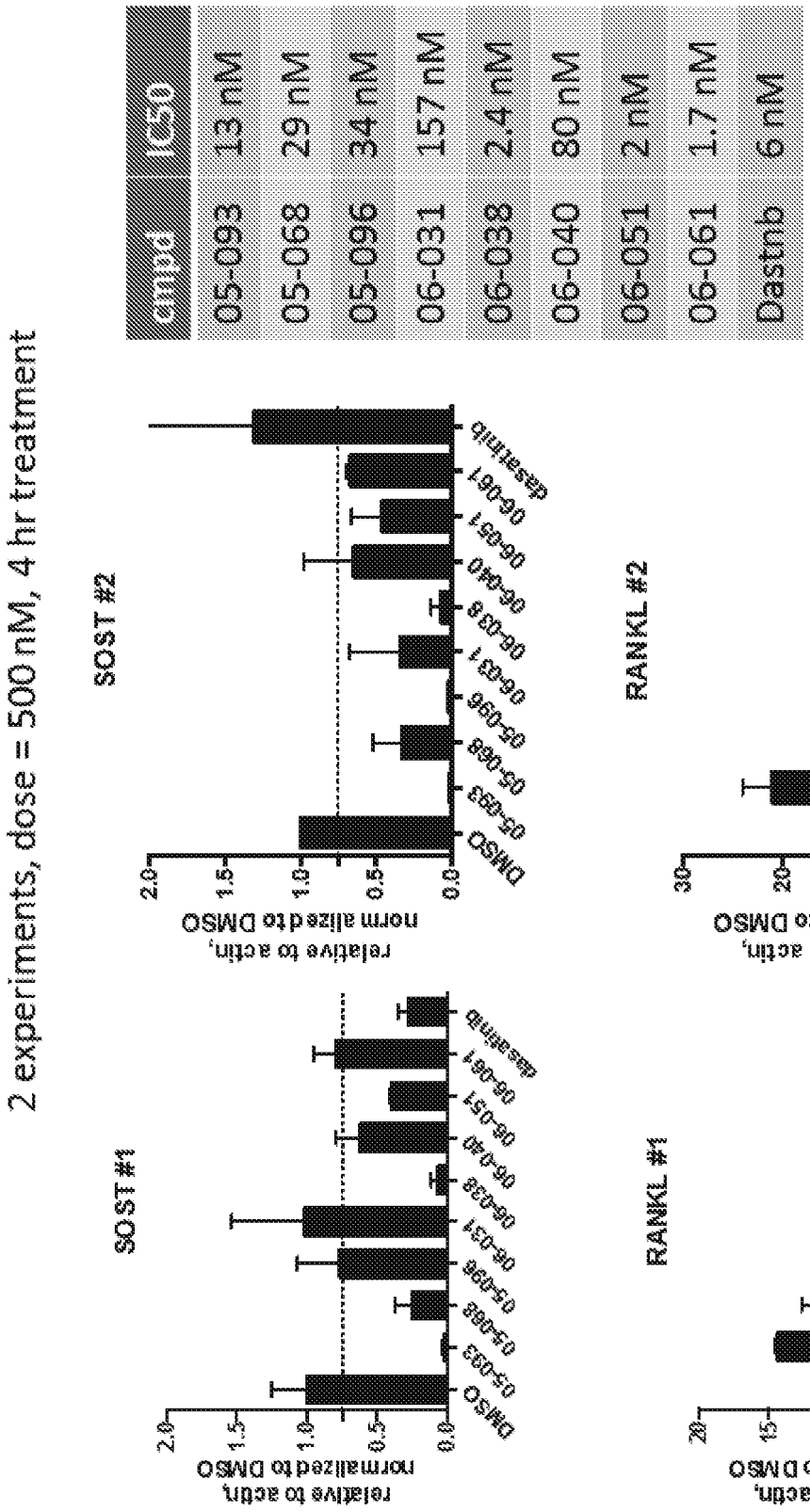


Figure 22A

cmpd	IC50
05-093	13 nM
05-068	29 nM
05-096	34 nM
06-031	157 nM
06-038	2.4 nM
06-040	80 nM
06-051	2 nM
06-061	1.7 nM
Dastnb	6 nM

In vitro IC50 SIK2 data

Figure 22B

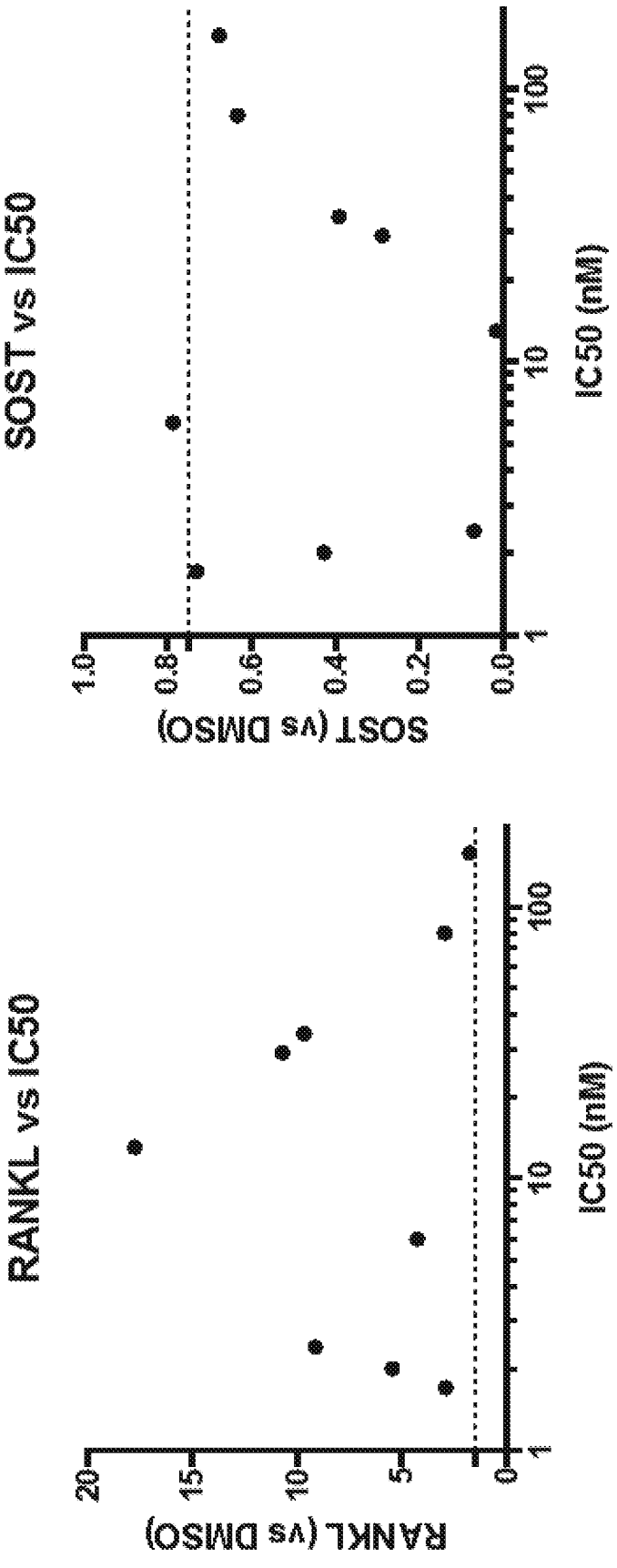

SOST vs IC50
SOST (vs DMSO)
1.0
0.8
0.6
0.4
0.2
0.0
1
10
100
IC50 (nM)
RANKL vs IC50
RANKL (vs DMSO)
20
15
10
5
0
1
10
100
IC50 (nM)

