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(56) Related Art
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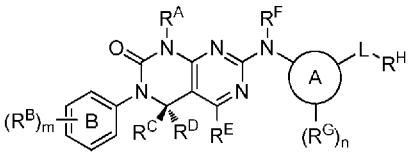
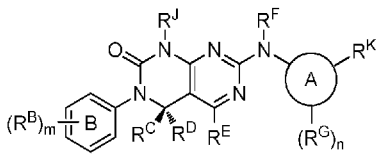
(54) Title: BICYCLIC UREA KINASE INHIBITORS AND USES THEREOF



(I)



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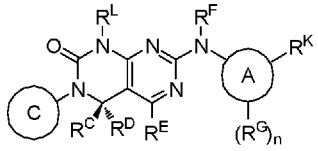

(III)

(57) Abstract: The present disclosure provides compounds of Formula (I), (II), and (III). The provided compounds are able to bind protein kinases (*e.g.*, SIK) and may be useful in modulating (*e.g.*, inhibiting) the activity of a protein kinase (*e.g.*, SIK, (*e.g.*, SIK1, SIK2, or SIK3)) in a subject or cell. The provided compounds may be useful in treating or preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. Also provided are pharmaceutical compositions, kits, methods, and uses that include or involve a compound described herein.

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[Continued on next page]

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BICYCLIC UREA KINASE INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] The present invention claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/358,524, filed July 5, 2016, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] A protein kinase inhibitor is an enzyme inhibitor that blocks the action of a protein kinase. A protein kinase is an enzyme that adds a phosphate group to a protein or other organic molecule. Phosphorylation is involved in a wide range of diseases, such as diseases associated with aberrant activity (*e.g.*, increased activity) of a protein kinase (*e.g.*, a salt-inducible kinase (SIK), *e.g.*, SIK1, SIK2 or SIK3). SIK's (*e.g.*, SIK1, SIK2 or SIK3) are serine/threonine kinases in the adenosine monophosphate-activated protein kinase (AMPK) family. (*See* 1-4).

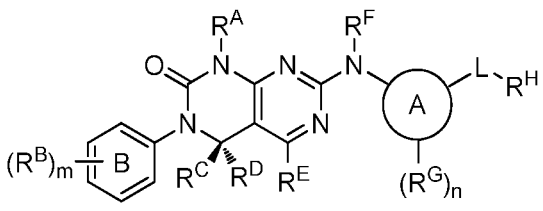
[0003] Exemplary protein kinase-related diseases include, but are not limited to, proliferative diseases (*e.g.*, cancers, benign neoplasms, pathological angiogenesis, inflammatory diseases, and autoimmune diseases) and musculoskeletal diseases. Inhibiting protein kinases, and therefore the phosphorylation of a substrate protein, has been shown to be useful in treating these diseases. For example, afatinib, an ErbB inhibitor, is useful in treating non-small cell lung cancer; axitinib, a VEGFR, PDGFR, and c-KIT inhibitor, is useful in treating renal cell carcinoma; bosutinib, a Bcr-Abl inhibitor, is useful in treating chronic myelogenous leukemia; cabozantinib, a c-Met and VEGFR2 inhibitor, is useful in treating thyroid cancer; crizotinib, an ALK, HGFR, and c-MET inhibitor, is useful in treating non-small cell lung cancer; dasatinib, a Bcr-Abl, Src, and c-KIT inhibitor, is useful in treating chronic myelogenous leukemia; erlotinib, an EGFR inhibitor, is useful in treating non-small cell lung cancer and pancreatic cancer; gefitinib, an EGFR inhibitor, is useful in treating non-small cell lung cancer; imatinib, a Bcr-Abl inhibitor, is useful in treating chronic myelogenous leukemia; lapatinib, a HER2 inhibitor, is useful in treating breast cancer; nilotinib, a Bcr-Abl inhibitor, is useful in treating chronic myelogenous leukemia; pazopanib, a VEGFR, PDGFR, and c-KIT inhibitor, is useful in treating renal cell carcinoma and soft tissue sarcoma; ponatinib, a Bcr-Abl, BEGFR, PDGFR, FGFR, EPH, SRC, c-KIT, RET, TIE2, and FLT3 inhibitor, is useful in treating

chronic myelogenous leukemia and acute lymphoblastic leukemia; regorafenib, a RET, VEGFR, and PDGFR inhibitor, is useful in treating colorectal cancer and gastrointestinal stromal tumor; ruxolitinib, a JAK inhibitor, is useful in treating myelofibrosis; sorafenib, a VEGFR, PDGFR, BRAF, and c-KIT inhibitor, is useful in treating renal cell carcinoma and hepatocellular carcinoma; sunitinib, a VEGFR and PDGFR inhibitor, is useful in treating renal cell carcinoma, gastrointestinal stromal tumor, and pancreatic neuroendocrine tumor; tofacitinib, a JAK inhibitor, is useful in treating rheumatoid arthritis; vandetanib, a VEGFR, EGFR, RET and BRK inhibitor, is useful in treating thyroid cancer; and vemurafenib, a BRAF inhibitor, is useful in treating malignant melanoma. There remains a need for protein kinase inhibitors, including inhibitors of SIK (*e.g.*, inhibitors of SIK1, SIK2 or SIK3), for improved treatment of diseases associated with the activity of protein kinases (*e.g.*, cancers, benign neoplasms, pathological angiogenesis, inflammatory diseases, and autoimmune diseases) and musculoskeletal diseases.

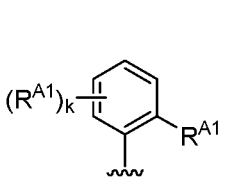
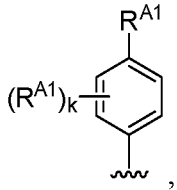
SUMMARY OF THE INVENTION

[0004] Described herein are bicyclic compounds of Formula (**I**), (**II**), and (**III**). The compounds described herein bind protein kinases and therefore may be useful in modulating (*e.g.*, inhibiting) the activity of a protein kinase (*e.g.*, a salt-inducible kinase (SIK)) in a subject or cell. The compounds may be useful in treating and/or preventing a disease or condition associated with kinase activity, *e.g.*, in treating and/or preventing a proliferative disease (*e.g.*, cancers, benign neoplasms, pathological angiogenesis, inflammatory diseases, and autoimmune diseases), musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder, in a subject in need thereof. Also provided are pharmaceutical compositions and kits including a compound described herein.

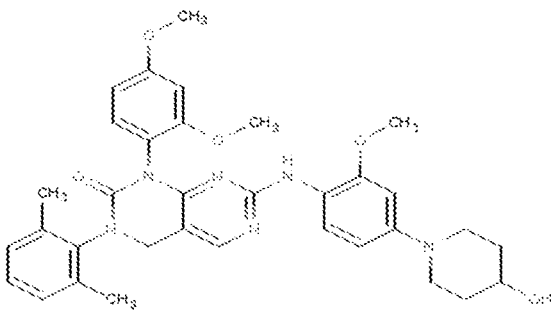
[0005] In one aspect, the present disclosure provides compounds of Formula (**I**):



(**I**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, Ring A, Ring B, m, n, and L are as defined herein. In Formula (**I**), R^A is substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  ,  , substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl. In Formula (**I**), 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(=O)–, –O–, –S–, –NR^b–, –N=, or =N–. In Formula (**I**), 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.

[0006] Exemplary compounds of Formula (**I**) include, but are not limited to:



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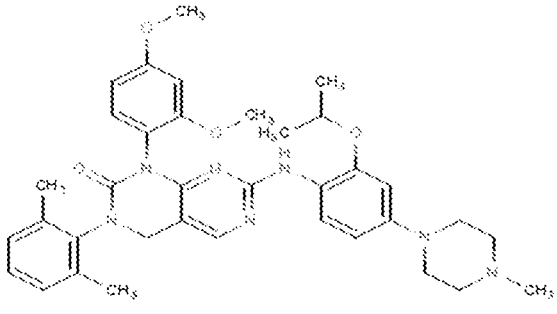

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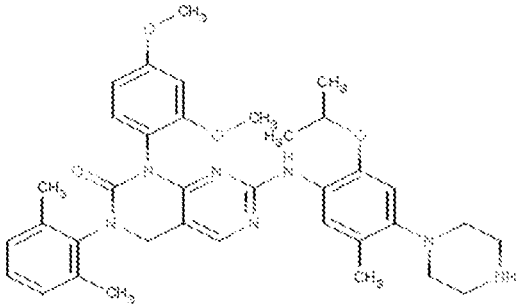

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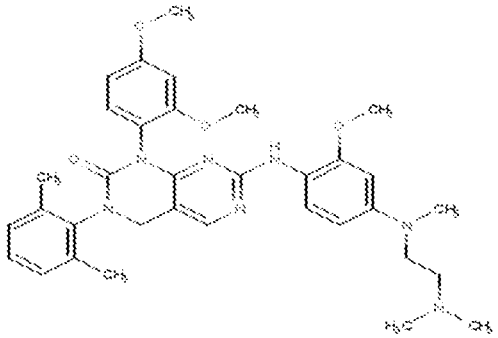

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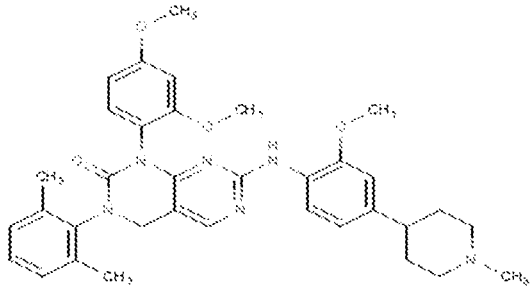

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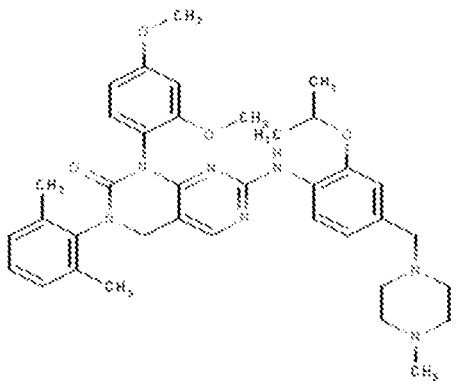

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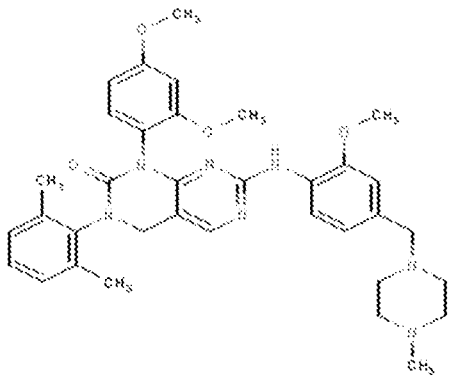

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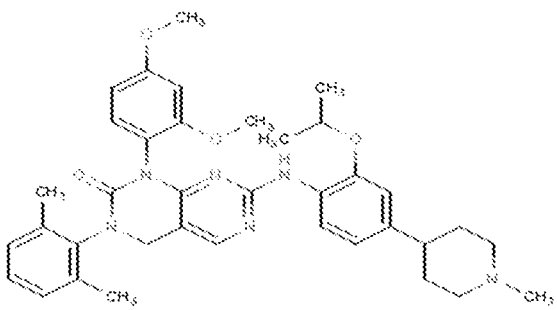

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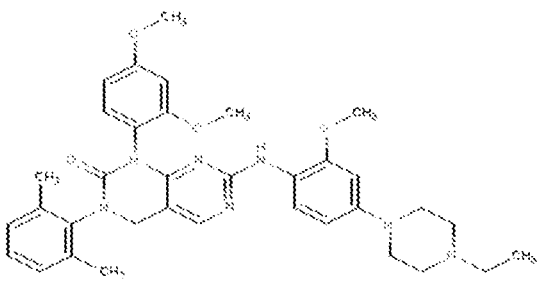

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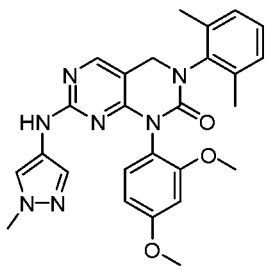

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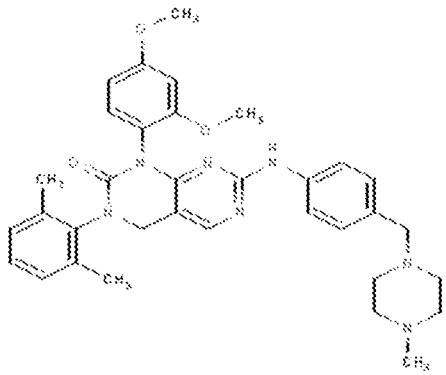

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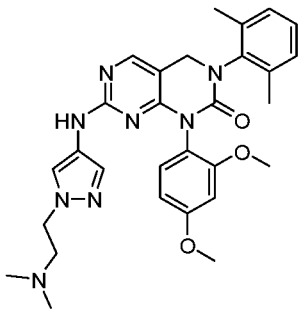

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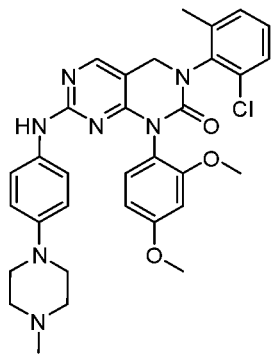

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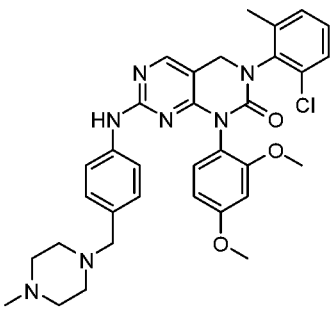

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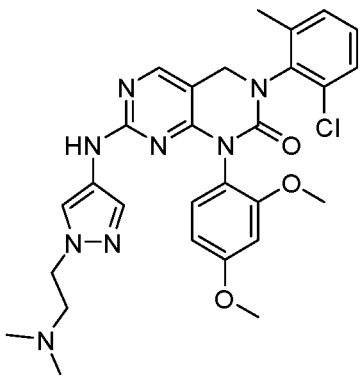

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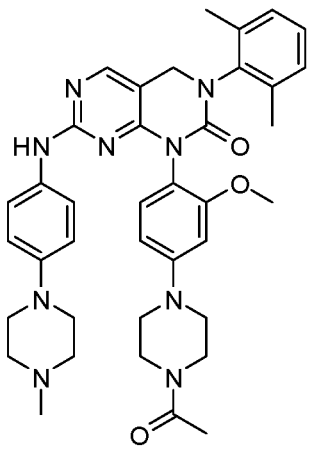

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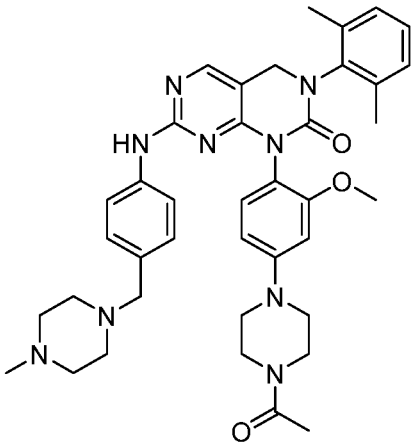

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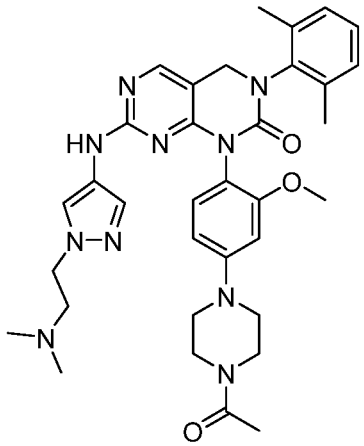

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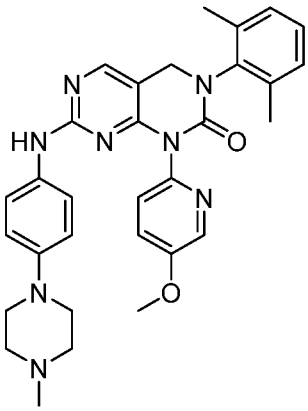

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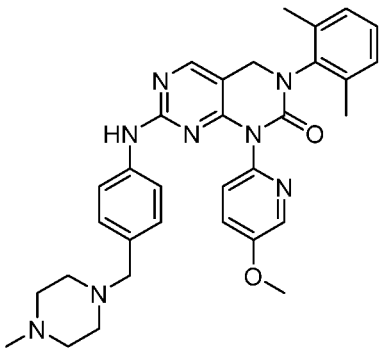

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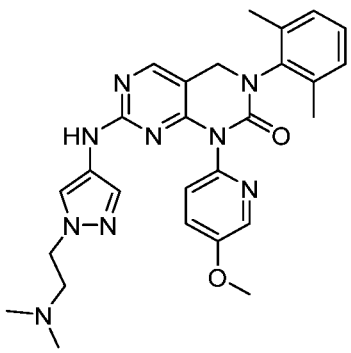

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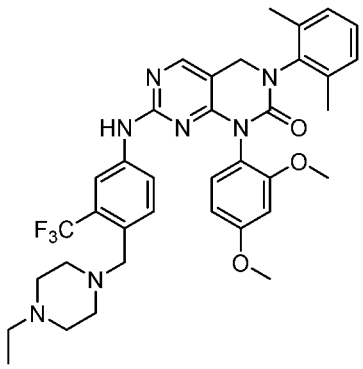

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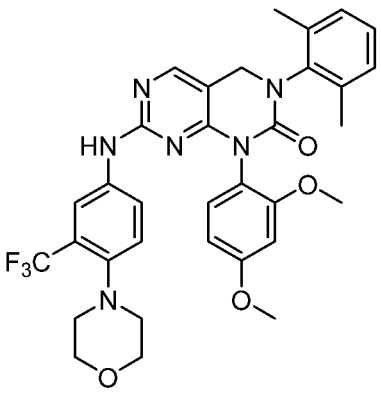

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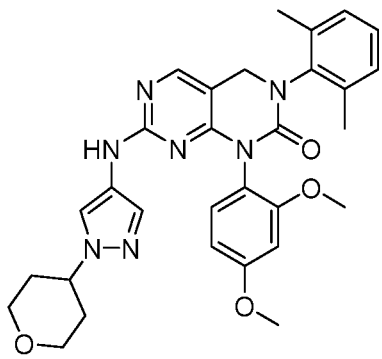

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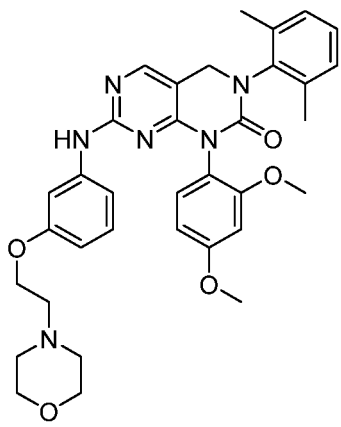