Figure 23

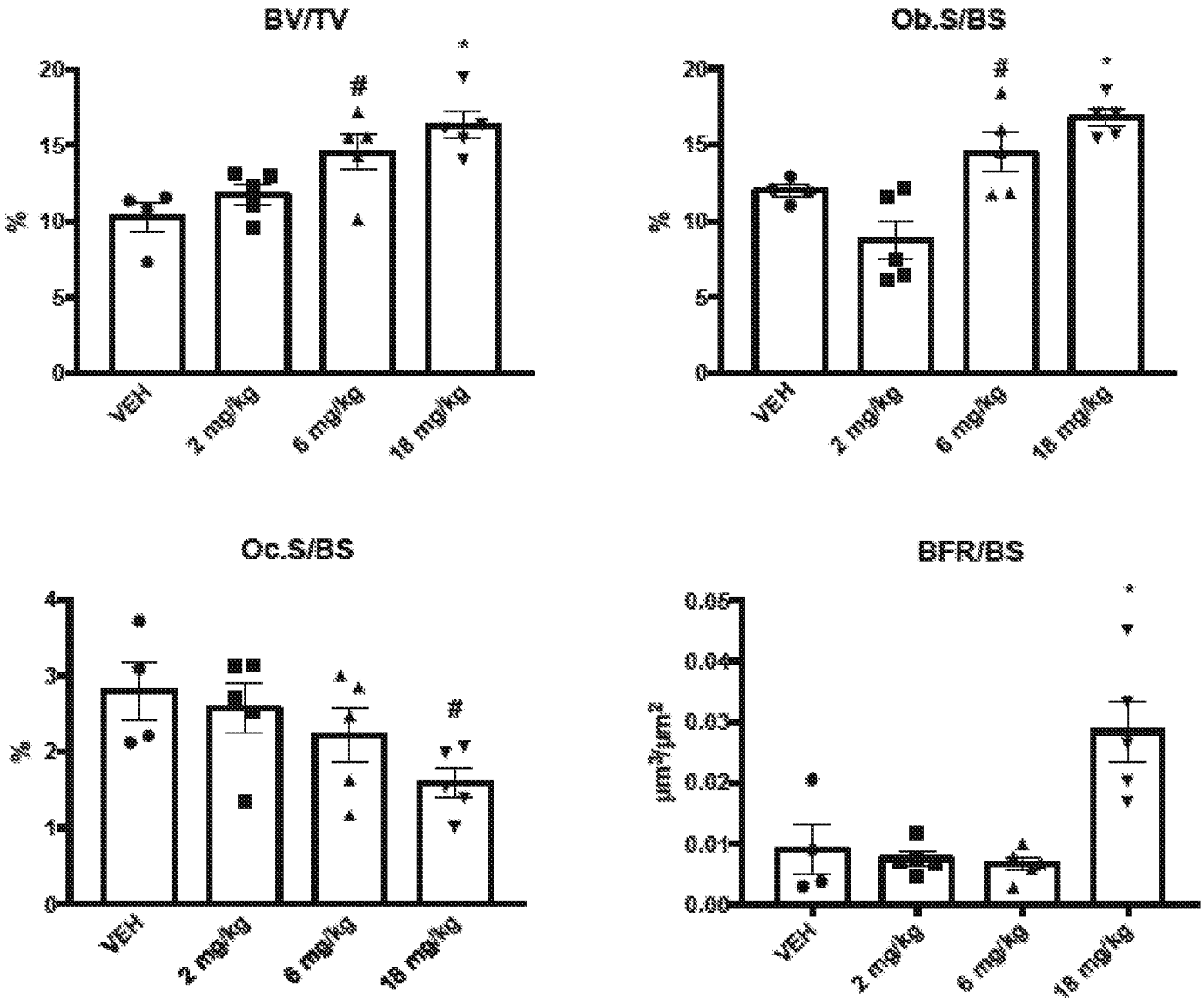
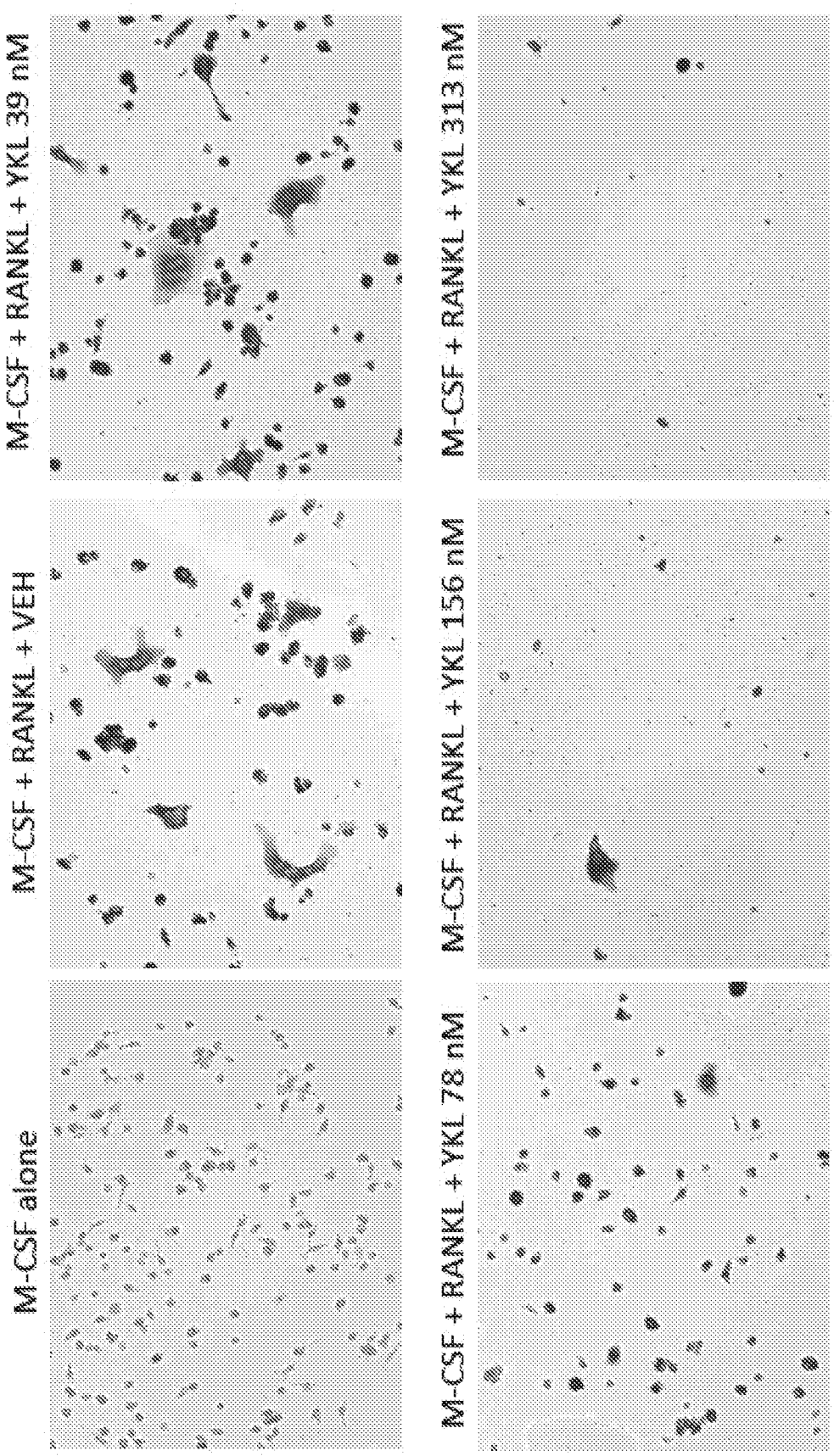

BV/TV
%
20
15
10
5
0
VEH
2 mg/kg
6 mg/kg
18 mg/kg
Ob.S/BS
%
Oc.S/BS
%
4
3
2
1
0
BFR/BS
µm²/µm²
0.05
0.04
0.03
0.02
0.01
0.00