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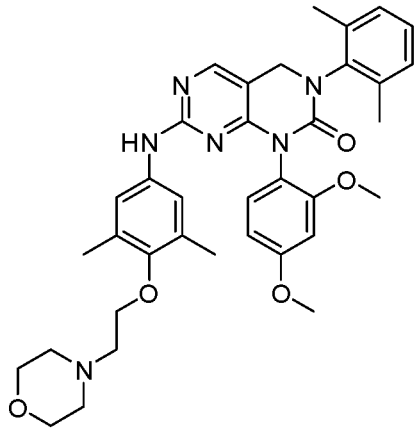

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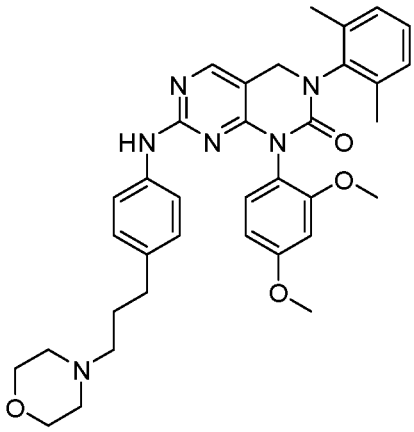

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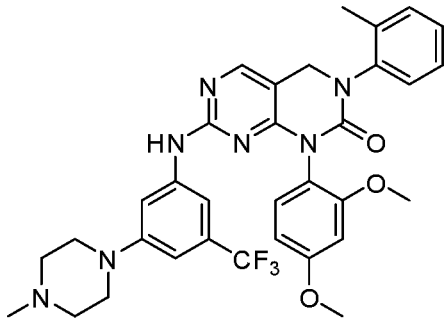

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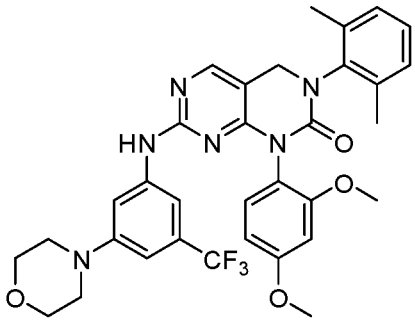

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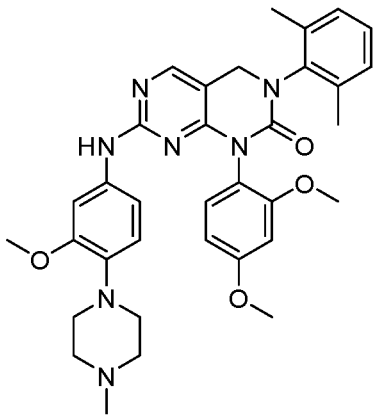

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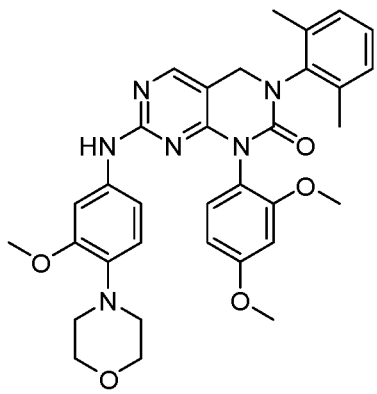

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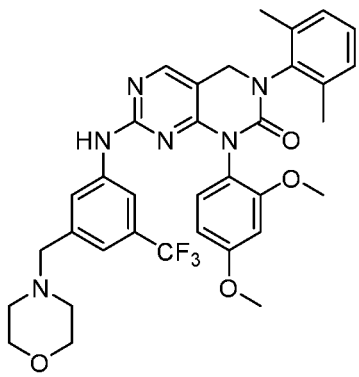
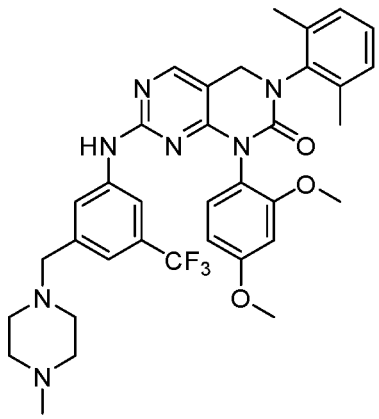
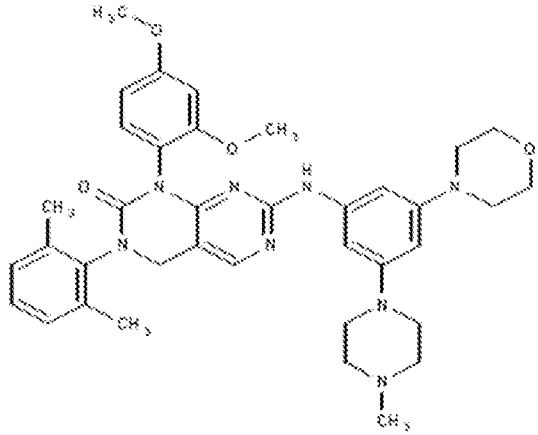


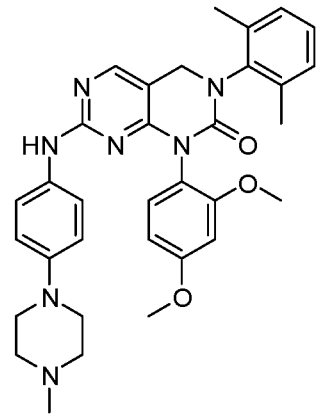
(YKL-04-118)



(YKL-04-125)



(HG-11-143-01)



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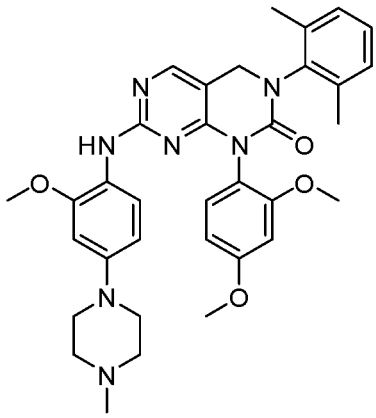
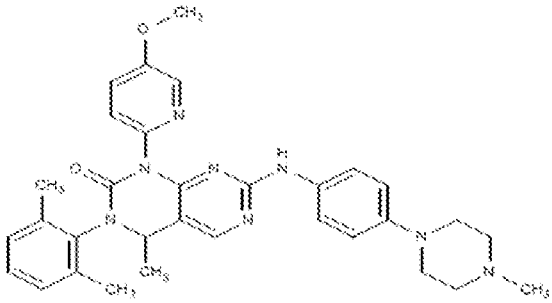
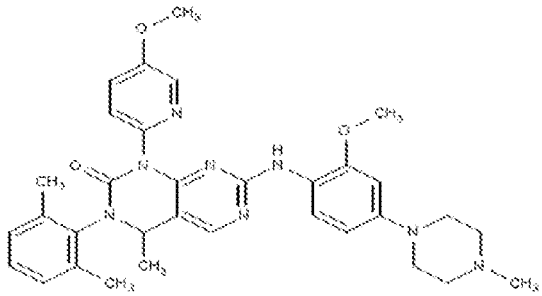


(HG-11-139-01)



(YKL-06-038)

(SB1-D-40)



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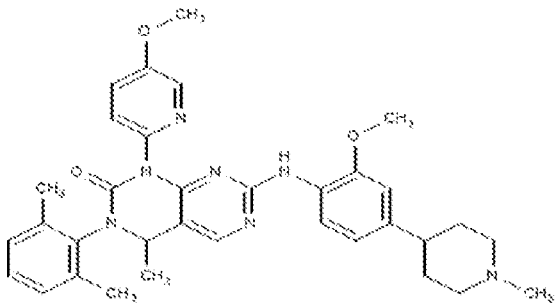

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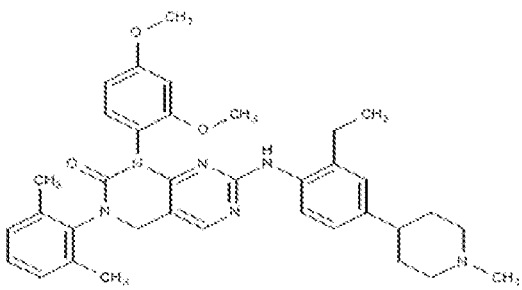

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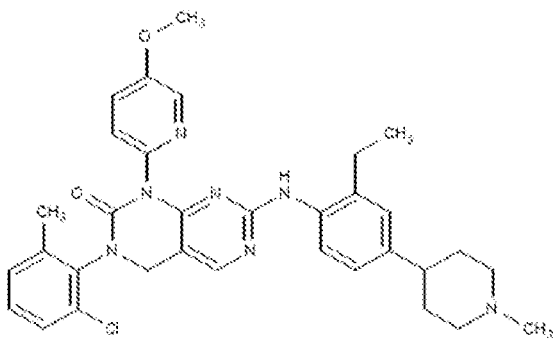

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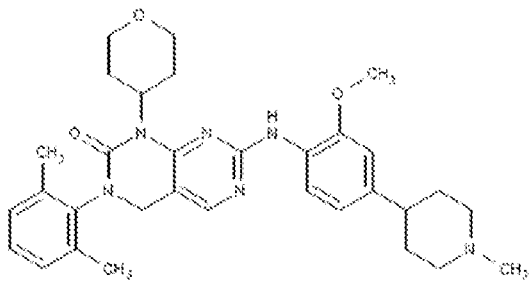
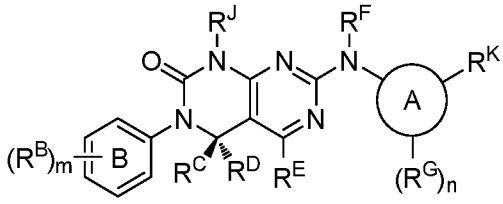


(YKL-06-051)

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

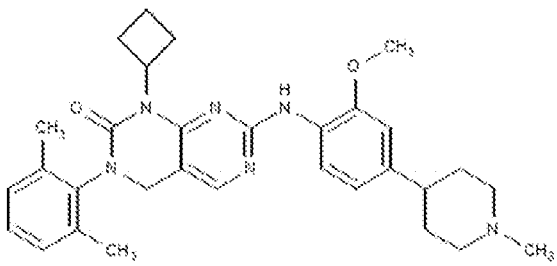
[0007] In some embodiments, the present invention provides compounds of Formula (**II**):



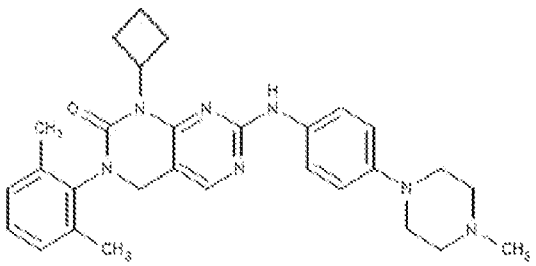
(**II**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^B, R^C, R^D, R^E, R^F, R^G, R^J, R^K, Ring A, Ring B, m, and n are as defined herein. In Formula (**II**), R^J is substituted or unsubstituted carbocyclyl. In Formula (**II**) and in Formula (**III**) below, 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.

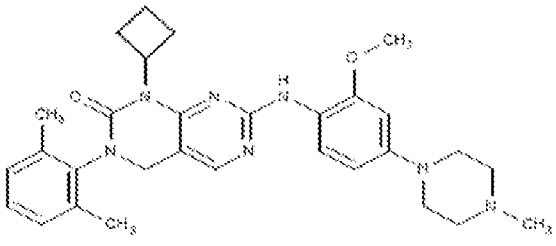
[0008] Exemplary compounds of Formula (**II**) include, but are not limited to:



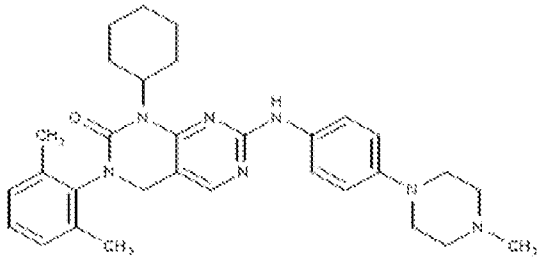
(YKL-06-050)



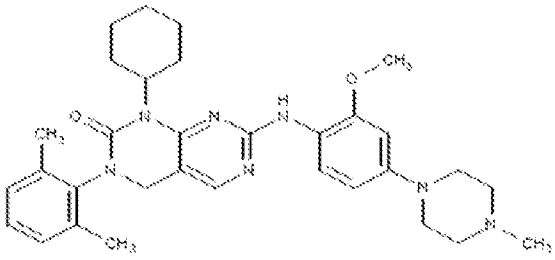
(YKL-06-060)



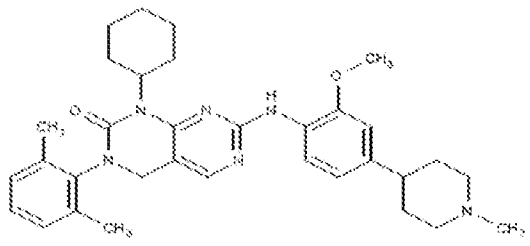
(YKL-06-061)



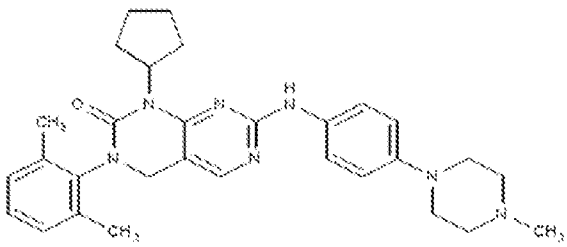
(YKL-06-062)



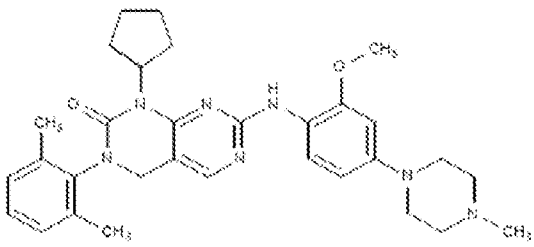
(YKL-06-063)



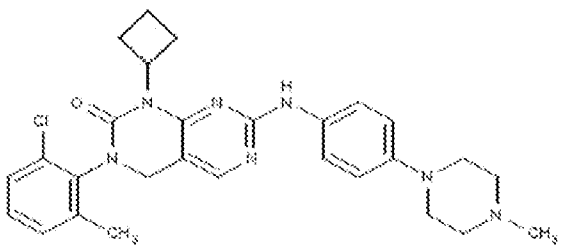
(YKL-06-064)



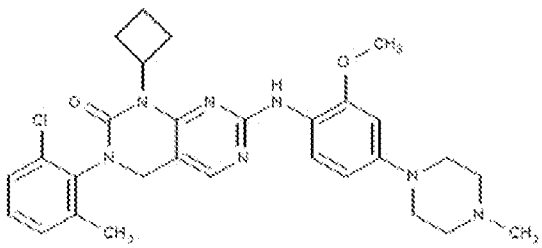
(YKL-06-075)



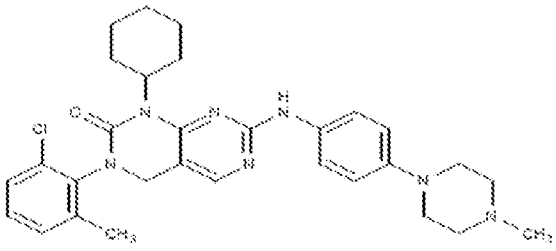
(YKL-06-076)

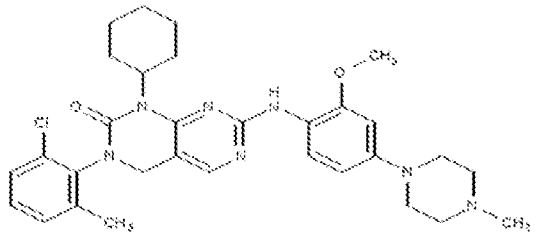


(YKL-06-088)



(YKL-06-089)



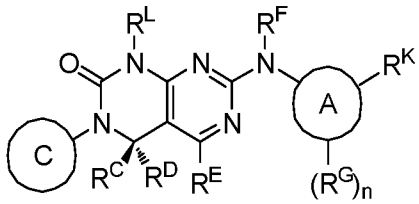


,

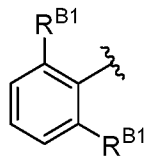
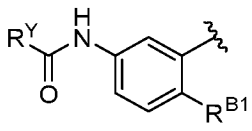
(YKL-06-090) (YKL-06-091)

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

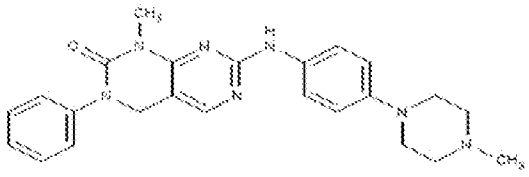
[0009] In some embodiments, the present invention provides compounds of Formula (**III**):



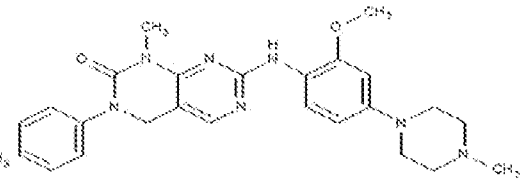
(**III**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^C, R^D, R^E, R^F, R^G, R^K, R^L, Ring A, Ring C, and n are as defined herein. In Formula (**III**), R^L is R^L is substituted or unsubstituted alkyl. In Formula (**III**), Ring C is unsubstituted phenyl or of the formula:  or  , wherein R^{B1} is as defined herein, and R^Y is substituted phenyl. In Formula (**II**) above and in Formula (**III**), 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.

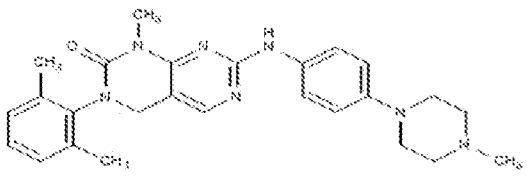
[0010] Exemplary compounds of Formula (**III**) include, but are not limited to:



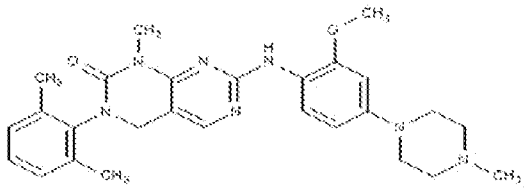
(HG-11-137-01)



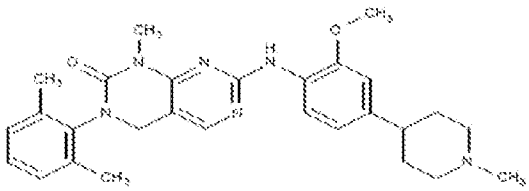
(HG-11-139-02)



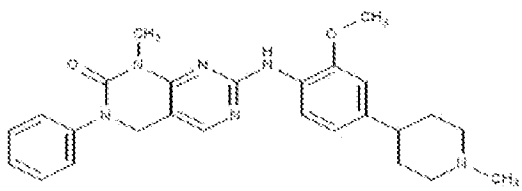
(YKL-06-029)



(YKL-06-030)



(YKL-06-031)



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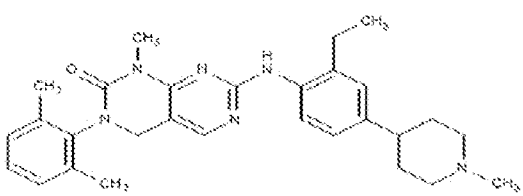
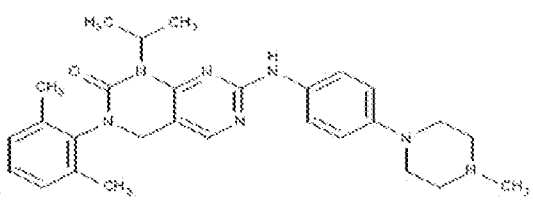
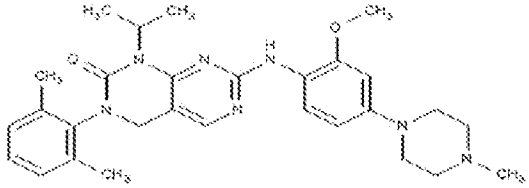


(YKL-06-046)



(YKL-06-058)



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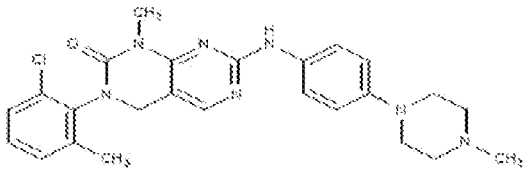
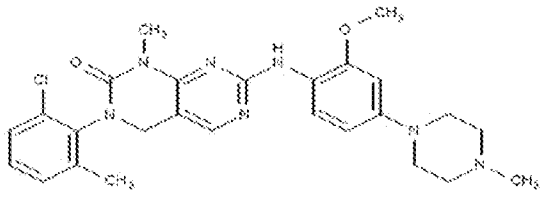
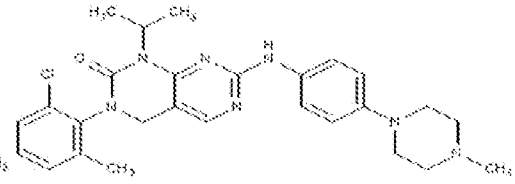


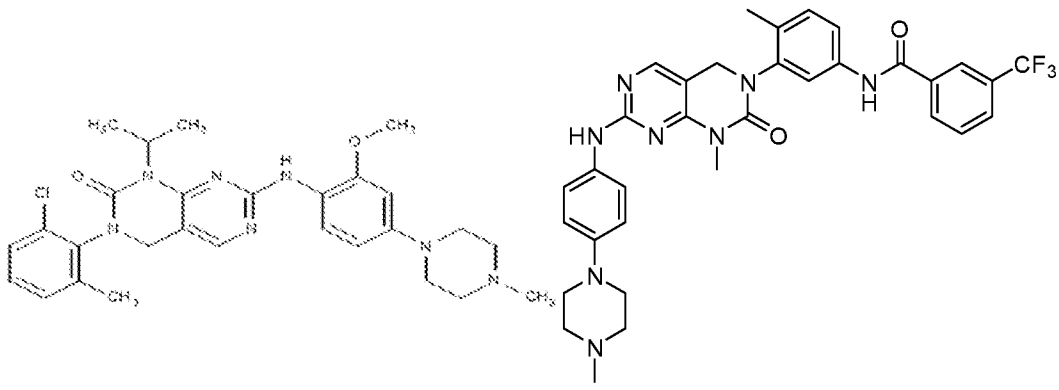
(YKL-06-084)



(YKL-06-085)

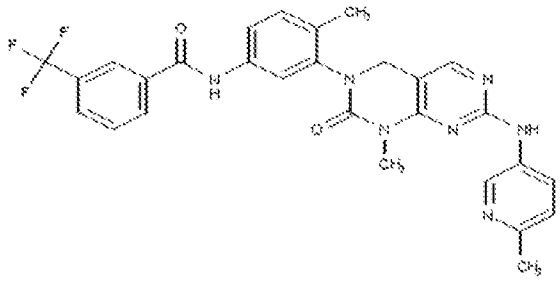


(YKL-06-086)



(YKL-06-087)

(HG-11-23-01)



(HG-4-34-01),

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

[0011] In another aspect, described herein are pharmaceutical compositions including a compound described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, a pharmaceutical composition described herein includes a therapeutically or prophylactically effective amount of a compound described herein. The pharmaceutical compositions may be useful in modulating (*e.g.*, inhibiting) the activity of a protein kinase in a subject or cell, in treating a disease (*e.g.*, a proliferative disease or a musculoskeletal disease) in a subject in need thereof, or in preventing a disease in a subject in need thereof. In certain embodiments, the compound being administered or used selectively inhibits the activity of a salt-inducible protein kinase (SIK). In certain embodiments, the compound selectively inhibits SIK1. In certain embodiments, the compound selectively inhibits SIK2. In certain embodiments, the compound selectively inhibits SIK3.

[0012] In certain embodiments, the subject being administered a compound or pharmaceutical composition described herein is a human. In certain embodiments, the subject being administered a compound or pharmaceutical composition described herein is a non-human animal. In certain embodiments, the protein kinase activity is modulated in a cell that is *in vitro*. In certain embodiments, protein kinase activity is modulated in a cell that is *in vivo*.

[0013] In certain embodiments, the disease is associated with aberrant (*e.g.*, increased) kinase activity. In certain embodiments, the disease is a proliferative disease (*e.g.*, cancer, benign neoplasm, pathological angiogenesis, inflammatory disease, or autoimmune disease), musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder.

[0014] In still another aspect, described herein are kits including a container with a compound or pharmaceutical composition described herein. A kit described herein may include a single dose or multiple doses of the compound or pharmaceutical composition. The described kits may be useful in inhibiting the activity of a protein kinase (kinase of SIK, *e.g.*, kinase of SIK1, SIK2, or SIK3) in a subject or cell, in treating a disease or condition associated with aberrant kinase activity (kinase activity of SIK, *e.g.*, kinase activity of SIK1, SIK2, or SIK3) in a subject in need thereof, in preventing a disease or condition associated with aberrant kinase activity (kinase activity of SIK, *e.g.*, kinase activity of SIK1, SIK2, or SIK3) in a subject in need thereof, in treating a disease (*e.g.*, proliferative disease, musculoskeletal disease,

genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof, and/or in preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, a kit described herein further includes instructions for using the kit.

[0015] In another aspect, the present disclosure provides methods of modulating (*e.g.*, inhibiting) the activity of a protein kinase in a subject or cell. In certain embodiments, the activity of a protein kinase is aberrant or unwanted activity (*e.g.*, increased activity) of the protein kinase. In certain embodiments, the compound being administered or used selectively inhibits the activity of a particular protein kinase. In certain embodiments, the compound being administered or used selectively inhibits the activity of a SIK (*e.g.*, SIK1, SIK2, or SIK3).

[0016] Another aspect of the present disclosure relates to methods of treating and/or preventing a disease in a subject in need thereof.

[0017] The methods of the present disclosure include administering to the subject or contacting a cell with an effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[0018] In yet another aspect, the present disclosure provides compounds and pharmaceutical compositions described herein for use in a method of the disclosure (*e.g.*, a method of inhibiting a protein kinase (*e.g.*, SIK), a method of treating a disease (*e.g.*, a proliferative or musculoskeletal disease), or a method of preventing a disease (*e.g.*, a proliferative or musculoskeletal disease)).

[0019] Another aspect of the disclosure relates to methods of screening a library of compounds to identify a compound that is useful in a method of the disclosure (*e.g.*, inhibiting SIK).

[0020] The present application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Examples, and the Claims.

DEFINITIONS

[0021] 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.

[0022] 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 al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *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.

[0023] In a formula, --- is absent or a single bond, and ═══ or ═══ is a single or double bond.

[0024] 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.

[0025] 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, C_1,

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.

[0026] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

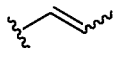
[0027] The term "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} 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), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) 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. In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (*e.g.*, $–CH_3$). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl.

[0028] 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. 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 ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). Examples of haloalkyl groups include $–CHF_2$,

$-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[0029] 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 ("heteroC_{1-10} 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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{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 ("heteroC_{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 ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 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 heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[0030] 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 (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), 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.

[0031] 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 1or 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.

[0032] 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 C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0033] 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 1or 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.

[0034] 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), cyclopentenyl (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 (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–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.

[0035] 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 ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} 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 (C_8). 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. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits.

[0036] 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.

[0037] 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.

[0038] 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 3 heteroatoms include, without limitation, triazinyl. 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, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, , and the like.

[0039] 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_{10} 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.

[0040] "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.

[0041] 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.

[0042] 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.

[0043] 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 thiadiazolyl. 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, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0044] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0045] The term "unsaturated bond" refers to a double or triple bond.

[0046] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0047] The term "saturated" refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[0048] 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.

[0049] 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.

[0050] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$,

$-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_3{}^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, 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 =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, 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, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, 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 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;

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, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ 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), $-CO_2H$, $-CO_2(C_{1-6}$ 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), $-SO_2N(C_{1-6}$ alkyl$)_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ 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.

[0051] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, or $-OS(=O)R^{aa}$. In certain embodiments, the carbon atom substituents are independently halogen,

substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$. In certain embodiments, the carbon atom substituents are independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, 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, or 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; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, the carbon atom substituents are independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, or $-NO_2$. In certain embodiments, the carbon atom substituents are independently halogen, substituted (*e.g.*, substituted with one or more halogen moieties) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, or $-NO_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, 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, or 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; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[0052] The term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0053] 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 $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb}))_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0054] 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.

[0055] The term "amino" refers to the group $-NH_2$. 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.

[0056] 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 $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, 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.

[0057] 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 $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, 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.

[0058] 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.

[0059] The term "sulfonyl" refers to a group selected from $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, and $-SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0060] The term "sulfinyl" refers to the group $-S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0061] 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 ($-CO_2H$), aldehydes (–CHO), esters ($-CO_2R^{aa}$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$), amides ($-C(=O)N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-C(=S)N(R^{bb})_2$), 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.

[0062] The term "silyl" refers to the group $-Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[0063] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0064] 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, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(OR^{cc})_2$, $-P(=O)(R^{aa})_2$, $-P(=O)(N(R^{cc})_2)_2$, 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^{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.

[0065] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), 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 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.

[0066] For example, nitrogen protecting groups such as amide groups *(e.g.,* –C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 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*–nitrobenzamide, and *o*–(benzoyloxymethyl)benzamide.

[0067] Nitrogen protecting groups such as carbamate groups (*e.g.,* –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamate, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]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), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–

methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 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.

[0068] 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.

[0069] 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]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N–p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N–p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– 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). In certain embodiments, the nitrogen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a nitrogen

protecting group. In certain embodiments, the nitrogen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a nitrogen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, the nitrogen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or a nitrogen protecting group. In certain embodiments, a nitrogen protecting group is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[0070] 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, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, 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.

[0071] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–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, α–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, *p*–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*–nitrobenzyl carbonate, *p*–nitrobenzyl carbonate, *S*–benzyl thiocarbonate, 4–ethoxy–1–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, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). In certain embodiments, the oxygen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group. In certain embodiments, the oxygen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, the oxygen atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or an oxygen protecting group. In certain embodiments, an oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

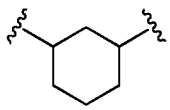
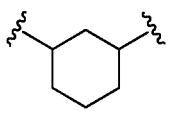
[0072] In certain embodiments, the sulfur atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a sulfur protecting group. In certain embodiments, the sulfur atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a sulfur protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, the sulfur atom substituents are independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or a sulfur protecting group. 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

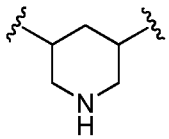
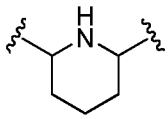
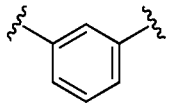
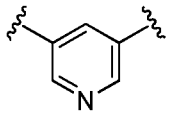
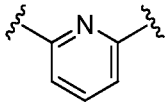
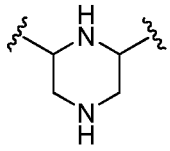
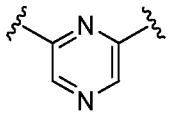
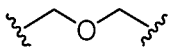
are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein; wherein X^- is a counterion. 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.

[0073] 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.

[0074] 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 $(HCB_{11}Me_5Br_6)^-$). 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.

[0075] 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, $-CH(C_2H_5)-$ is a C_1 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 $C_{3\text{-}10}$ 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, $-CH=CH-(CH_2)_2-$, $-CH_2-C\equiv C-CH_2-$, and $-C\equiv C-CH=CH-$ are all examples of a unsubstituted and unsaturated hydrocarbon chain. In certain embodiments, the hydrocarbon chain is unsubstituted (*e.g.*, $-C\equiv C-$ or $-(CH_2)_4-$). In certain embodiments, the hydrocarbon chain is substituted (*e.g.*, $-CH(C_2H_5)-$ 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.

[0076] As used herein, a "leaving group" (LG) is an art-understood term referring to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. See, for example, Smith, March Advanced Organic Chemistry 6th ed. (501-502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, chloro, bromo, iodo) and activated substituted hydroxyl groups (*e.g.*, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-OP(=O)_2R^{aa}$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-OP(=O)_2N(R^{bb})_2$, and $-OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein).

[0077] 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.

[0078] The term “solvate” refers to forms of the compound, or a 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.

[0079] 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)).

[0080] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds 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.

[0081] 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".

[0082] 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".

[0083] 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.

[0084] 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-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds described herein may be preferred.

[0085] 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.

[0086] The terms "composition" and "formulation" are used interchangeably.

[0087] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult, or senior adult)) and/or other non–human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female at any

stage of development. The animal may be a transgenic animal or genetically engineered animal. In certain embodiments, the subject is a non-human animal. In certain embodiments, the animal is a fish or reptile. A "patient" refers to a human subject in need of treatment of a disease.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] The terms "condition," "disease," and "disorder" are used interchangeably.

[0092] 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 prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses.

[0093] 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.

[0094] 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.

[0095] 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. Salt-inducible kinase (SIK) is one exemplary human protein kinase (*e.g.*, SIK1, SIK2, or SIK3). Exemplary human protein kinases include, but are not limited to, AAK1, ABL, ACK, ACTR2, ACTR2B, AKT1, AKT2, AKT3, ALK, ALK1, ALK2, ALK4, ALK7, AMPKa1, AMPKa2, ANKRD3, ANPa, ANPb, ARAF, ARAFps, ARG, AurA, AurAps1, AurAps2, AurB, AurBps1, AurC, AXL, BARK1, BARK2, BIKE, BLK, BMPR1A, BMPR1Aps1, BMPR1Aps2, BMPR1B, BMPR2, BMX, BRAF, BRAFps, BRK, BRSK1, BRSK2, BTK, BUB1, BUBR1, CaMK1a, CaMK1b, CaMK1d, CaMK1g, CaMK2a, CaMK2b, CaMK2d, CaMK2g, CaMK4, CaMKK1, CaMKK2, caMLCK, CASK, CCK4, CCRK, CDC2, CDC7, CDK10, CDK11, CDK2, CDK3, CDK4, CDK4ps, CDK5, CDK5ps, CDK6, CDK7, CDK7ps, CDK8, CDK8ps, CDK9,

CDKL1, CDKL2, CDKL3, CDKL4, CDKL5, CGDps, CHED, CHK1, CHK2, CHK2ps1, CHK2ps2, CK1a, CK1a2, CK1aps1, CK1aps2, CK1aps3, CK1d, CK1e, CK1g1, CK1g2, CK1g2ps, CK1g3, CK2a1, CK2a1–rs, CK2a2, CLIK1, CLIK1L, CLK1, CLK2, CLK2ps, CLK3, CLK3ps, CLK4, COT, CRIK, CRK7, CSK, CTK, CYGD, CYGF, DAPK1, DAPK2, DAPK3, DCAMKL1, DCAMKL2, DCAMKL3, DDR1, DDR2, DLK, DMPK1, DMPK2, DRAK1, DRAK2, DYRK1A, DYRK1B, DYRK2, DYRK3, DYRK4, EGFR, EphA1, EphA10, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB6, Erk1, Erk2, Erk3, Erk3ps1, Erk3ps2, Erk3ps3, Erk3ps4, Erk4, Erk5, Erk7, FAK, FER, FERps, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT1ps, FLT3, FLT4, FMS, FRK, Fused, FYN, GAK, GCK, GCN2, GCN22, GPRK4, GPRK5, GPRK6, GPRK6ps, GPRK7, GSK3A, GSK3B, Haspin, HCK, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4, HH498, HIPK1, HIPK2, HIPK3, HIPK4, HPK1, HRI, HRIps, HSER, HUNK, ICK, IGF1R, IKKa, IKKb, IKKe, ILK, INSR, IRAK1, IRAK2, IRAK3, IRAK4, IRE1, IRE2, IRR, ITK, JAK1, JAK2, JAK3, JNK1, JNK2, JNK3, KDR, KHS1, KHS2, KIS, KIT, KSGCps, KSR1, KSR2, LATS1, LATS2, LCK, LIMK1, LIMK2, LIMK2ps, LKB1, LMR1, LMR2, LMR3, LOK, LRRK1, LRRK2, LTK, LYN, LZK, MAK, MAP2K1, MAP2K1ps, MAP2K2, MAP2K2ps, MAP2K3, MAP2K4, MAP2K5, MAP2K6, MAP2K7, MAP3K1, MAP3K2, MAP3K3, MAP3K4, MAP3K5, MAP3K6, MAP3K7, MAP3K8, MAPKAPK2, MAPKAPK3, MAPKAPK5, MAPKAPKps1, MARK1, MARK2, MARK3, MARK4, MARKps01, MARKps02, MARKps03, MARKps04, MARKps05, MARKps07, MARKps08, MARKps09, MARKps10, MARKps11, MARKps12, MARKps13, MARKps15, MARKps16, MARKps17, MARKps18, MARKps19, MARKps20, MARKps21, MARKps22, MARKps23, MARKps24, MARKps25, MARKps26, MARKps27, MARKps28, MARKps29, MARKps30, MAST1, MAST2, MAST3, MAST4, MASTL, MELK, MER, MET, MISR2, MLK1, MLK2, MLK3, MLK4, MLKL, MNK1, MNK1ps, MNK2, MOK, MOS, MPSK1, MPSK1ps, MRCKa, MRCKb, MRCKps, MSK1, MSK12, MSK2, MSK22, MSSK1, MST1, MST2, MST3, MST3ps, MST4, MUSK, MYO3A, MYO3B, MYT1, NDR1, NDR2, NEK1, NEK10, NEK11, NEK2, NEK2ps1, NEK2ps2, NEK2ps3, NEK3, NEK4, NEK4ps, NEK5, NEK6, NEK7, NEK8, NEK9, NIK, NIM1, NLK, NRBP1, NRBP2, NuaK1, NuaK2, Obscn, Obscn2, OSR1, p38a, p38b, p38d, p38g, p70S6K, p70S6Kb, p70S6Kps1, p70S6Kps2, PAK1, PAK2, PAK2ps, PAK3, PAK4, PAK5, PAK6, PASK, PBK, PCTAIRE1,