Figure 24



Bone marrow macrophages
Purple = TRAP (osteoclast marker) stain

Figure 25

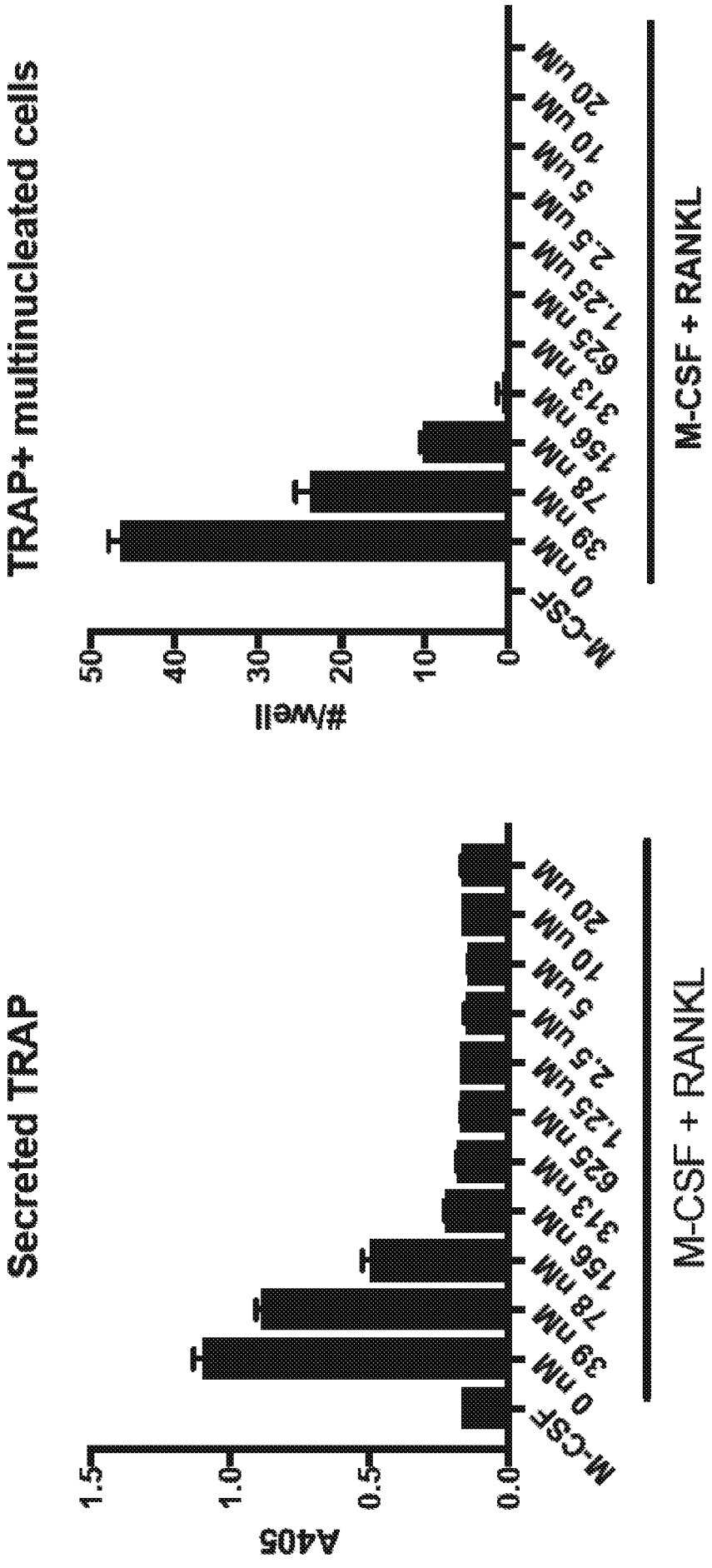

TRAP+ multinucleated cells
#/well
0
10
20
30
40
50
M-CSF
0 nM
39 nM
78 nM
156 nM
313 nM
625 nM
1.25 uM
2.5 uM
5 uM
10 uM
20 uM
M-CSF + RANKL
Secreted TRAP
A405
0.0
0.5
1.0
1.5
M-CSF
0 nM
39 nM
78 nM
156 nM
313 nM
625 nM
1.25 uM
2.5 uM
5 uM
10 uM
20 uM
M-CSF + RANKL

Figure 26

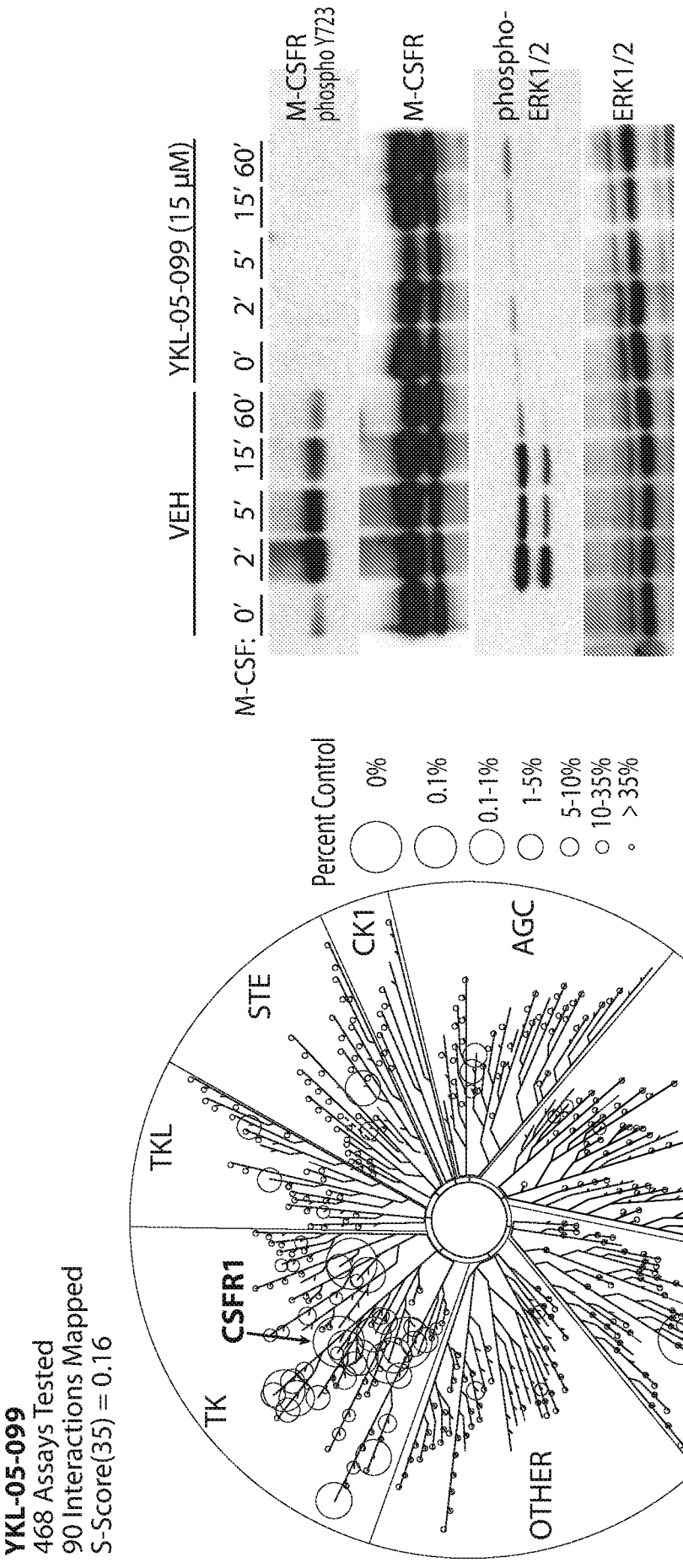

YKL-05-099
468 Assays Tested
90 Interactions Mapped
S-Score(35) = 0.16
CSFR1
SIK2
TK
TKL
STE
CK1
AGC
CAMK
CMGC
OTHER
Percent Control
0%
0.1%
0.1-1%
1-5%
5-10%
10-35%
> 35%
M-CSF: 0′ 2′ 5′ 15′ 60′ 0′ 2′ 5′ 15′ 60′
VEH
YKL-05-099 (15 μM)
M-CSFR phospho Y723
M-CSFR
phospho-ERK1/2
ERK1/2