PCTAIRE2, PCTAIRE3, PDGFRa, PDGFRb, PDK1, PEK, PFTAIRE1, PFTAIRE2, PHKg1, PHKg1ps1, PHKg1ps2, PHKg1ps3, PHKg2, PIK3R4, PIM1, PIM2, PIM3, PINK1, PITSLRE, PKACa, PKACb, PKACg, PKCa, PKCb, PKCd, PKCe, PKCg, PKCh, PKCi, PKCips, PKCt, PKCz, PKD1, PKD2, PKD3, PKG1, PKG2, PKN1, PKN2, PKN3, PKR, PLK1, PLK1ps1, PLK1ps2, PLK2, PLK3, PLK4, PRKX, PRKXps, PRKY, PRP4, PRP4ps, PRPK, PSKH1, PSKH1ps, PSKH2, PYK2, QIK, QSK, RAF1, RAF1ps, RET, RHOK, RIPK1, RIPK2, RIPK3, RNAseL, ROCK1, ROCK2, RON, ROR1, ROR2, ROS, RSK1, RSK12, RSK2, RSK22, RSK3, RSK32, RSK4, RSK42, RSKL1, RSKL2, RYK, RYKps, SAKps, SBK, SCYL1, SCYL2, SCYL2ps, SCYL3, SGK, SgK050ps, SgK069, SgK071, SgK085, SgK110, SgK196, SGK2, SgK223, SgK269, SgK288, SGK3, SgK307, SgK384ps, SgK396, SgK424, SgK493, SgK494, SgK495, SgK496, skMLCK, SLK, Slob, smMLCK, SNRK, SPEG, SPEG2, SRC, SRM, SRPK1, SRPK2, SRPK2ps, SSTK, STK33, STK33ps, STLK3, STLK5, STLK6, STLK6ps1, STLK6–rs, SuRTK106, SYK, TAK1, TAO1, TAO2, TAO3, TBCK, TBK1, TEC, TESK1, TESK2, TGFbR1, TGFbR2, TIE1, TIE2, TLK1, TLK1ps, TLK2, TLK2ps1, TLK2ps2, TNK1, Trad, Trb1, Trb2, Trb3, Trio, TRKA, TRKB, TRKC, TSSK1, TSSK2, TSSK3, TSSK4, TSSKps1, TSSKps2, TTBK1, TTBK2, TTK, TTN, TXK, TYK2, TYK22, TYRO3, TYRO3ps, ULK1, ULK2, ULK3, ULK4, VACAMKL, VRK1, VRK2, VRK3, VRK3ps, Wee1, Wee1B, Wee1Bps, Wee1ps1, Wee1ps2, Wnk1, Wnk2, Wnk3, Wnk4, YANK1, YANK2, YANK3, YES, YESps, YSK1, ZAK, ZAP70, ZC1/HGK, ZC2/TNIK, ZC3/MINK, and ZC4/NRK.

[0096] The term "salt-inducible kinase" or "SIK" refers to a subfamily of serine/threonine protein kinases including SIK1, SIK2, and SIK3 that belong to an AMP-activated protein kinase family. In certain embodiments, the SIK is SIK1. In certain embodiments, the SIK is SIK2. In certain embodiments, the SIK is SIK3.

[0097] 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.*, SIK kinase activity) in a cell relative to vehicle.

[0098] When a compound, pharmaceutical composition, method, use, or kit 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, use, or kit modulates the activity of the first protein kinase (*e.g.*, SIK) 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 a second protein kinase that is different from the first protein kinase.

[0099] A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases.

[00100] The term "angiogenesis" refers to the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors. The first vessels in a developing embryo form through vasculogenesis, after which angiogenesis is responsible for most blood vessel growth during normal or abnormal development. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, angiogenesis is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer. Angiogenesis may be chemically stimulated by angiogenic proteins, such as growth factors (*e.g.*, VEGF). "Pathological angiogenesis" refers to abnormal (*e.g.*, excessive or insufficient) angiogenesis that amounts to and/or is associated with a disease.

[00101] The terms "neoplasm" and "tumor" are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A "benign neoplasm" is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to

infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain "benign" tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor's neoplastic cells, and these tumors are referred to as "pre-malignant neoplasms." An exemplary pre-malignant neoplasm is a teratoma. In contrast, a "malignant neoplasm" is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites. The term "metastasis," "metastatic," or "metastasize" refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a "secondary tumor" or "secondary cell mass" of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[00102] The term "cancer" refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. See, *e.g.*, *Stedman's Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus,

Barrett's adenocarcinoma); Ewing's sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential

thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*,bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[00103] The term "inflammatory disease" refers to a disease caused by, resulting from, or resulting in inflammation. The term "inflammatory disease" may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthrosteitis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis,

dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis. An ocular inflammatory disease includes, but is not limited to, post-surgical inflammation.

[00104] The term "musculoskeletal disease" or "MSD" refers to an injury and/or pain in a subject's joints, ligaments, muscles, nerves, tendons, and structures that support limbs, neck, and back. In certain embodiments, an MSD is a degenerative disease. In certain embodiments, an MSD includes an inflammatory condition. Body parts of a subject that may be associated with MSDs include upper and lower back, neck, shoulders, and extremities (arms, legs, feet, and hands). In certain embodiments, an MSD is a bone disease, such as achondroplasia, acromegaly, bone callus, bone demineralization, bone fracture, bone marrow disease, bone marrow neoplasm, dyskeratosis congenita, leukemia (*e.g.*, hairy cell leukemia, lymphocytic leukemia, myeloid leukemia, Philadelphia chromosome-positive leukemia, plasma cell

leukemia, stem cell leukemia), systemic mastocytosis, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, myeloid sarcoma, myeloproliferative disorders, multiple myeloma, polycythemia vera, pearson marrow-pancreas syndrome, bone neoplasm, bone marrow neoplasm, Ewing sarcoma, osteochondroma, osteoclastoma, osteosarcoma, brachydactyly, Camurati-Engelmann syndrome, Craniosynostosis, Crouzon craniofacial dysostosis, dwarfism, achondroplasia, bloom syndrome, Cockayne syndrome, Ellis-van Creveld syndrome, Seckel syndrome, spondyloepiphyseal dysplasia, spondyloepiphyseal dysplasia congenita, Werner syndrome, hyperostosis, osteophyte, Klippel-Trenaunay-Weber syndrome, Marfan syndrome, McCune-Albright syndrome, osteitis, osteoarthritis, osteochondritis, osteochondrodysplasia, Kashin-Beck disease, Leri-Weill dyschondrosteosis, osteochondrosis, osteodystrophy, osteogenesis imperfecta, osteolysis, Gorham-Stout syndrome, osteomalacia, osteomyelitis, osteonecrosis, osteopenia, osteopetrosis, osteoporosis, osteosclerosis, otospondylomegaepiphyseal dysplasia, pachydermoperiostosis, Paget disease of bone, Polydactyly, Meckel syndrome, rickets, Rothmund-Thomson syndrome, Sotos syndrome, spondyloepiphyseal dysplasia, spondyloepiphyseal dysplasia congenita, syndactyly, Apert syndrome, syndactyly type II, or Werner syndrome. In certain embodiments, an MSD is a cartilage disease, such as cartilage neoplasm, osteochondritis, osteochondrodysplasia, Kashin-Beck disease, or Leri-Weill dyschondrosteosis. In certain embodiments, an MSD is hernia, such as intervertebral disk hernia. In certain embodiments, an MSD is a joint disease, such as arthralgia, arthritis (*e.g.*, gout (*e.g.*, Kelley-Seegmiller syndrome, Lesch-Nyhan syndrome), Lyme disease, osteoarthritis, psoriatic arthritis, reactive arthritis, rheumatic fever, rheumatoid arthritis, Felty syndrome, synovitis, Blau syndrome, nail-patella syndrome, spondyloarthropathy, reactive arthritis, Stickler syndrome, synovial membrane disease, synovitis, or Blau syndrome. In certain embodiments, an MSD is Langer-Giedion syndrome. In certain embodiments, an MSD is a muscle disease, such as Barth syndrome, mitochondrial encephalomyopathy, MELAS syndrome, MERRF syndrome, MNGIE syndrome, mitochondrial myopathy, Kearns-Sayre syndrome, myalgia, fibromyalgia, polymyalgia rheumatica, myoma, myositis, dermatomyositis, neuromuscular disease, Kearns-Sayre syndrome, muscular dystrophy, myasthenia, congenital myasthenic syndrome, Lambert-Eaton myasthenic syndrome, myasthenia gravis, myotonia, myotonia congenita, spinal muscular atrophy, tetany, ophthalmoplegia, or

rhabdomyolysis. In certain embodiments, an MSD is Proteus syndrome. In certain embodiments, an MSD is a rheumatic diseases, such as arthritis (*e.g.*, gout (*e.g.*, Kelley-Seegmiller syndrome, Lesch-Nyhan lyme disease)), osteoarthritis, psoriatic arthritis, reactive arthritis, rheumatic fever, rheumatoid arthritis, Felty syndrome, synovitis, Blau syndrome, gout (*e.g.*, Kelley-Seegmiller syndrome, Lesch-Nyhan syndrome), polymyalgia rheumatica, rheumatic fever, rheumatic heart disease, or Sjogren syndrome. In certain embodiments, an MSD is Schwartz-Jampel syndrome. In certain embodiments, an MSD is a skeleton disease, such as Leri-Weill dyschondrosteosis, skeleton malformations, Melnick-Needles syndrome, pachydermoperiostosis, Rieger syndrome, spinal column disease, intervertebral disk hernia, scoliosis, spina bifida, spondylitis, ankylosing spondylitis, spondyloarthropathy, reactive arthritis, spondyloepiphyseal dysplasia, spondyloepiphyseal dysplasia congenita, or spondylosis. In certain embodiments, a MSD is rheumatoid arthritis.

[00105] An "autoimmune disease" refers to a disease arising from an inappropriate immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture's disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, rheumatoid arthritis, glomerulonephritis, Goodpasture's syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosis, psoriatic arthritis, systemic lupus erythematosis, psoriasis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener's granulomatosis, microscopic polyangiitis), uveitis, Sjogren's syndrome, Reiter's syndrome, ankylosing spondylitis, Lyme disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, and cardiomyopathy. In certain embodiments, the autoimmune disease is rheumatoid arthritis.

[00106] The term "genetic disease" refers to a disease caused by one or more abnormalities in the genome of a subject, such as a disease that is present from birth of the subject. Genetic diseases may be heritable and may be passed down from the

parents' genes. A genetic disease may also be caused by mutations or changes of the DNAs and/or RNAs of the subject. In such cases, the genetic disease will be heritable if it occurs in the germline. Exemplary genetic diseases include, but are not limited to, Aarskog-Scott syndrome, Aase syndrome, achondroplasia, acrodysostosis, addiction, adreno-leukodystrophy, albinism, ablepharon-macrostomia syndrome, alagille syndrome, alkaptonuria, alpha-1 antitrypsin deficiency, Alport's syndrome, Alzheimer's disease, asthma, autoimmune polyglandular syndrome, androgen insensitivity syndrome, Angelman syndrome, ataxia, ataxia telangiectasia, atherosclerosis, attention deficit hyperactivity disorder (ADHD), autism, baldness, Batten disease, Beckwith-Wiedemann syndrome, Best disease, bipolar disorder, brachydactyl), breast cancer, Burkitt lymphoma, chronic myeloid leukemia, Charcot-Marie-Tooth disease, cleft lip, Cockayne syndrome, Coffin Lowry syndrome, colon cancer, congenital adrenal hyperplasia, Cornelia de Lange syndrome, Costello syndrome, Cowden syndrome, craniofrontonasal dysplasia, Crigler-Najjar syndrome, Creutzfeldt-Jakob disease, cystic fibrosis, deafness, depression, diabetes, diastrophic dysplasia, DiGeorge syndrome, Down's syndrome, dyslexia, Duchenne muscular dystrophy, Dubowitz syndrome, ectodermal dysplasia Ellis-van Creveld syndrome, Ehlers-Danlos, epidermolysis bullosa, epilepsy, essential tremor, familial hypercholesterolemia, familial Mediterranean fever, fragile X syndrome, Friedreich's ataxia, Gaucher disease, glaucoma, glucose galactose malabsorption, glutaricaciduria, gyrate atrophy, Goldberg Shprintzen syndrome (velocardiofacial syndrome), Gorlin syndrome, Hailey-Hailey disease, hemihypertrophy, hemochromatosis, hemophilia, hereditary motor and sensory neuropathy (HMSN), hereditary non polyposis colorectal cancer (HNPCC), Huntington's disease, immunodeficiency with hyper-IgM, juvenile onset diabetes, Klinefelter's syndrome, Kabuki syndrome, Leigh's disease, long QT syndrome, lung cancer, malignant melanoma, manic depression, Marfan syndrome, Menkes syndrome, miscarriage, mucopolysaccharide disease, multiple endocrine neoplasia, multiple sclerosis, muscular dystrophy, myotrophic lateral sclerosis, myotonic dystrophy, neurofibromatosis, Niemann-Pick disease, Noonan syndrome, obesity, ovarian cancer, pancreatic cancer, Parkinson's disease, paroxysmal nocturnal hemoglobinuria, Pendred syndrome, peroneal muscular atrophy, phenylketonuria (PKU), polycystic kidney disease, Prader-Willi syndrome, primary biliary cirrhosis, prostate cancer, REAR syndrome, Refsum disease, retinitis pigmentosa, retinoblastoma, Rett syndrome, Sanfilippo syndrome, schizophrenia,

severe combined immunodeficiency, sickle cell anemia, spina bifida, spinal muscular atrophy, spinocerebellar atrophy, sudden adult death syndrome, Tangier disease, Tay-Sachs disease, thrombocytopenia absent radius syndrome, Townes-Brocks syndrome, tuberous sclerosis, Turner syndrome, Usher syndrome, von Hippel-Lindau syndrome, Waardenburg syndrome, Weaver syndrome, Werner syndrome, Williams syndrome, Wilson's disease, xeroderma piginentosum, and Zellweger syndrome.

[00107] A "hematological disease" includes a disease which affects a hematopoietic cell or tissue. Hematological diseases include diseases associated with aberrant hematological content and/or function. Examples of hematological diseases include diseases resulting from bone marrow irradiation or chemotherapy treatments for cancer, diseases such as pernicious anemia, hemorrhagic anemia, hemolytic anemia, aplastic anemia, sickle cell anemia, sideroblastic anemia, anemia associated with chronic infections such as malaria, trypanosomiasis, HTV, hepatitis virus or other viruses, myelophthisic anemias caused by marrow deficiencies, renal failure resulting from anemia, anemia, polycythemia, infectious mononucleosis (EVI), acute non-lymphocytic leukemia (ANLL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), acute myelomonocytic leukemia (AMMoL), polycythemia vera, lymphoma, acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia, Wilm's tumor, Ewing's sarcoma, retinoblastoma, hemophilia, disorders associated with an increased risk of thrombosis, herpes, thalassemia, antibody-mediated disorders such as transfusion reactions and erythroblastosis, mechanical trauma to red blood cells such as micro-angiopathic hemolytic anemias, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation, infections by parasites such as *Plasmodium*, chemical injuries from, *e.g.*, lead poisoning, and hypersplenism.

[00108] The term "neurological disease" refers to any disease of the nervous system, including diseases that involve the central nervous system (brain, brainstem and cerebellum), the peripheral nervous system (including cranial nerves), and the autonomic nervous system (parts of which are located in both central and peripheral nervous system). Neurodegenerative diseases refer to a type of neurological disease marked by the loss of nerve cells, including, but not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, tauopathies (including frontotemporal dementia), and Huntington's disease. Examples of neurological diseases include, but are not limited to, headache, stupor and coma, dementia, seizure,

sleep disorders, trauma, infections, neoplasms, neuro-ophthalmology, movement disorders, demyelinating diseases, spinal cord disorders, and disorders of peripheral nerves, muscle and neuromuscular junctions. Addiction and mental illness, include, but are not limited to, bipolar disorder and schizophrenia, are also included in the definition of neurological diseases. Further examples of neurological diseases include acquired epileptiform aphasia; acute disseminated encephalomyelitis; adrenoleukodystrophy; agenesis of the corpus callosum; agnosia; Aicardi syndrome; Alexander disease; Alpers' disease; alternating hemiplegia; Alzheimer's disease; amyotrophic lateral sclerosis; anencephaly; Angelman syndrome; angiomatosis; anoxia; aphasia; apraxia; arachnoid cysts; arachnoiditis; Arnold-Chiari malformation; arteriovenous malformation; Asperger syndrome; ataxia telangiectasia; attention deficit hyperactivity disorder; autism; autonomic dysfunction; back pain; Batten disease; Behcet's disease; Bell's palsy; benign essential blepharospasm; benign focal; amyotrophy; benign intracranial hypertension; Binswanger's disease; blepharospasm; Bloch Sulzberger syndrome; brachial plexus injury; brain abscess; bbrain injury; brain tumors (including glioblastoma multiforme); spinal tumor; Brown-Sequard syndrome; Canavan disease; carpal tunnel syndrome (CTS); causalgia; central pain syndrome; central pontine myelinolysis; cephalic disorder; cerebral aneurysm; cerebral arteriosclerosis; cerebral atrophy; cerebral gigantism; cerebral palsy; Charcot-Marie-Tooth disease; chemotherapy-induced neuropathy and neuropathic pain; Chiari malformation; chorea; chronic inflammatory demyelinating polyneuropathy (CIDP); chronic pain; chronic regional pain syndrome; Coffin Lowry syndrome; coma, including persistent vegetative state; congenital facial diplegia; corticobasal degeneration; cranial arteritis; craniosynostosis; Creutzfeldt-Jakob disease; cumulative trauma disorders; Cushing's syndrome; cytomegalic inclusion body disease (CIBD); cytomegalovirus infection; dancing eyes-dancing feet syndrome; Dandy-Walker syndrome; Dawson disease; De Morsier's syndrome; Dejerine-Klumpke palsy; dementia; dermatomyositis; diabetic neuropathy; diffuse sclerosis; dysautonomia; dysgraphia; dyslexia; dystonias; early infantile epileptic encephalopathy; empty sella syndrome; encephalitis; encephaloceles; encephalotrigeminal angiomatosis; epilepsy; Erb's palsy; essential tremor; Fabry's disease; Fahr's syndrome; fainting; familial spastic paralysis; febrile seizures; Fisher syndrome; Friedreich's ataxia; frontotemporal dementia and other "tauopathies"; Gaucher's disease; Gerstmann's syndrome; giant cell arteritis; giant cell inclusion

disease; globoid cell leukodystrophy; Guillain-Barre syndrome; HTLV-1 associated myelopathy; Hallervorden-Spatz disease; head injury; headache; hemifacial spasm; hereditary spastic paraplegia; heredopathia atactica polyneuritiformis; herpes zoster oticus; herpes zoster; Hirayama syndrome; HIV-associated dementia and neuropathy (see also neurological manifestations of AIDS); holoprosencephaly; Huntington's disease and other polyglutamine repeat diseases; hydranencephaly; hydrocephalus; hypercortisolism; hypoxia; immune-mediated encephalomyelitis; inclusion body myositis; incontinentia pigmenti; infantile; phytanic acid storage disease; Infantile Refsum disease; infantile spasms; inflammatory myopathy; intracranial cyst; intracranial hypertension; Joubert syndrome; Kearns-Sayre syndrome; Kennedy disease; Kinsbourne syndrome; Klippel Feil syndrome; Krabbe disease; Kugelberg-Welander disease; kuru; Lafora disease; Lambert-Eaton myasthenic syndrome; Landau-Kleffner syndrome; lateral medullary (Wallenberg) syndrome; learning disabilities; Leigh's disease; Lennox-Gastaut syndrome; Lesch-Nyhan syndrome; leukodystrophy; Lewy body dementia; lissencephaly; locked-in syndrome; Lou Gehrig's disease (aka motor neuron disease or amyotrophic lateral sclerosis); lumbar disc disease; lyme disease-neurological sequelae; Machado-Joseph disease; macrencephaly; megalencephaly; Melkersson-Rosenthal syndrome; Menieres disease; meningitis; Menkes disease; metachromatic leukodystrophy; microcephaly; migraine; Miller Fisher syndrome; mini-strokes; mitochondrial myopathies; Mobius syndrome; monomelic amyotrophy; motor neurone disease; moyamoya disease; mucopolysaccharidoses; multi-infarct dementia; multifocal motor neuropathy; multiple sclerosis and other demyelinating disorders; multiple system atrophy with postural hypotension; muscular dystrophy; myasthenia gravis; myelinoclastic diffuse sclerosis; myoclonic encephalopathy of infants; myoclonus; myopathy; myotonia congenital; narcolepsy; neurofibromatosis; neuroleptic malignant syndrome; neurological manifestations of AIDS; neurological sequelae of lupus; neuromyotonia; neuronal ceroid lipofuscinosis; neuronal migration disorders; Niemann-Pick disease; O'Sullivan-McLeod syndrome; occipital neuralgia; occult spinal dysraphism sequence; Ohtahara syndrome; olivopontocerebellar atrophy; opsoclonus myoclonus; optic neuritis; orthostatic hypotension; overuse syndrome; paresthesia; Parkinson's disease; paramyotonia congenita; paraneoplastic diseases; paroxysmal attacks; Parry Romberg syndrome; Pelizaeus-Merzbacher disease; periodic paralyses; peripheral neuropathy; painful neuropathy and neuropathic pain; persistent vegetative state;

pervasive developmental disorders; photic sneeze reflex; phytanic acid storage disease; Pick's disease; pinched nerve; pituitary tumors; polymyositis; porencephaly; Post-Polio syndrome; postherpetic neuralgia (PHN); postinfectious encephalomyelitis; postural hypotension; Prader-Willi syndrome; primary lateral sclerosis; prion diseases; progressive; hemifacial atrophy; progressive multifocal leukoencephalopathy; progressive sclerosing poliodystrophy; progressive supranuclear palsy; pseudotumor cerebri; Ramsay-Hunt syndrome (Type I and Type II); Rasmussen's Encephalitis; reflex sympathetic dystrophy syndrome; Refsum disease; repetitive motion disorders; repetitive stress injuries; restless legs syndrome; retrovirus-associated myelopathy; Rett syndrome; Reye's syndrome; Saint Vitus Dance; Sandhoff disease; Schilder's disease; schizencephaly; septo-optic dysplasia; shaken baby syndrome; shingles; Shy-Drager syndrome; Sjogren's syndrome; sleep apnea; Soto's syndrome; spasticity; spina bifida; spinal cord injury; spinal cord tumors; spinal muscular atrophy; stiff-person syndrome; stroke; Sturge-Weber syndrome; subacute sclerosing panencephalitis; subarachnoid hemorrhage; subcortical arteriosclerotic encephalopathy; sydenham chorea; syncope; syringomyelia; tardive dyskinesia; Tay-Sachs disease; temporal arteritis; tethered spinal cord syndrome; Thomsen disease; thoracic outlet syndrome; tic douloureux; Todd's paralysis; Tourette syndrome; transient ischemic attack; transmissible spongiform encephalopathies; transverse myelitis; traumatic brain injury; tremor; trigeminal neuralgia; tropical spastic paraparesis; tuberous sclerosis; vascular dementia (multi-infarct dementia); vasculitis including temporal arteritis; Von Hippel-Lindau Disease (VHL); Wallenberg's syndrome; Werdnig-Hoffman disease; West syndrome; whiplash; Williams syndrome; Wilson's disease; and Zellweger syndrome.

[00109] A "painful condition" includes, but is not limited to, neuropathic pain (*e.g.*, peripheral neuropathic pain), central pain, deafferentiation pain, chronic pain (*e.g.*, chronic nociceptive pain, and other forms of chronic pain such as post–operative pain, *e.g.,* pain arising after hip, knee, or other replacement surgery), pre–operative pain, stimulus of nociceptive receptors (nociceptive pain), acute pain (*e.g.*, phantom and transient acute pain), noninflammatory pain, inflammatory pain, pain associated with cancer, wound pain, burn pain, postoperative pain, pain associated with medical procedures, pain resulting from pruritus, painful bladder syndrome, pain associated with premenstrual dysphoric disorder and/or premenstrual syndrome, pain associated with chronic fatigue syndrome, pain associated with pre–term labor, pain associated

with withdrawl symptoms from drug addiction, joint pain, arthritic pain (*e.g.*, pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, or Reiter's arthritis), lumbosacral pain, musculo–skeletal pain, headache, migraine, muscle ache, lower back pain, neck pain, toothache, dental/maxillofacial pain, visceral pain and the like. One or more of the painful conditions contemplated herein can comprise mixtures of various types of pain provided above and herein (*e.g.* nociceptive pain, inflammatory pain, neuropathic pain, *etc.*). In some embodiments, a particular pain can dominate. In other embodiments, the painful condition comprises two or more types of pains without one dominating. A skilled clinician can determine the dosage to achieve a therapeutically effective amount for a particular subject based on the painful condition.

[00110] The term "psychiatric disorder" refers to a disease of the mind and includes diseases and disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders* - Fourth Edition (DSM-IV), published by the American Psychiatric Association, Washington D. C. (1994). Psychiatric disorders include, but are not limited to, anxiety disorders (*e.g.*, acute stress disorder agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social phobia, and specific phobia), childhood disorders, (*e.g.*, attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder), eating disorders (*e.g.*, anorexia nervosa and bulimia nervosa), mood disorders (*e.g.*, depression, bipolar disorder, cyclothymic disorder, dysthymic disorder, and major depressive disorder), personality disorders (*e.g.*, antisocial personality disorder, avoidant personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, narcissistic personality disorder, obsessive-compulsive personality disorder, paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder), psychotic disorders (*e.g.*, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, schizophrenia, and shared psychotic disorder), substance-related disorders (*e.g.*, alcohol dependence, amphetamine dependence, cannabis dependence, cocaine dependence, hallucinogen dependence, inhalant dependence, nicotine dependence, opioid dependence, phencyclidine dependence, and sedative dependence), adjustment disorder, autism, delirium, dementia, multi-infarct dementia, learning and memory disorders (*e.g.*, amnesia and age-related memory loss), and Tourette's disorder.

[00111] The term "metabolic disorder" refers to any disorder that involves an alteration in the normal metabolism of carbohydrates, lipids, proteins, nucleic acids, or a combination thereof. A metabolic disorder is associated with either a deficiency or excess in a metabolic pathway resulting in an imbalance in metabolism of nucleic acids, proteins, lipids, and/or carbohydrates. Factors affecting metabolism include, and are not limited to, the endocrine (hormonal) control system (*e.g.*, the insulin pathway, the enteroendocrine hormones including GLP-1, PYY, or the like), the neural control system (*e.g.*, GLP-1 in the brain), or the like. Examples of metabolic disorders include, but are not limited to, diabetes (*e.g.*, type 1 diabetes, type 2 diabetes, gestational diabetes), hyperglycemia, hyperinsulinemia, insulin resistance, and obesity.

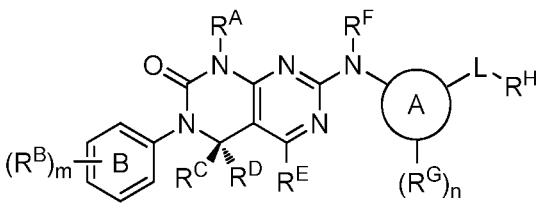
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[00112] Described herein are bicyclic compounds of Formula (**I**), (**II**), and (**III**), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. Certain compounds described herein bind protein kinases and may be useful in modulating (*e.g.*, inhibiting) the activity of a protein kinase (*e.g.*, a SIK kinase) in a subject or cell, in treating or preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof, and/or in treating or preventing a disease or condition associated with kinase activity in a subject in need thereof. Also provided are pharmaceutical compositions and kits including a compound described herein.

Compounds

Compounds of Formula (I)

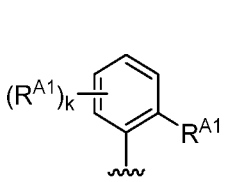
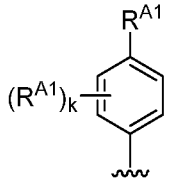
[00113] In one aspect, the present disclosure provides compounds of Formula (**I**):



(**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,


, 
, 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, $–OR^a$, –

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

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;

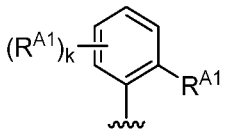
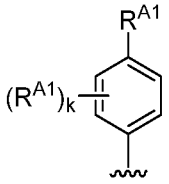
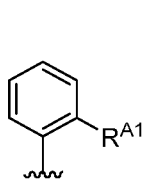
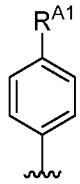
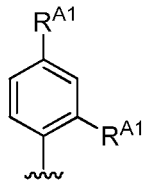
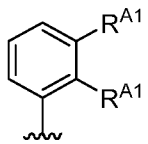
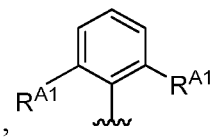
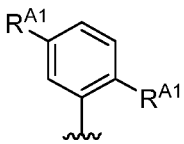
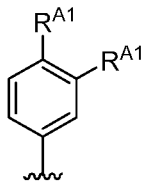
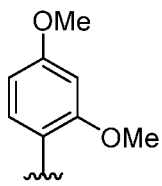
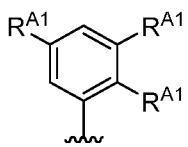
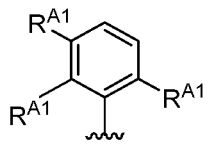
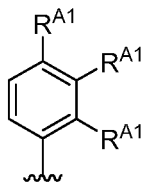
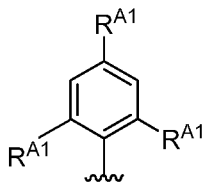
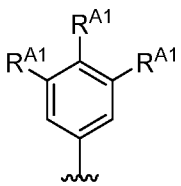
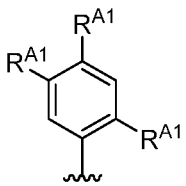
each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted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

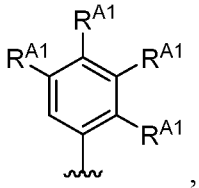
n is 0, 1, 2, 3, or 4, as valency permits;

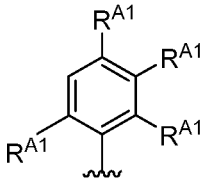
L is a bond or a substituted or unsubstituted C_{1-6} hydrocarbon chain, optionally wherein one or more chain atoms of the hydrocarbon chain are independently replaced with $-C(=O)-$, $-O-$, $-S-$, $-NR^b-$, $-N=$, or $=N-$; and

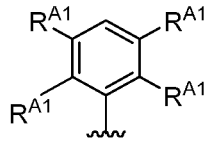
R^H is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocyclyl, $-OH$, or $-N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together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

[00114] 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,

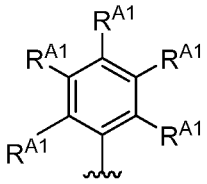
R^A is of the formula:  or  . In certain embodiments, k is 0. In certain embodiments, R^A is of the formula:  or  . In certain embodiments, k is 1. In certain embodiments, R^A is of the formula:  ,  ,  , or  . In certain embodiments, R^A is of the formula:  . In certain embodiments, R^A is  . In certain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

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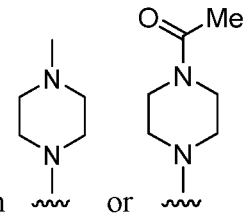
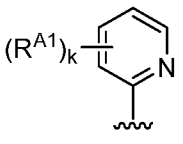
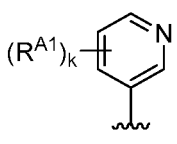
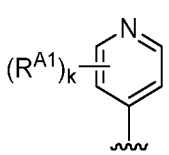
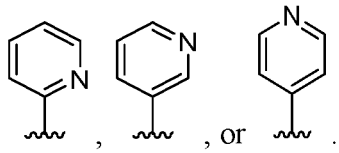
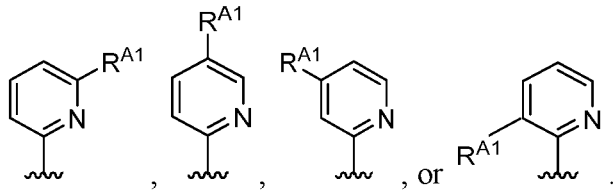
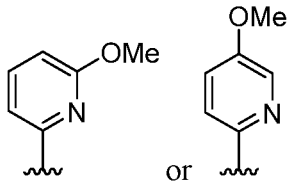
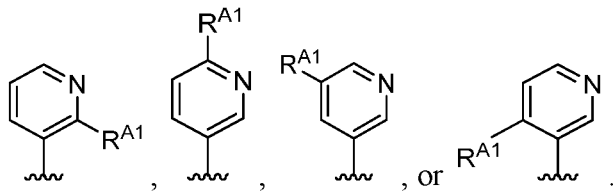
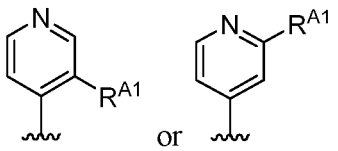
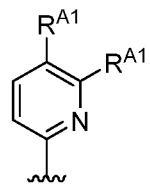
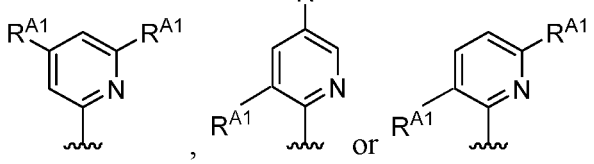
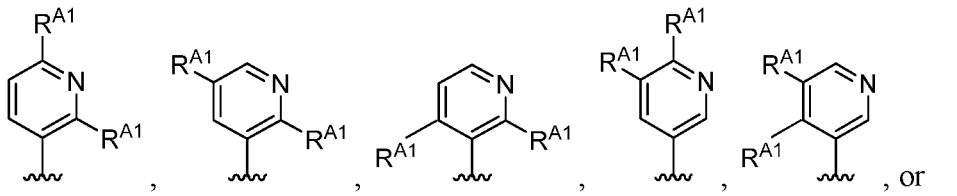
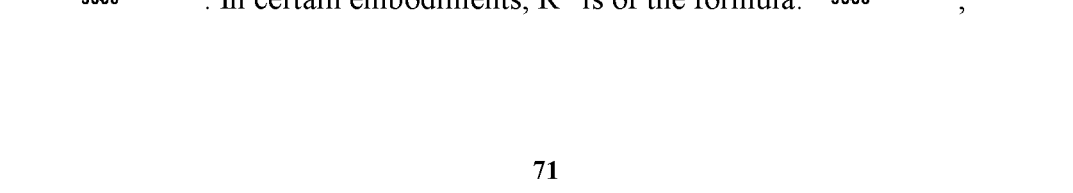
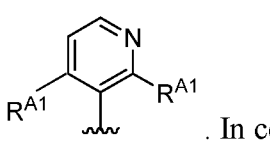
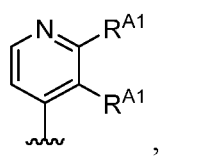
[00115] In certain embodiments, when R^A is substituted phenyl, R^A includes one or more R^{A1} substituents. In certain embodiments, at least one instance of R^{A1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one R^{A1} is substituted or unsubstituted alkyl (*e.g.*, substituted 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

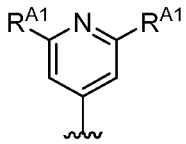
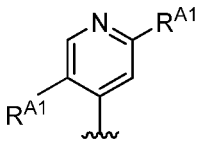
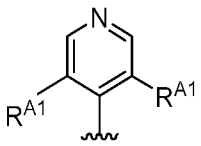
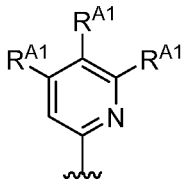
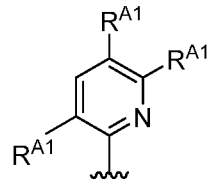
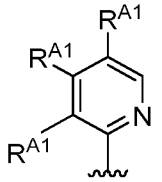
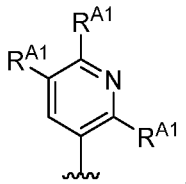
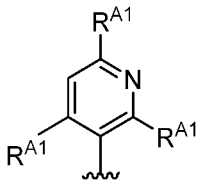
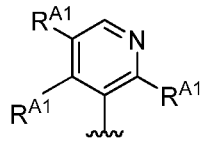
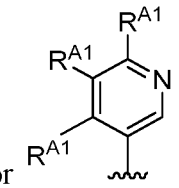
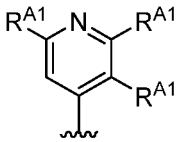
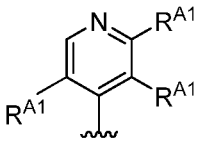
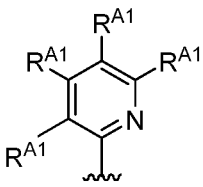
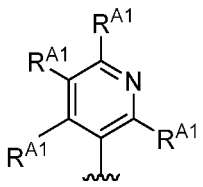
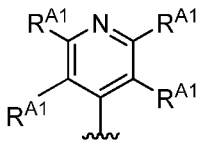
system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A1} is $-OR^a$ (*e.g.*, –OH or –OMe). In certain embodiments, at least one instance of R^{A1} is $-N(R^b)_2$, $-SR^a$, –CN, –SCN, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, $-C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

[00116] 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, Cl, 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 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^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, 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^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.