Figure 27

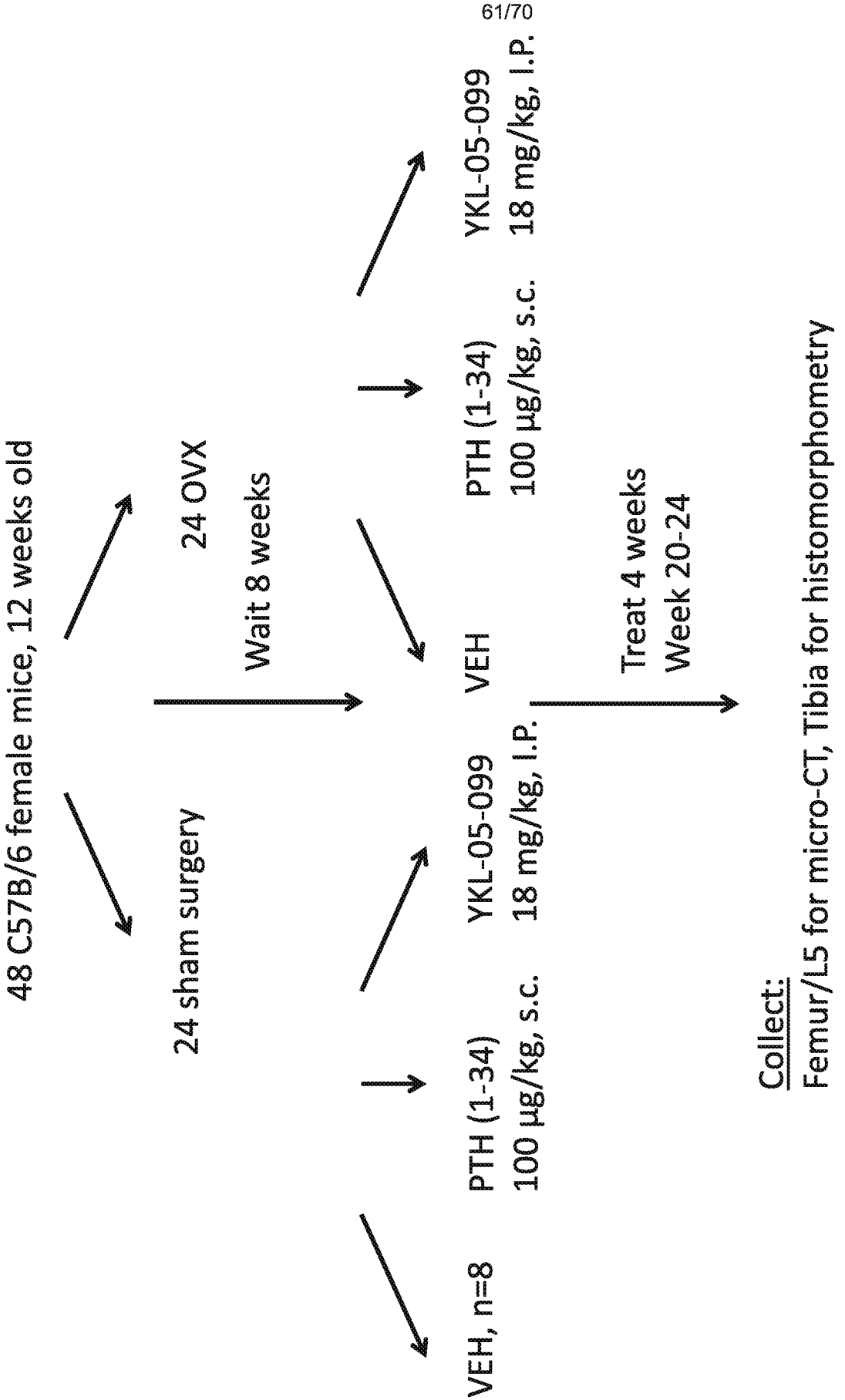

48 C57B/6 female mice, 12 weeks old
24 sham surgery
24 OVX
Wait 8 weeks
VEH, n=8
PTH (1-34)
100 µg/kg, s.c.
YKL-05-099
18 mg/kg, I.P.
VEH
PTH (1-34)
100 µg/kg, s.c.
YKL-05-099
18 mg/kg, I.P.
Treat 4 weeks
Week 20-24
Collect:
Femur/L5 for micro-CT, Tibia for histomorphometry
Femur for 3-point bending, Tibia for histology
Serum, whole blood
Solid organs