[00117] 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 bicyclic 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 .

[00118] 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:  ,  ,  . In certain embodiments, R^A is of the formula:  ,




. 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:

,



. 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

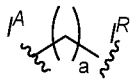
one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur), provided that the substituted or unsubstituted heterocyclyl is not substituted or unsubstituted 3-pyrrolidinyl. In certain embodiments, R^A is substituted or unsubstituted tetrahydropyranyl. In certain embodiments, 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.

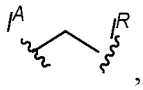
[00119] Formula (**I**) includes Ring B. Ring B is described in the Detailed Description for Formula (**II**) below.

[00120] Formula (**I**) includes substituents R^C, R^D, R^E, and R^F. Substituents R^C, R^D, R^E, and R^F are described in the Detailed Description for Formula (**III**) below.

[00121] Formula (**I**) includes Ring A and one or more instances of substituent R^G. Ring A and substituent R^G are described in the Detailed Description for Formula (**III**) below.

[00122] 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 chain atoms of the hydrocarbon chain of L are independently replaced with –C(=O)–, –O–, –S–, –NR^b–, –N=, or =N–. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain.

[00123] 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: 

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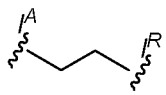
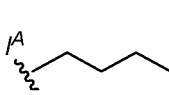
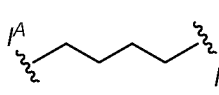
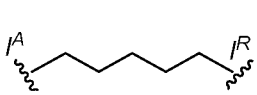
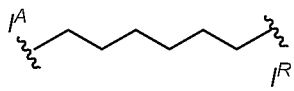


, or 

, 

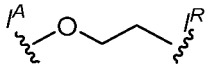
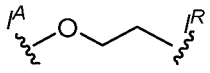
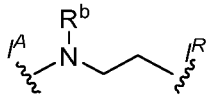
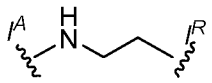
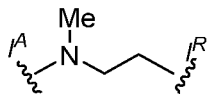
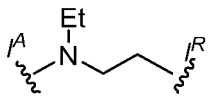
, 

, or



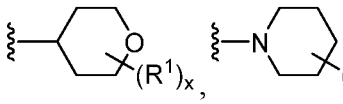
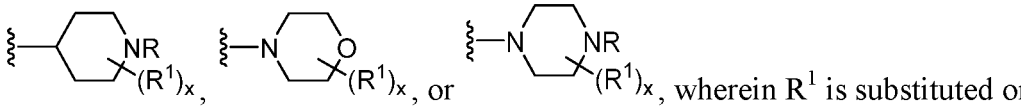
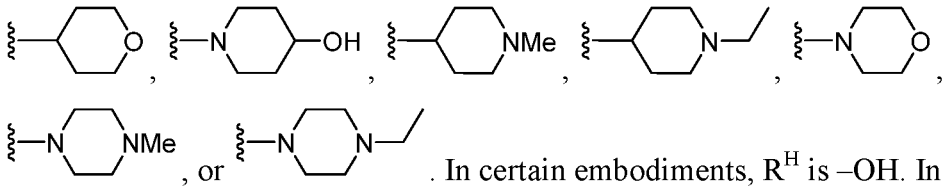
, wherein l^A indicates the point of attachment to Ring A, and l^R indicates the point of attachment to R^H.

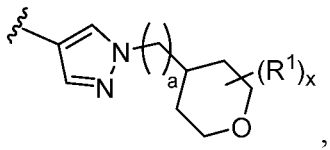
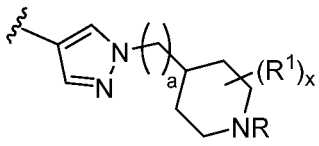
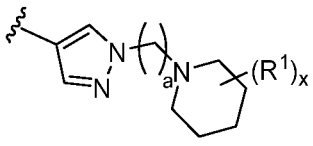
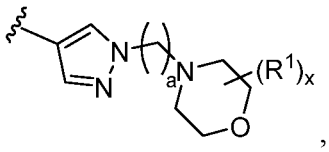
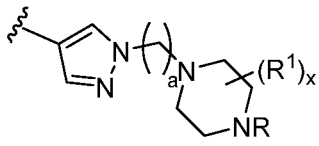
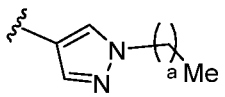
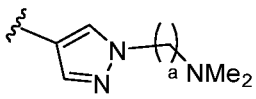
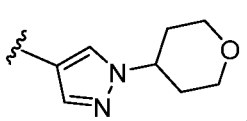
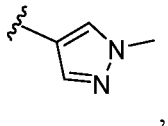
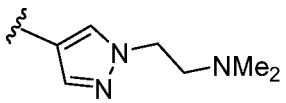
[00124] In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one or more chain atoms of the hydrocarbon chain are independently

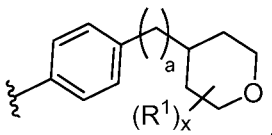
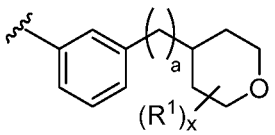
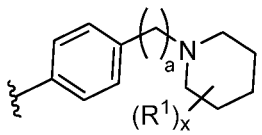
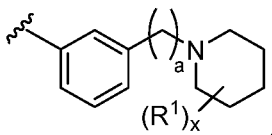
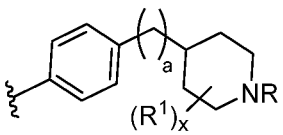
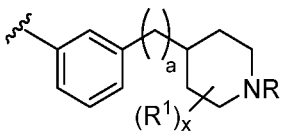
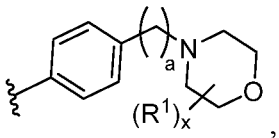
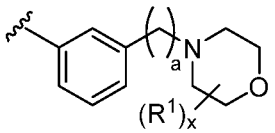
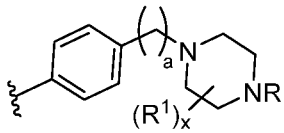
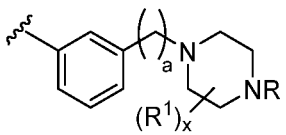
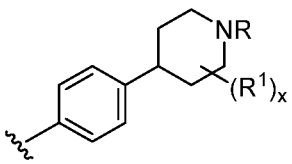
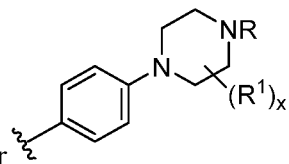
replaced with –O– or –NR^b–. In certain embodiments, L is an unsubstituted C_{1-3} hydrocarbon chain, wherein one chain atom of the hydrocarbon chain is replaced with –O–. In certain embodiments, L is of the formula:  , wherein l^A indicates the point of attachment to Ring A, and l^R indicates the point 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(=O)–. 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–.

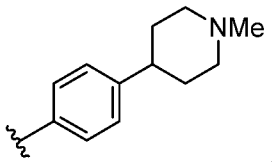
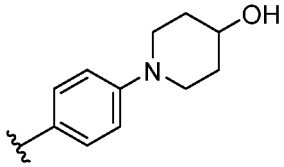
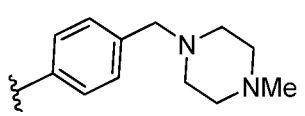
[00125] Formula (**I**) includes substituent R^H. In certain embodiments, R^H is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^H is methyl. In certain embodiments, R^H is ethyl. In certain embodiments, R^H is propyl. In certain embodiments, R^H 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,

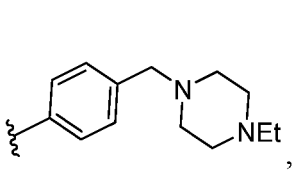
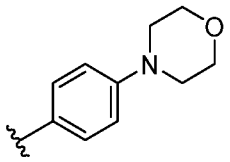
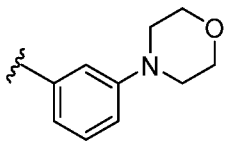
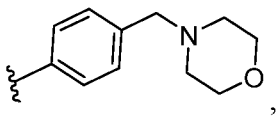
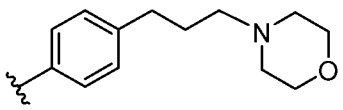
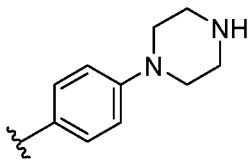
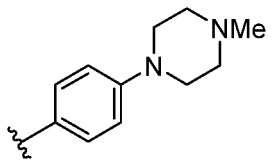
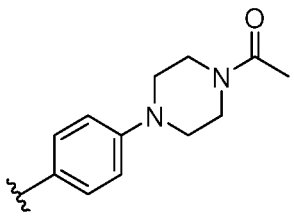
substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

In certain embodiments, R^H is of the formula:  ,  , 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^H is of the formula:  . In certain embodiments, R^H is –OH. In certain embodiments, R^H is $-N(R^c)_2$. As generally described herein, 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).

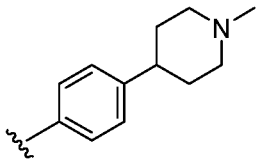
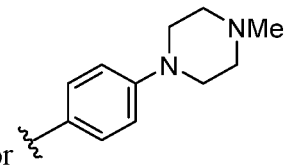
[00126] In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  ,  ,  ,  ,  , or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:  ,  , or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

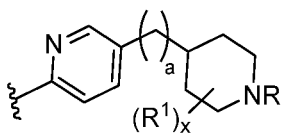
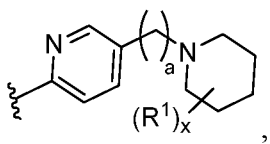
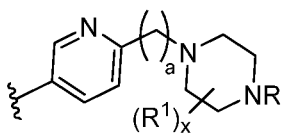
 ,  ,  ,  ,  ,  ,  ,  ,  , or  . In certain embodiments, Ring A with linker L and substituent R^H is not of the formula:  or  . In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

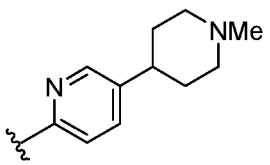
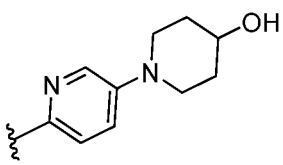
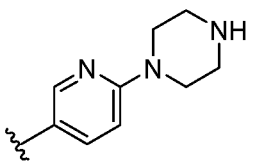
 ,  ,  ,

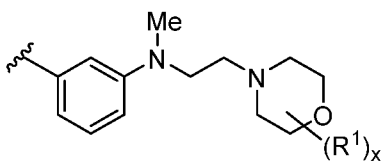
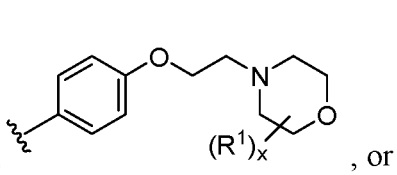
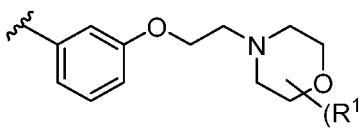
. In certain embodiments, Ring A with linker L and substituent R^H is not of the formula:

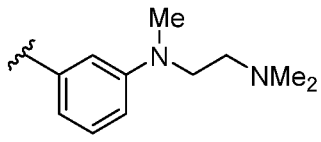
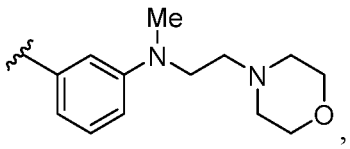
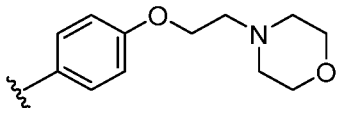
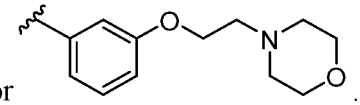
[00127] In certain embodiments, Ring A with linker L and substituent R^H is of the formula: 


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




.

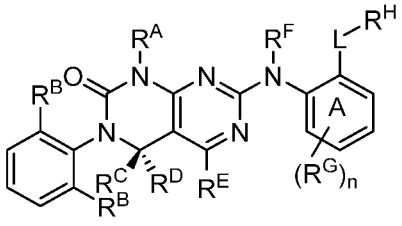
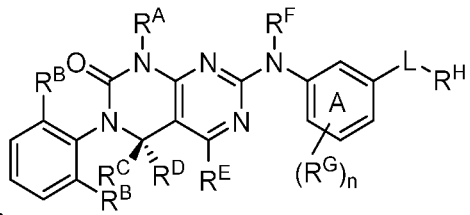
In certain embodiments, Ring A with linker L and substituent R^H is of the formula:

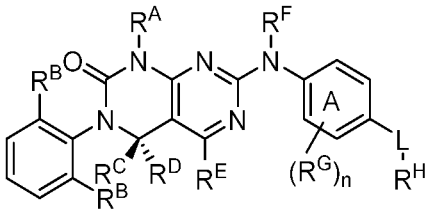




. In certain embodiments, Ring A with linker L and

substituent R^H is of the formula:  ,  ,  , or  .

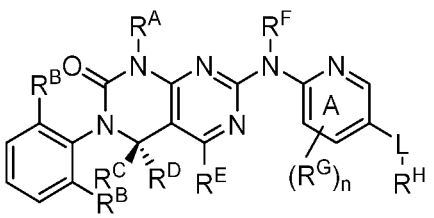
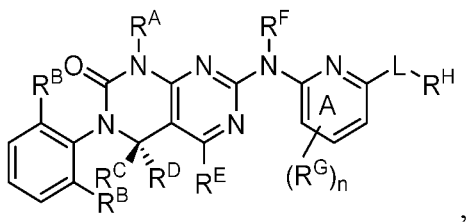
[00128] In certain embodiments, the compound of Formula (**I**) is of the formula:

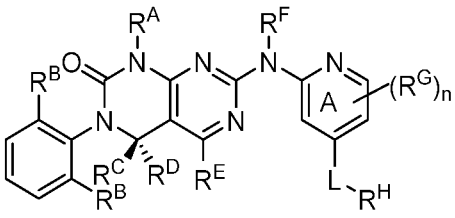
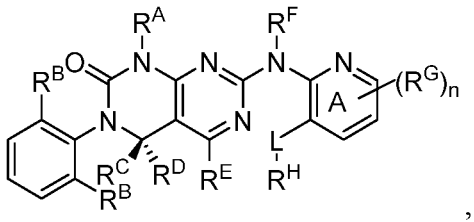
 ,  , or

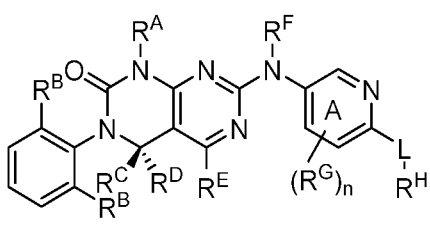
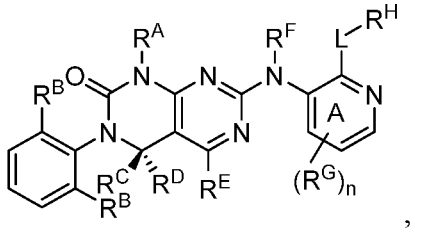
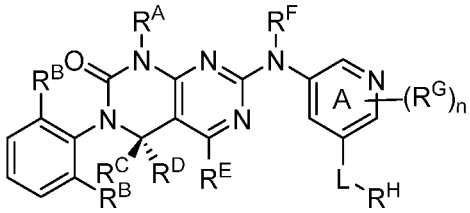
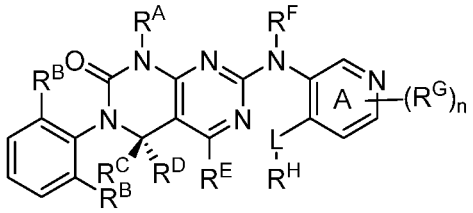
 ,

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

[00129] In certain embodiments, the compound of Formula (**I**) is of the formula:

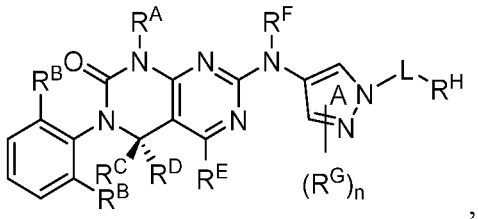
 ,  ,

 ,  ,or


,

,

,

,

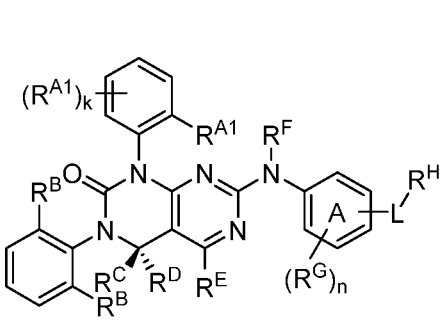
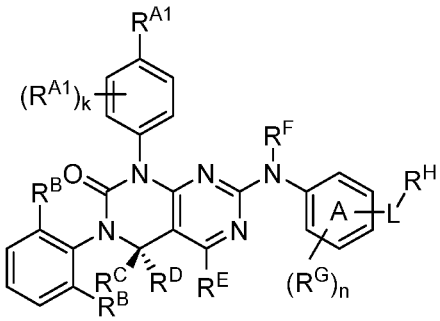
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00130] In certain embodiments, the compound of Formula (**I**) is of the formula:


,

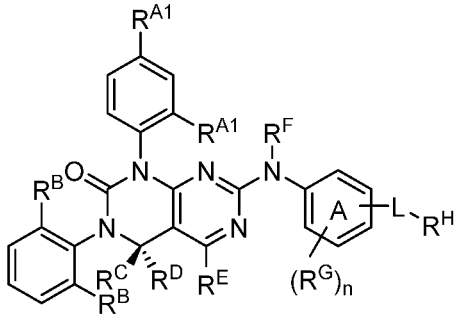
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00131] 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.

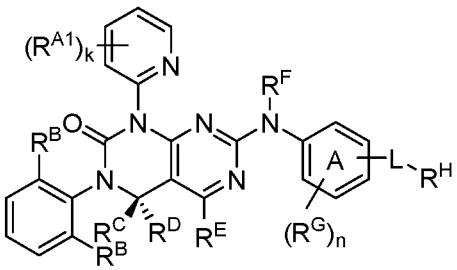
[00132] In certain embodiments, the compound of Formula (**I**) is of the formula:



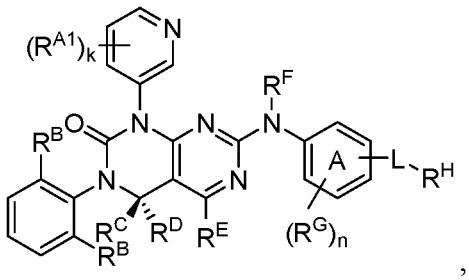
,

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

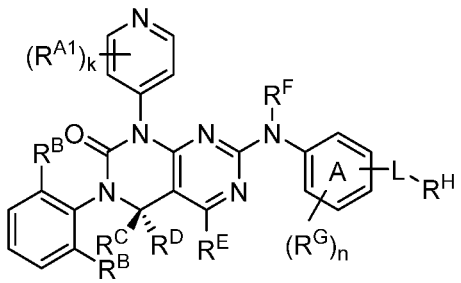
[00133] In certain embodiments, the compound of Formula (**I**) is of the formula:



,



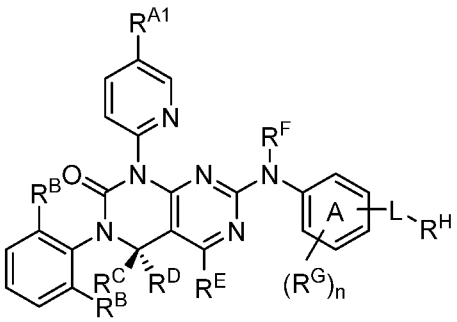
,



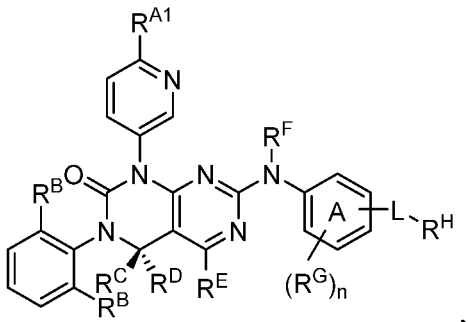
,

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

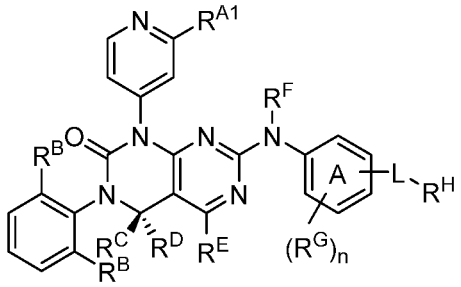
[00134] In certain embodiments, the compound of Formula (**I**) is of the formula:



,



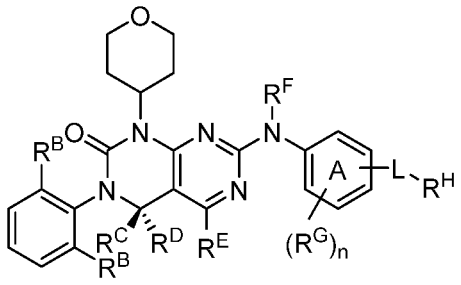
,



,

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

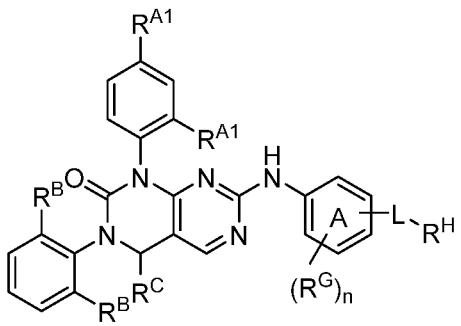
[00135] In certain embodiments, the compound of Formula (**I**) is of the formula:



,

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

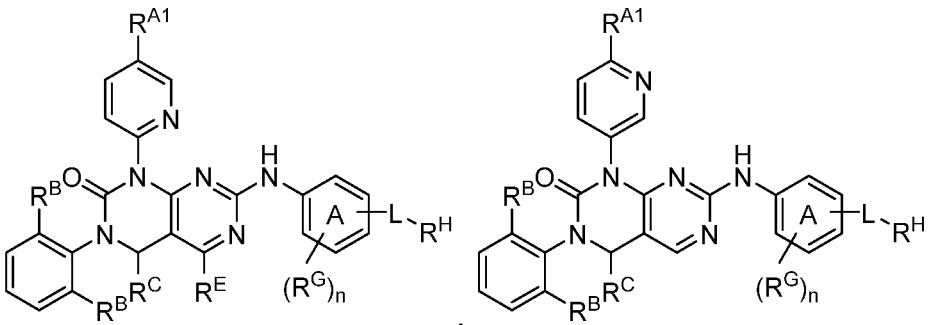
[00136] In certain embodiments, the compound of Formula (**I**) is of the formula:



,

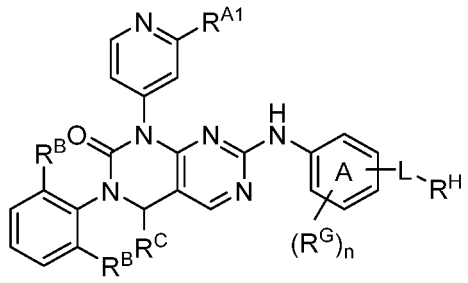
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00137] In certain embodiments, the compound of Formula (**I**) is of the formula:



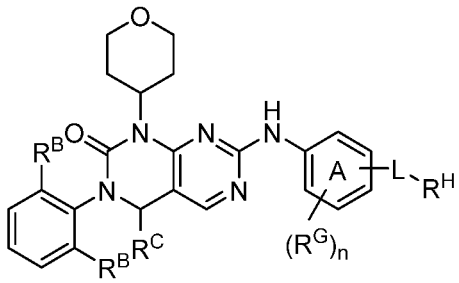
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, the compound of Formula (**I**) is of the formula:



,

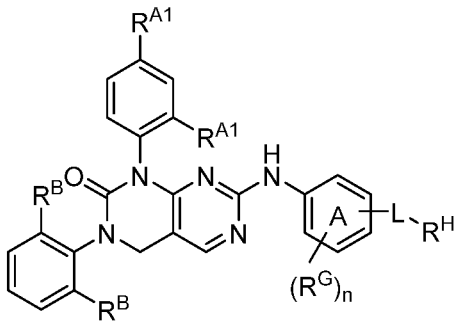
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, the compound of Formula (**I**) is of the formula:



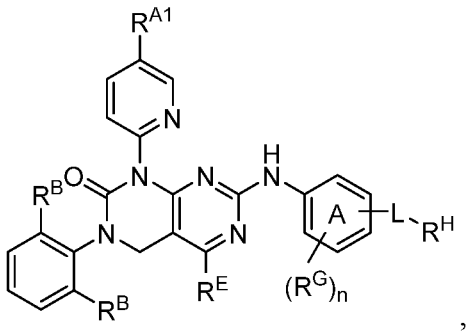
,

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

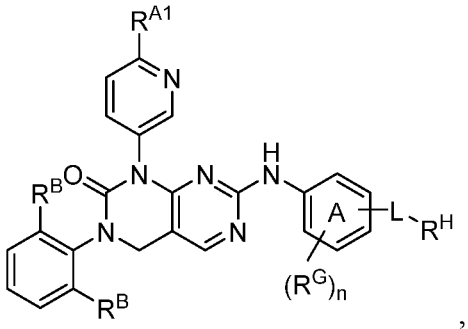
[00138] In certain embodiments, the compound of Formula (**I**) is of the formula:



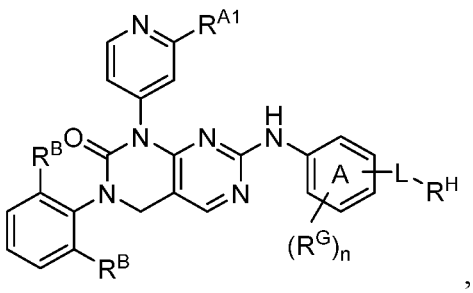
,



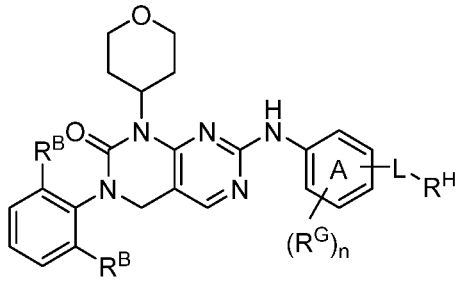
,



,



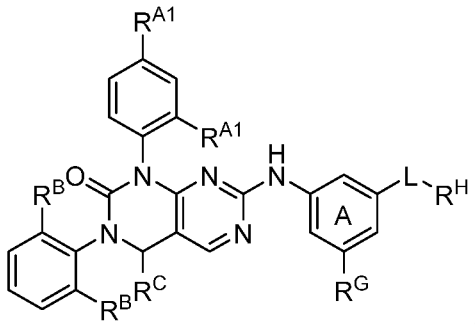
,



,

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

[00139] In certain embodiments, the compound of Formula (**I**) is of the formula:



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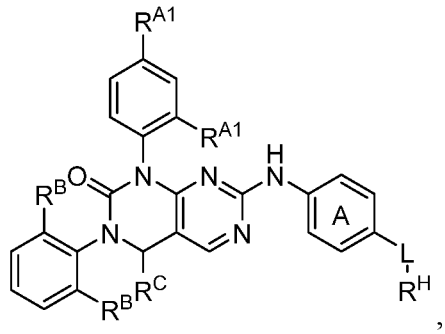

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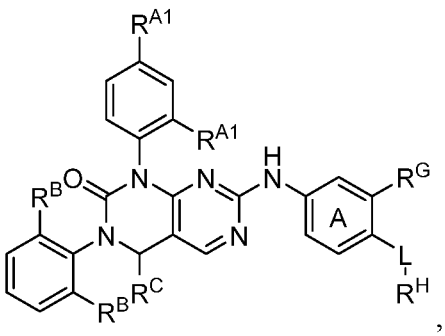

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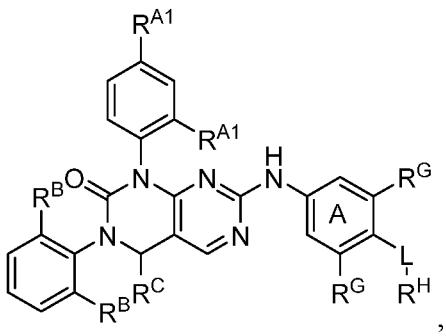

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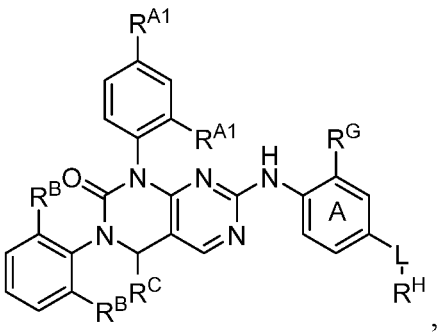

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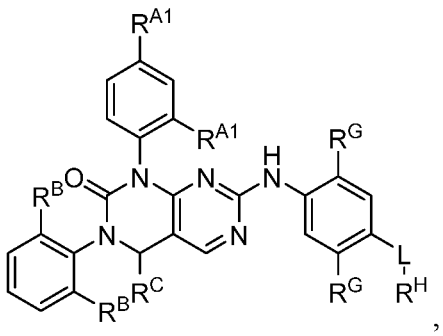

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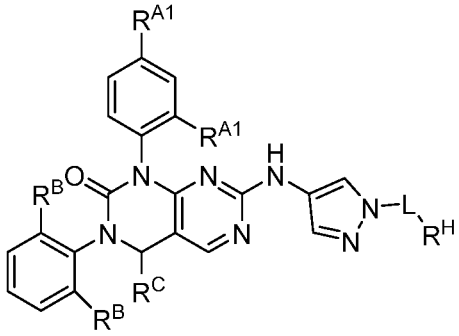
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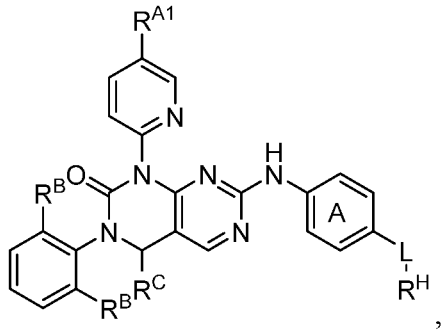
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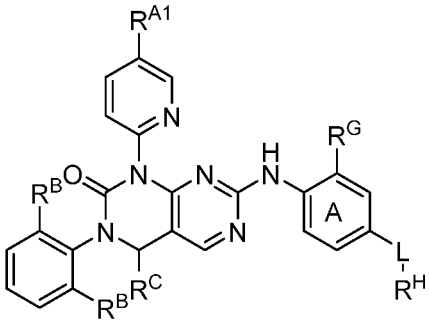
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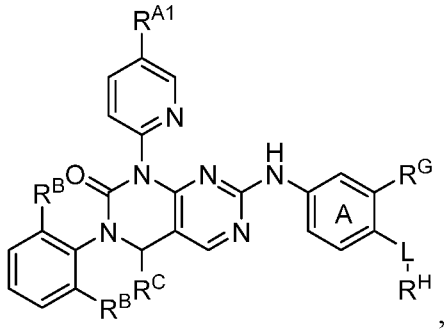
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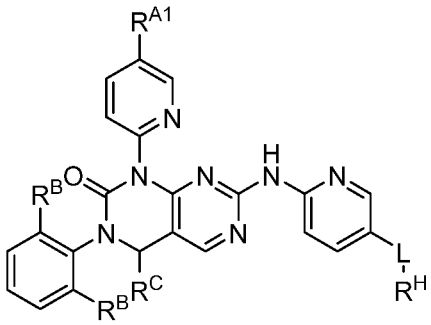
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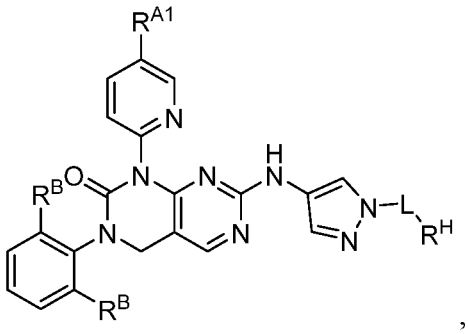
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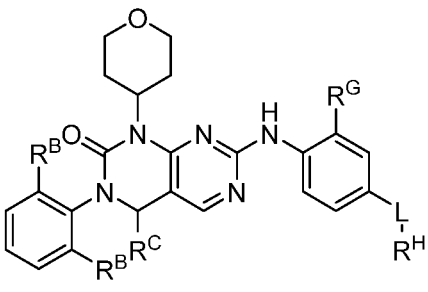
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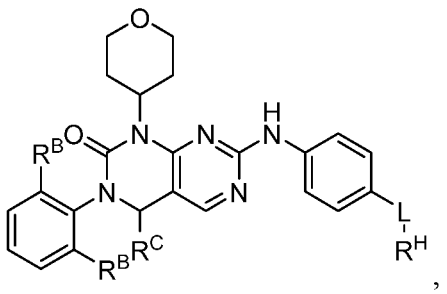
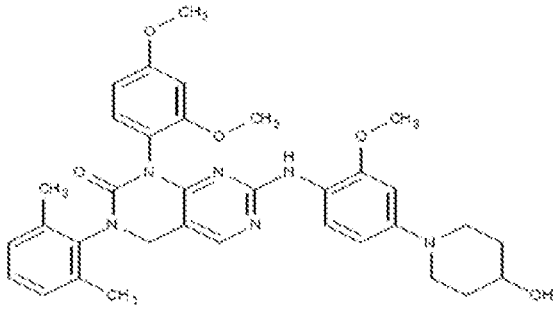
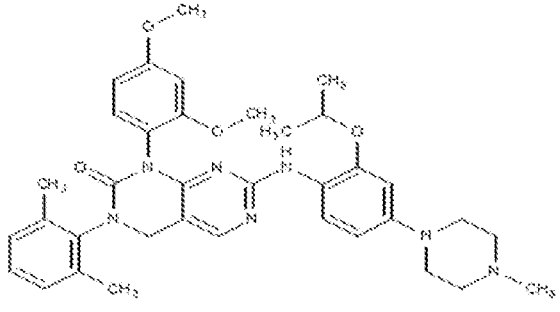

,

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

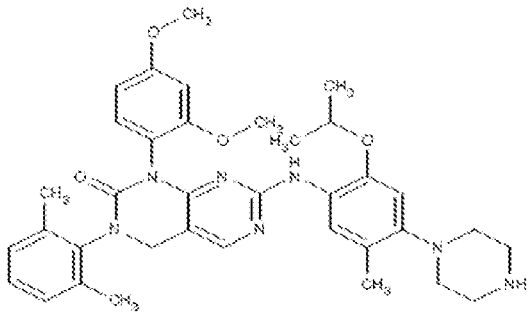
[00140] In certain embodiments, the compound of Formula (**I**) is of the formula:



(YKL-05-57)



(YKL-05-58)



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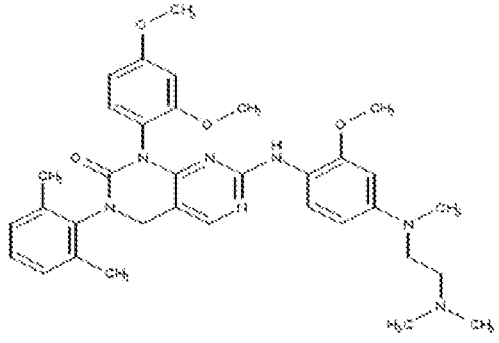