Figure 28

Femur, distal metaphysis µ-CT

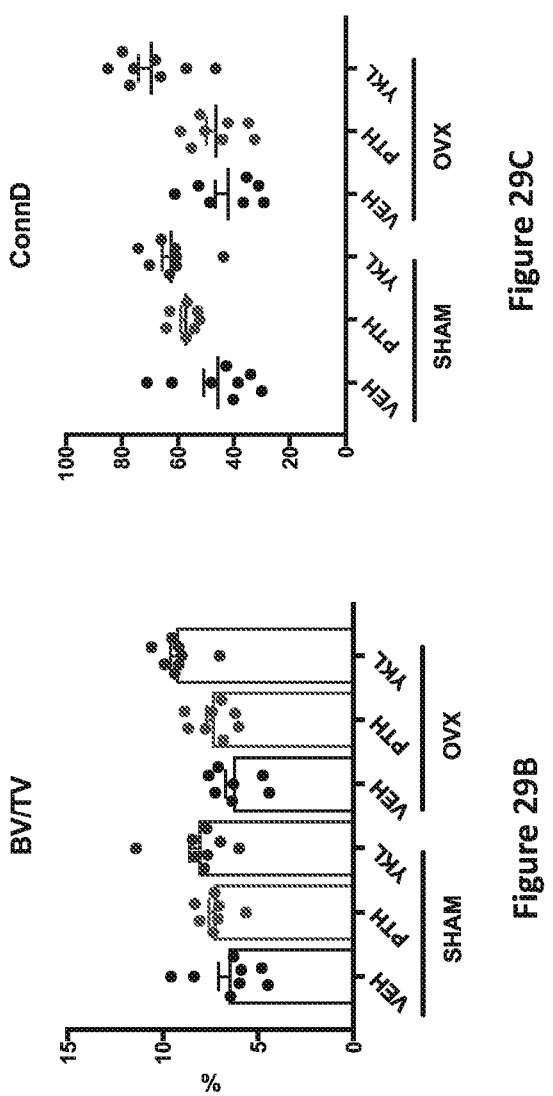


Figure 29A

Figure 29B

Figure 29C

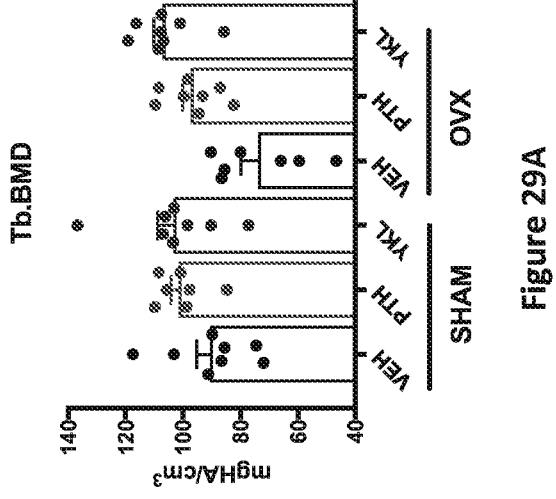


Figure 29D

Figure 29E

Figure 29F

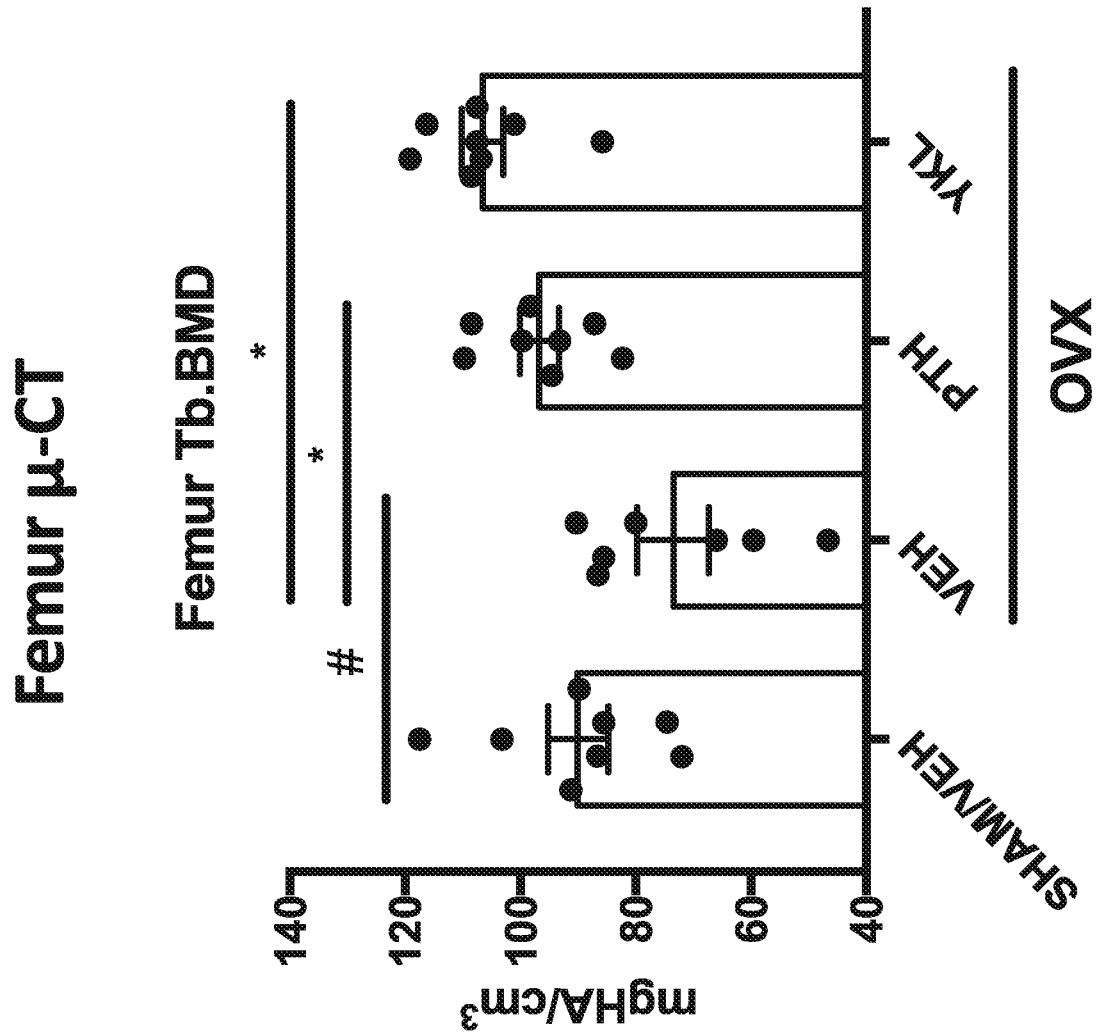

Femur µ-CT
Femur Tb.BMD
mgHA/cm3
140
120
100
80
60
40
SHAM/VEH
VEH
PTH
VKL
OVX
*
*
#

Figure 30

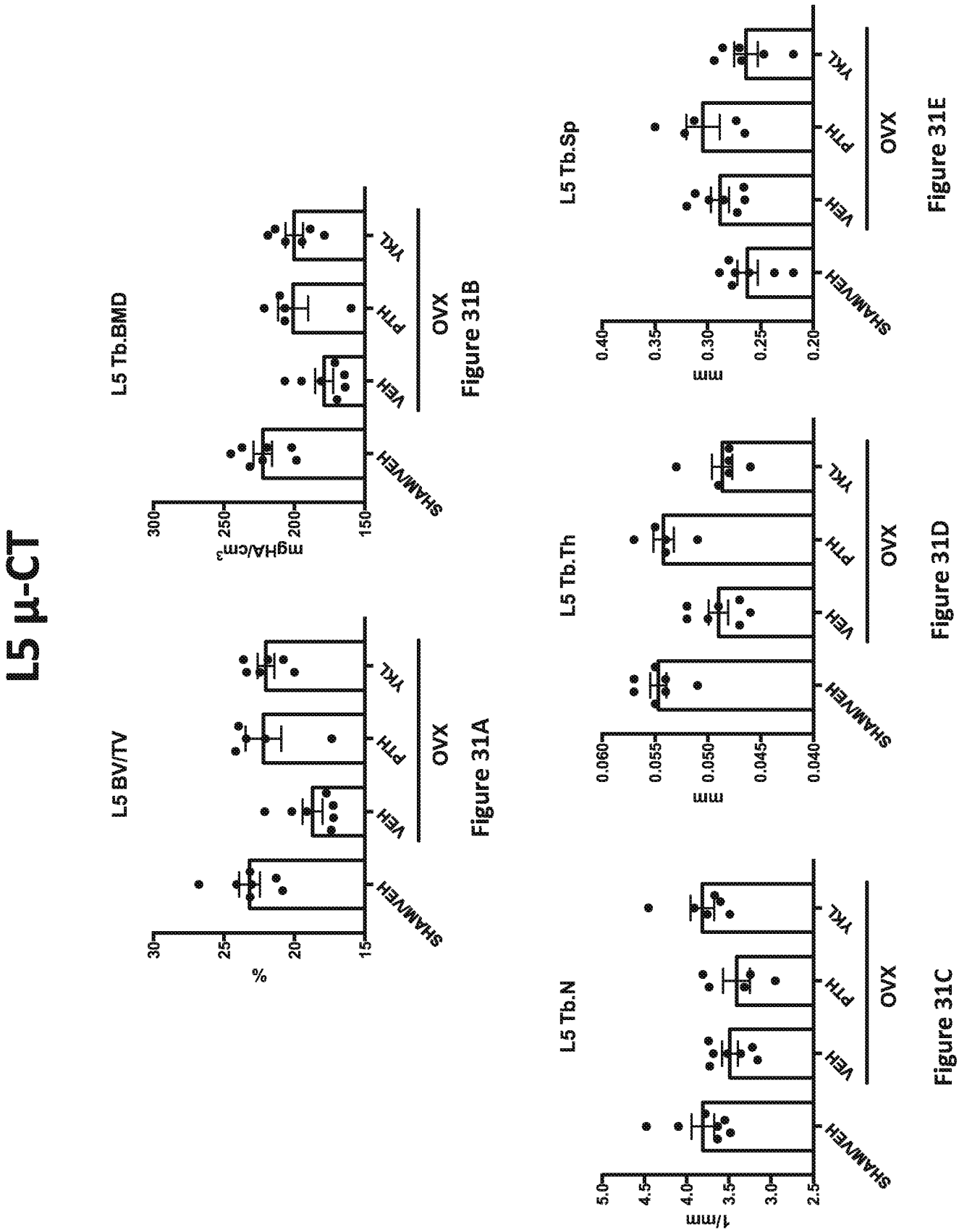


Figure 31A

Figure 31B

Figure 31C

Figure 31D

Figure 31E

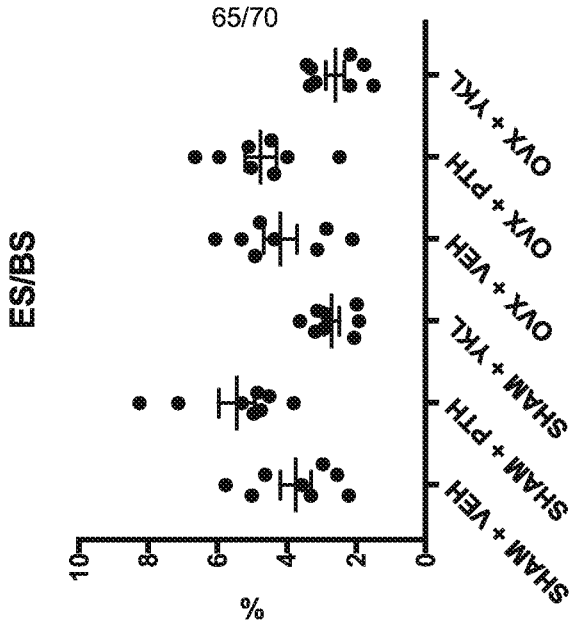


Figure 32C

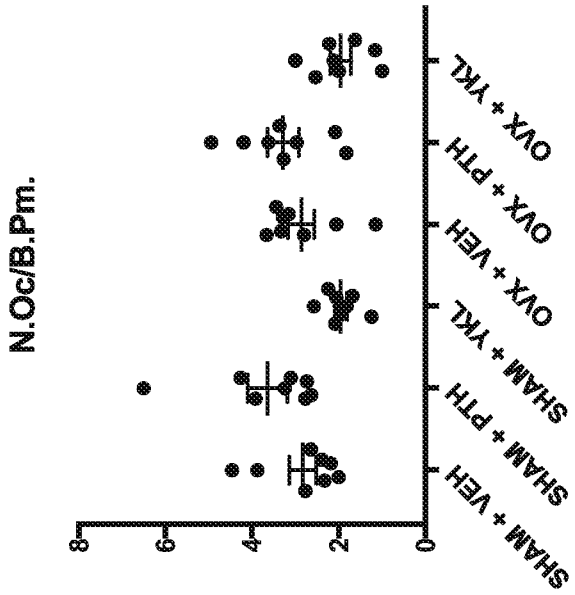


Figure 32B

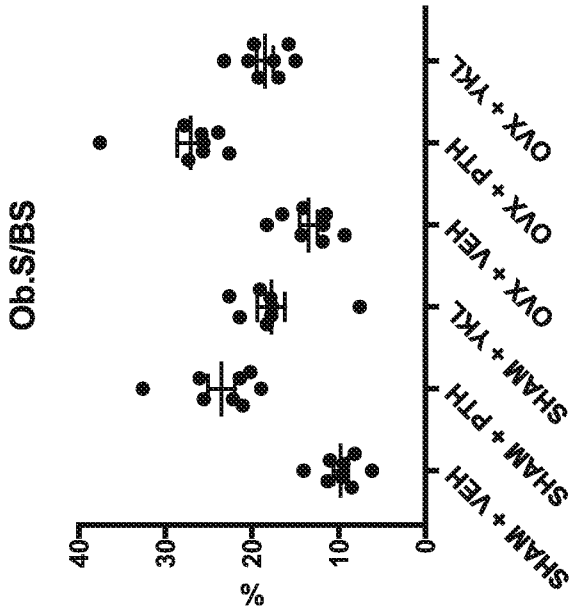


Figure 32A

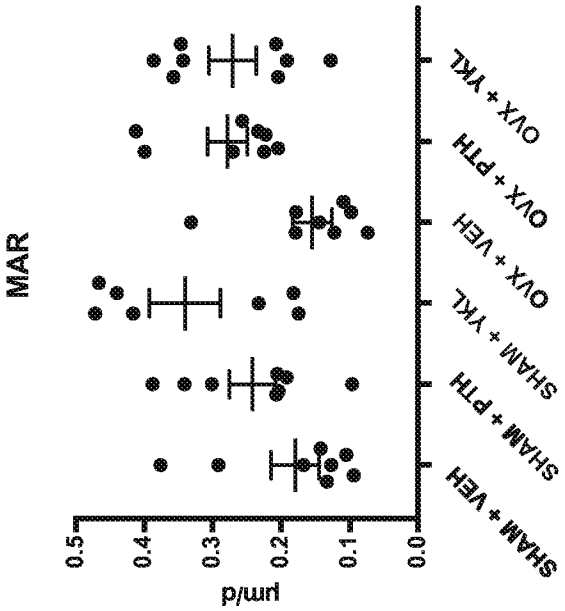


Figure 33B

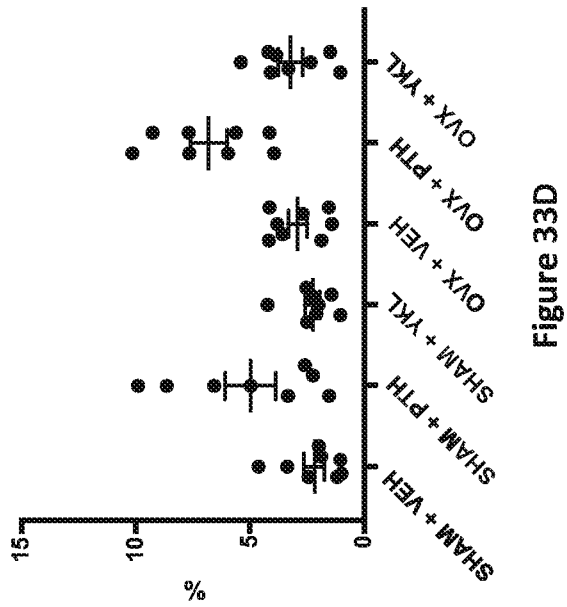


Figure 33D

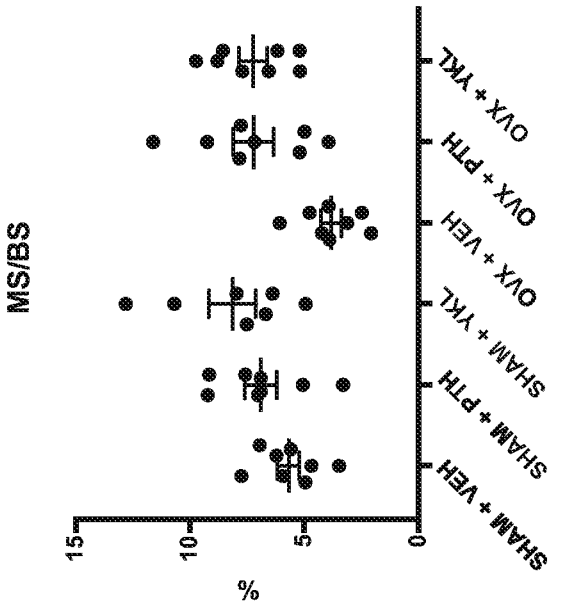


Figure 33A

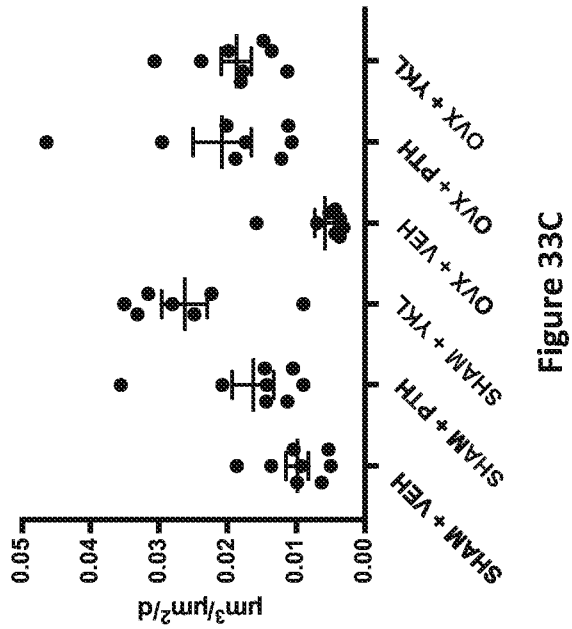


Figure 33C

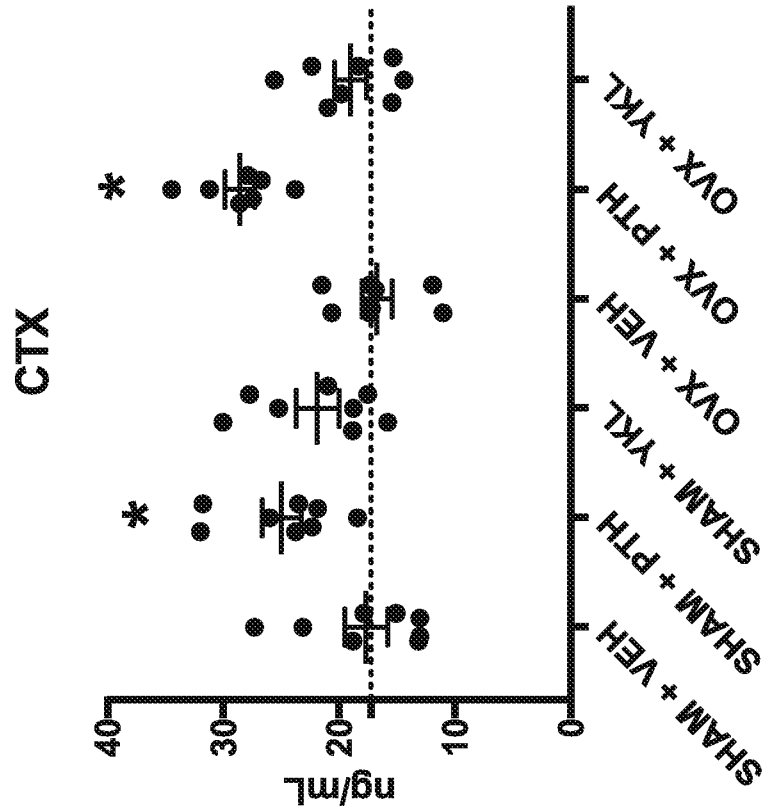


Figure 34B

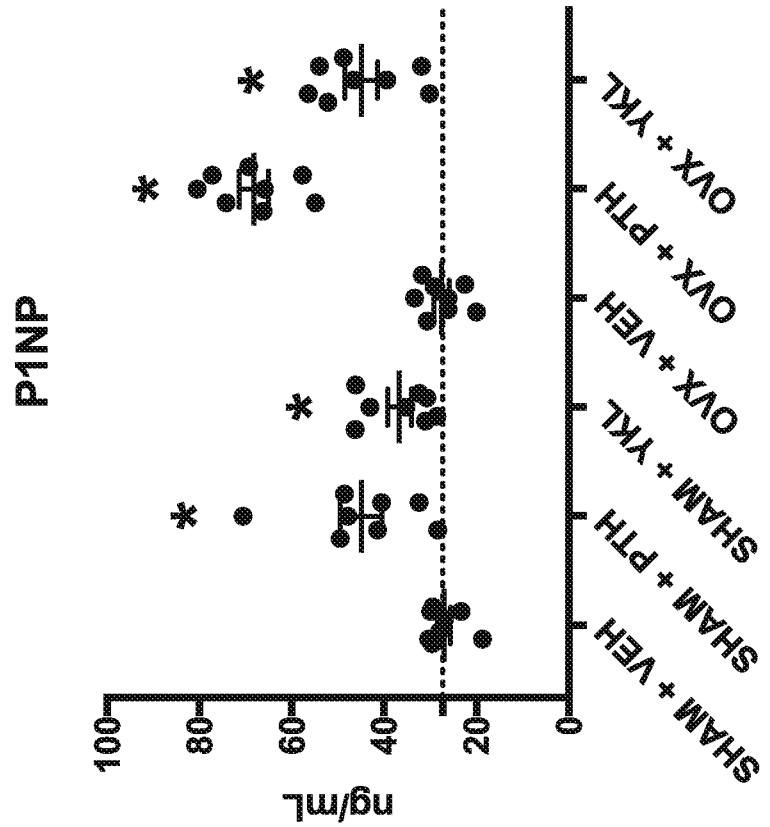


Figure 34A

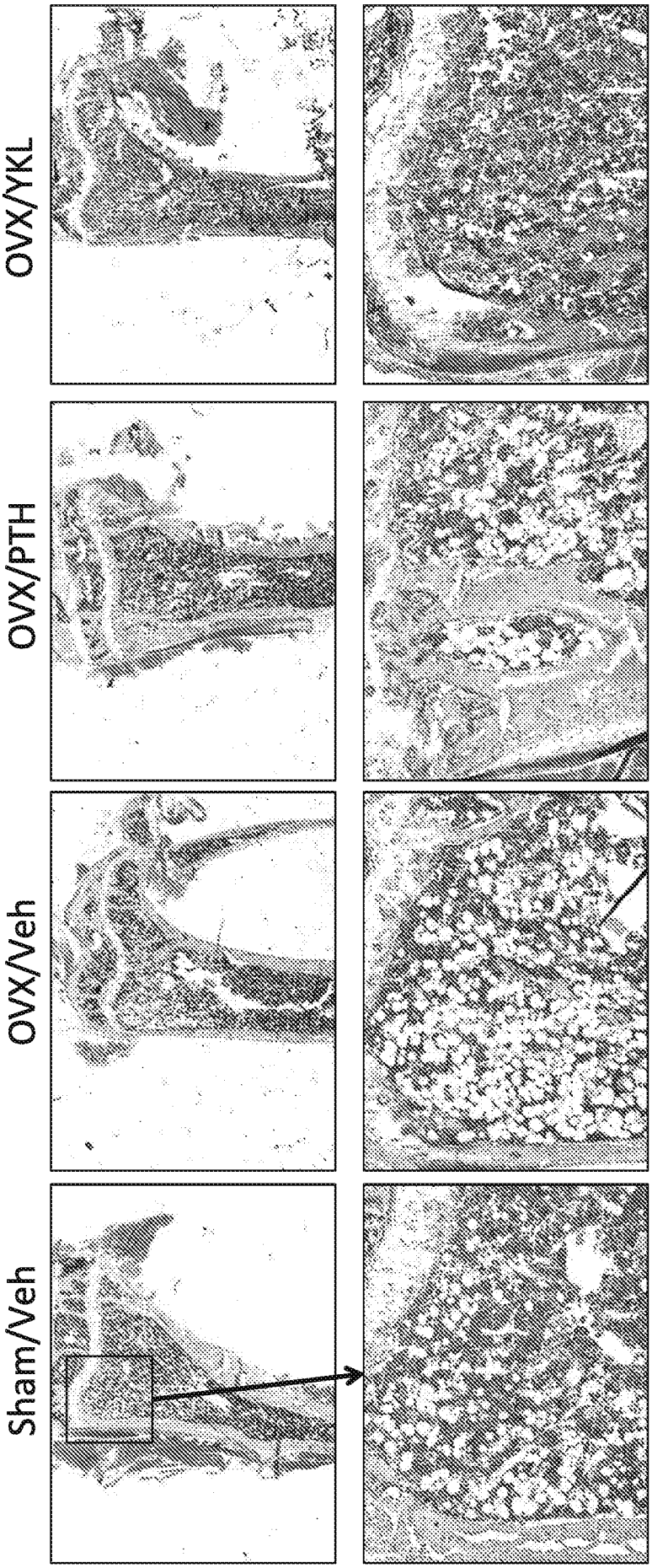


Figure 35

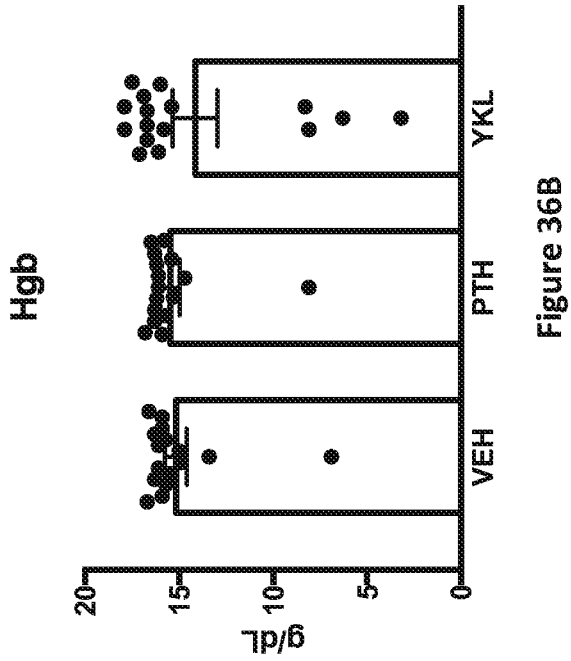


Figure 36B

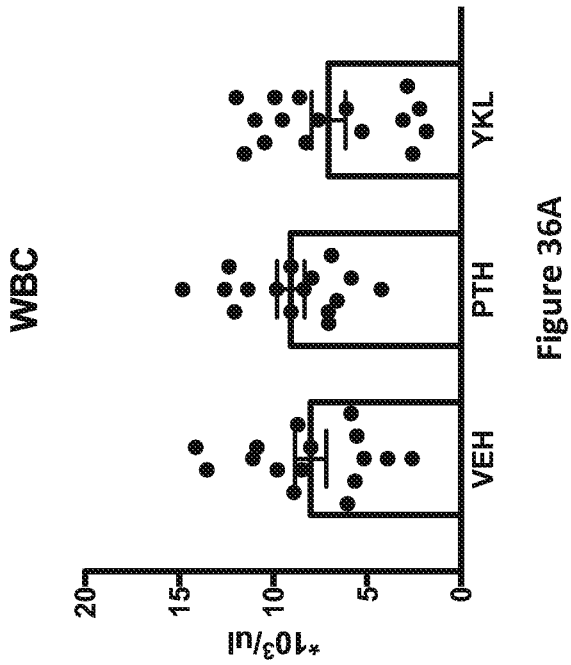


Figure 36A

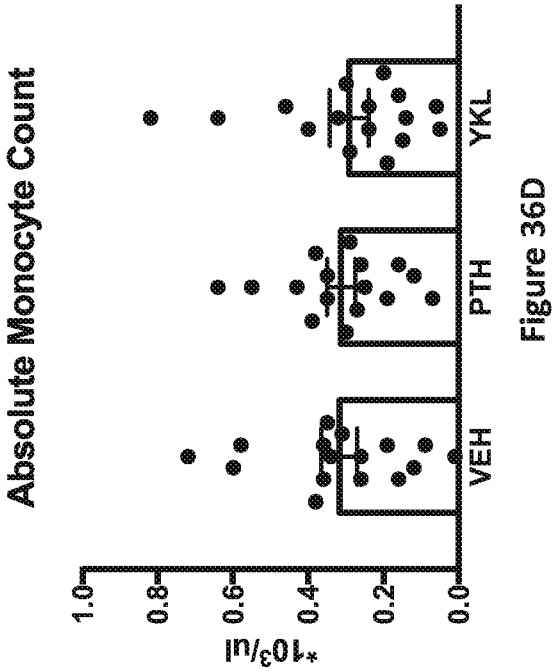


Figure 36D

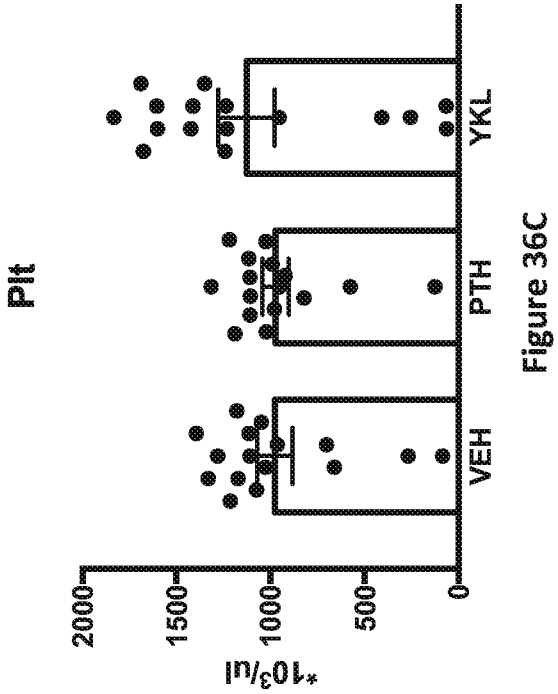


Figure 36C

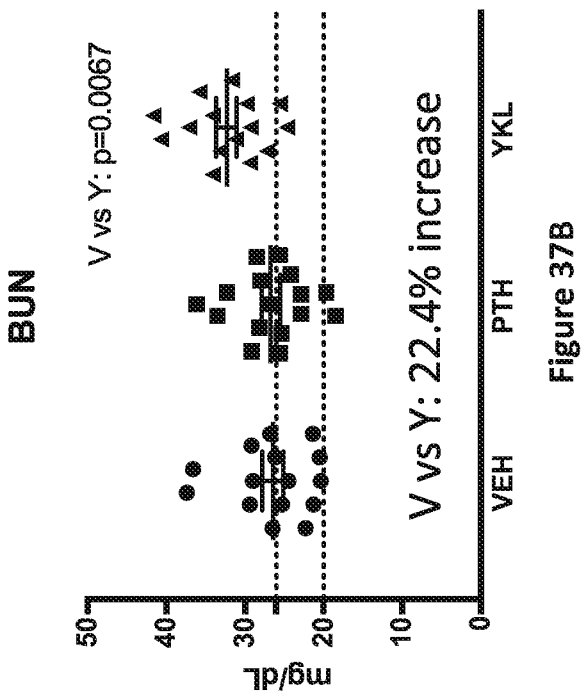


Figure 37B

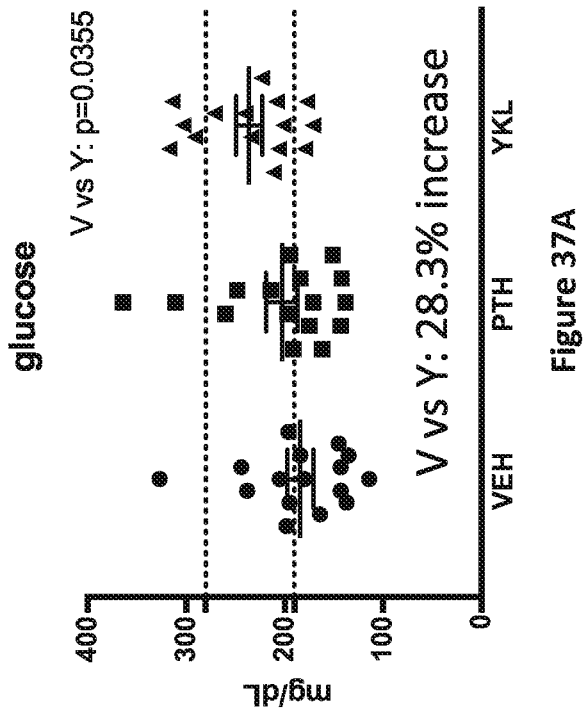


Figure 37A

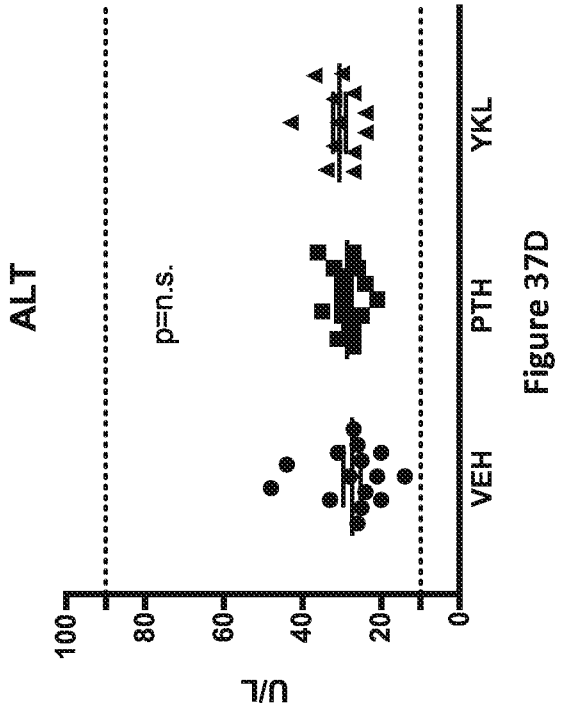


Figure 37D

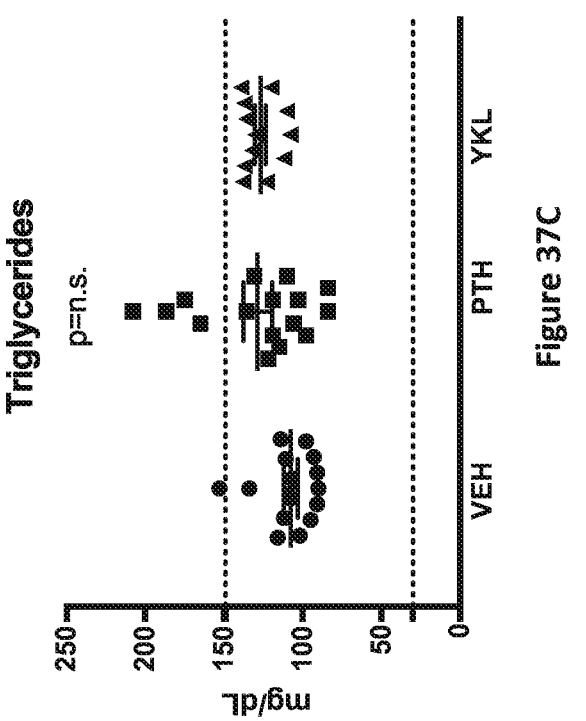


Figure 37C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2017/051937

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14, 15, 29-102
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2017/051937

A. CLASSIFICATION OF SUBJECT MATTER
A61K 31/5377 *(2006.01)*
A61K 31/519 *(2006.01)*
A61P 19/10 *(2006.01)*
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)

A61K 31/5377, 31/519, A61P 19/10, 19/00

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)

EAPO, RUPAT, PCT Online, DWPI, NCBI (PubMed), SpringerLink.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GALLAGHER JC et al. Prevention and treatment of postmenopausal osteoporosis. J Steroid Biochem Mol Biol., 2014 ul; 142: 155-70.doi: 10.1016/j.jsbmb.2013.09.008, pp. 1- 42, especially abstract, pp.16-19	1-13, 18-28
Y	WO 2014/140313 A1 (ONCODESIGN S.A) 18.09.2014, abstract, p.l, p.34, line 14 - p. 39, line 2, claim 11	1-13, 16-28
Y	WO 2014/ 093383 A1 (ARRIEN PHARMACEUTICALS LLC) 19.06.2014, abstract, paragraphs [0001H0008], [00107] -[00 109], claims 1, 51	1-13, 18-28
Y	YAHARA Y. Pterosin B prevents chondrocyte hypertrophy and osteoarthritis in mice by inhibiting Sik3. Nat Commun., 2016 Mar 24; 7:10959. doi: 10. 1038/ncommsl0959, pp. 1-10, especially abstract, p.9, col. 1, paragraph 3	1-13, 18-28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principte or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2017 (20. 12.2017)	28 December 2017 (28. 12.2017)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	Authorized officer N.Chudina Telephone No. 495 531 65 15

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2017/05 1937

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GARCIA-GOMEZ A. Dasatinib as a bone-modifying agent: anabolic and anti-resorptive effects. PLoS One, 2012;7(4):e34914. doi: 10. 1371/journal.pone.0034914. Epub 2012 Apr 2, abstract, PMID: 22539950	16
Y	MANTHEY CL et al. JNJ-28312141, a novel orally active colony-stimulating factor-1 receptor/FMS -related receptor tyrosine kinase-3 receptor tyrosine kinase inhibitor with potential utility in solid tumors, bone metastases, and acute myeloid leukemia. Mol Cancer Ther. 2009 Nov; 8(1 1):3 151-3 161 . doi: 10.1 158/1535-7163.MCT-09-0255. Epub 2009 Nov 3, abstract, PMID:19887542	17