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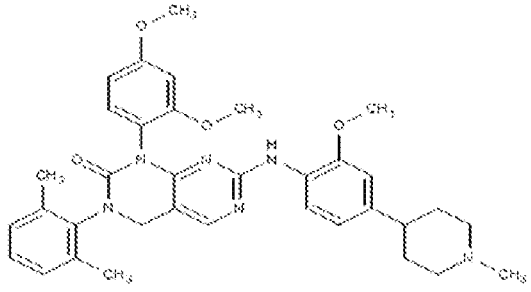
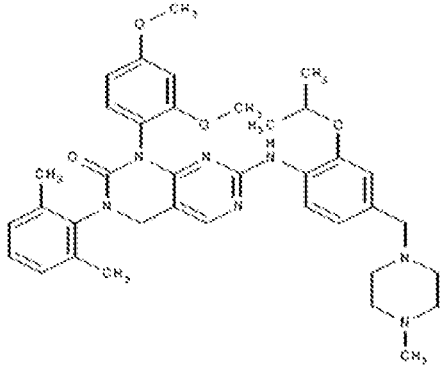
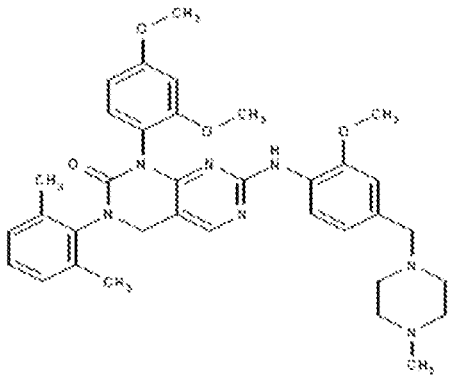


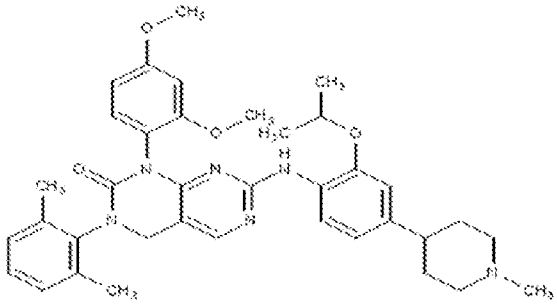
(YKL-05-68)



(YKL-05-69)



(YKL-05-70)



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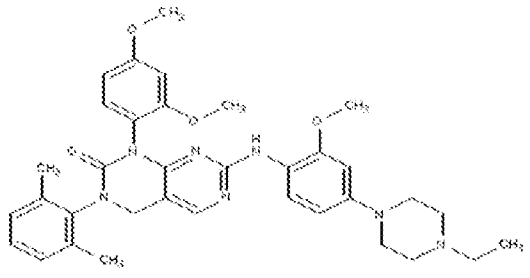

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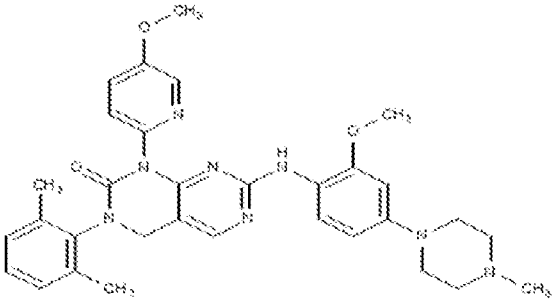

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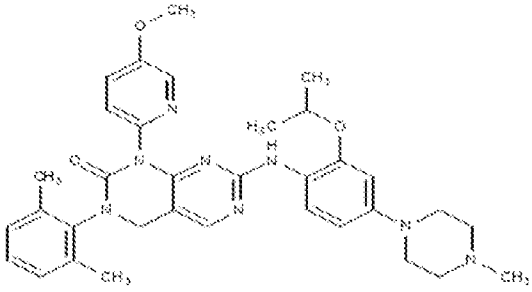

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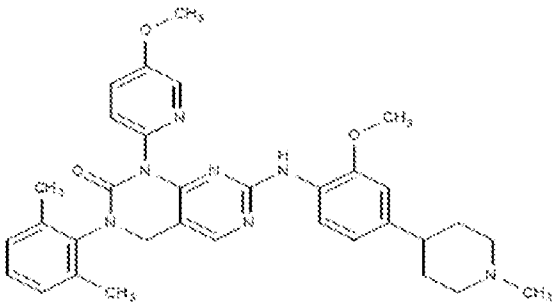

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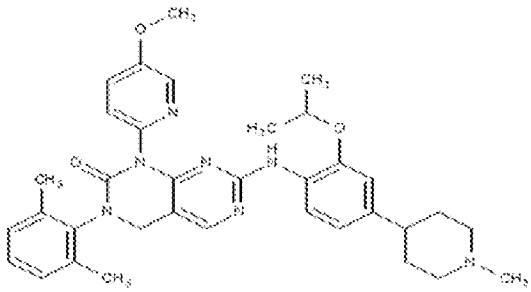

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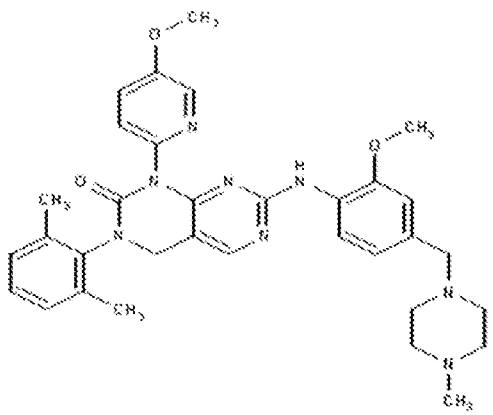

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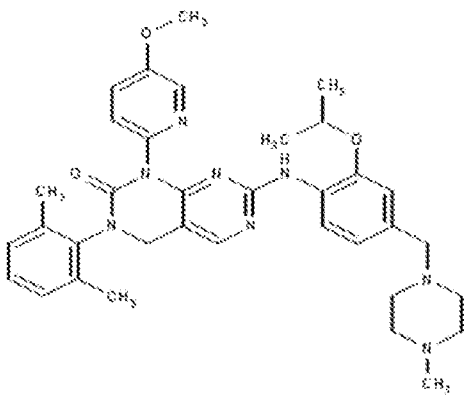

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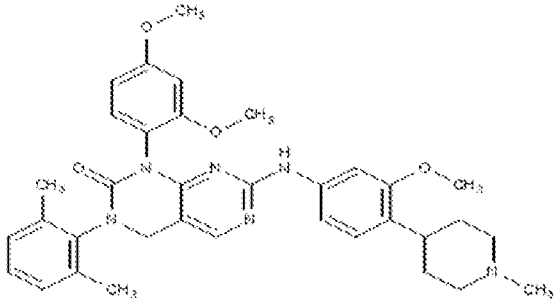
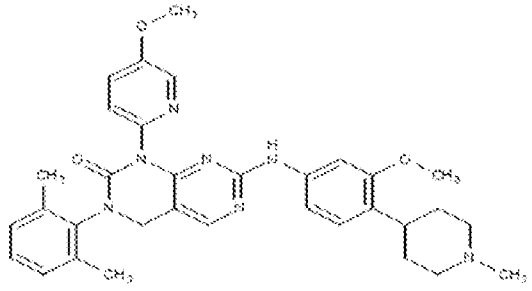


(YKL-05-93)



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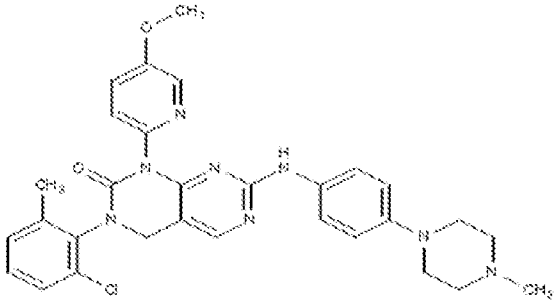
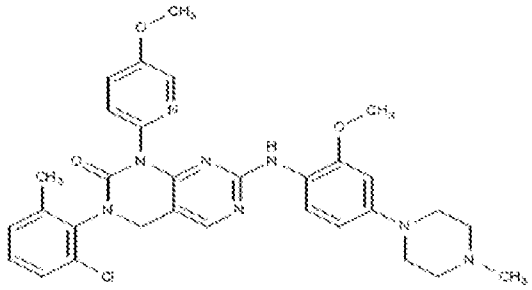


(YKL-05-95)



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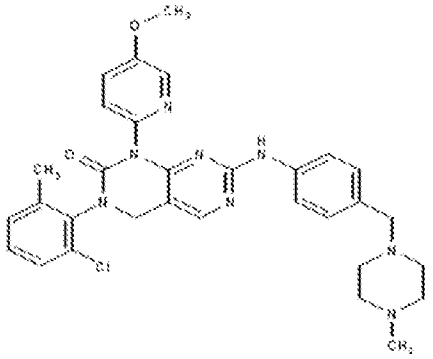

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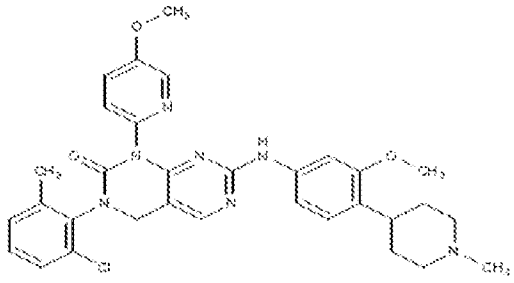

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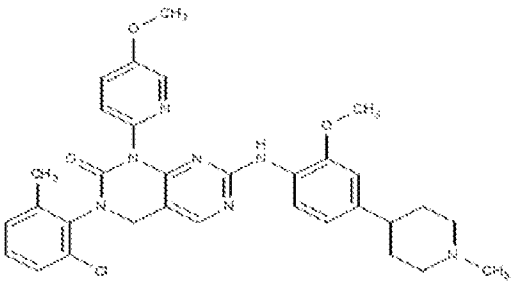

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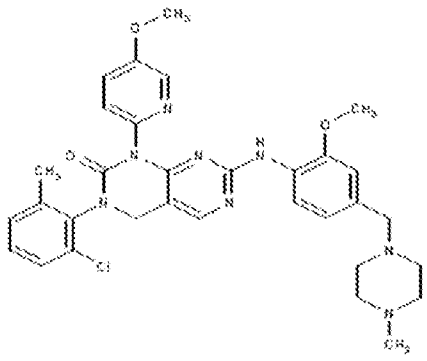

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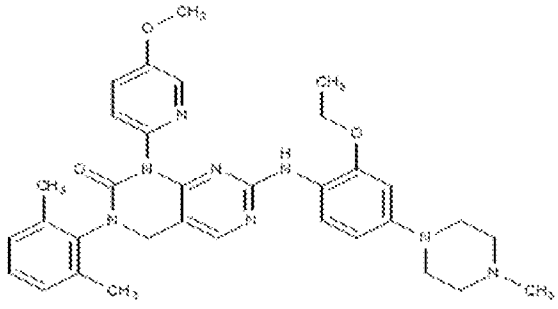

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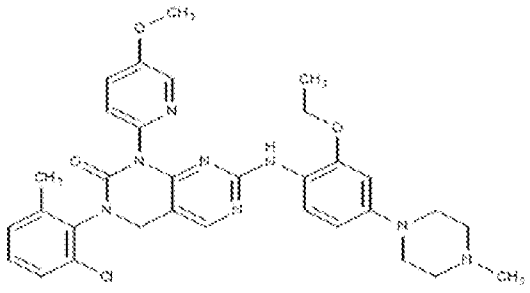

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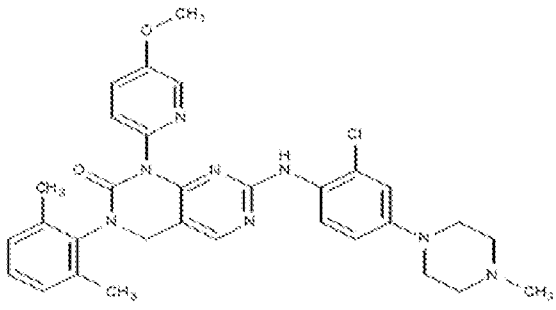

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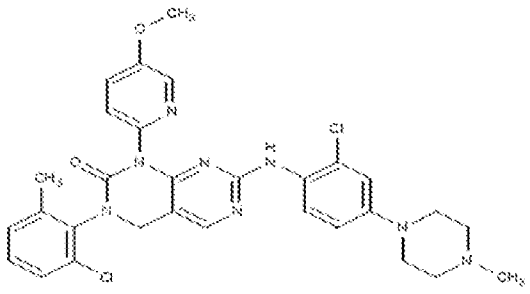

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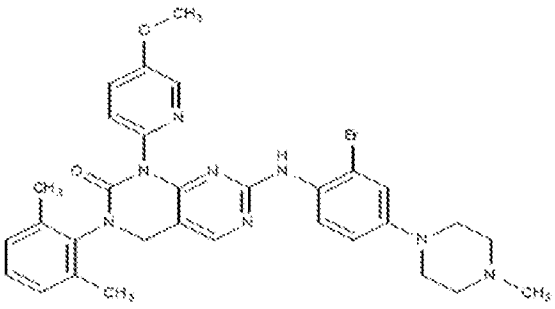

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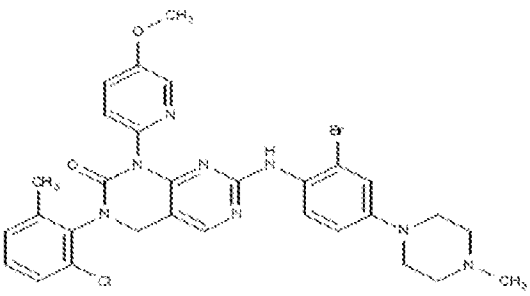
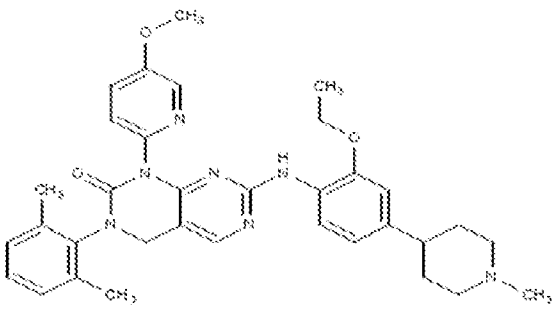
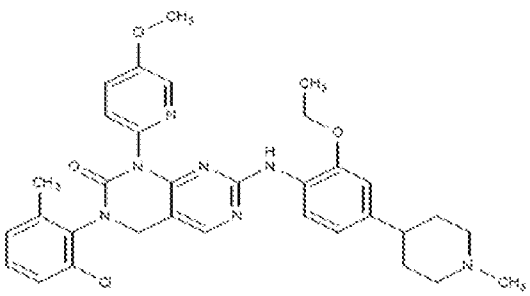


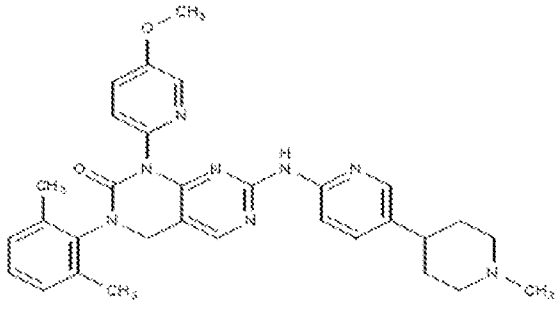
(YKL-05-156)



(YKL-05-163)



(YKL-05-164)



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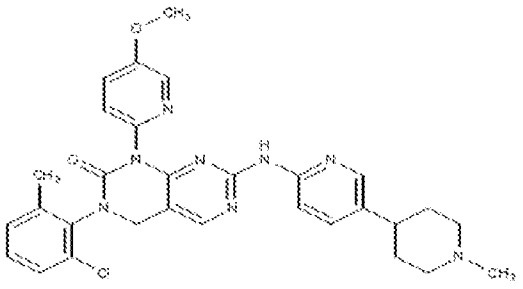

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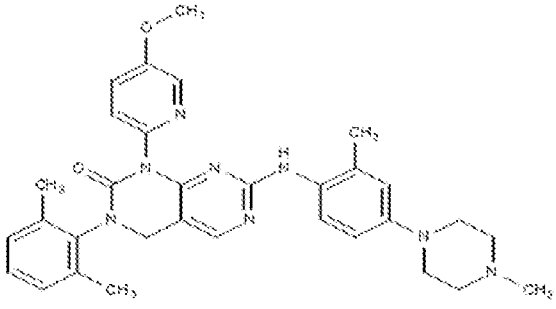

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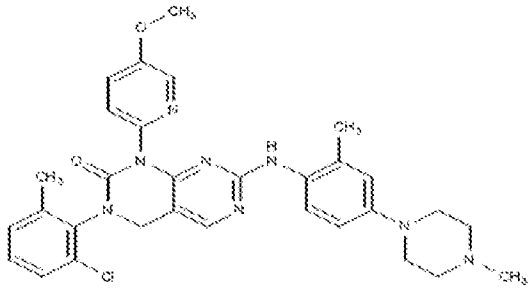

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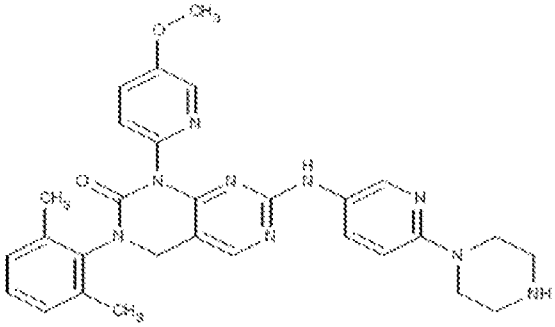
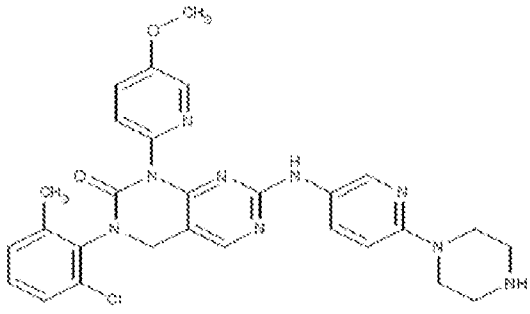


(YKL-05-180)



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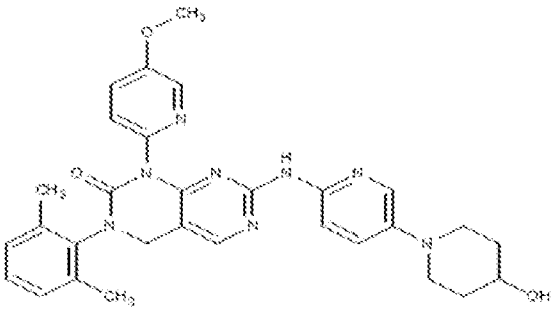

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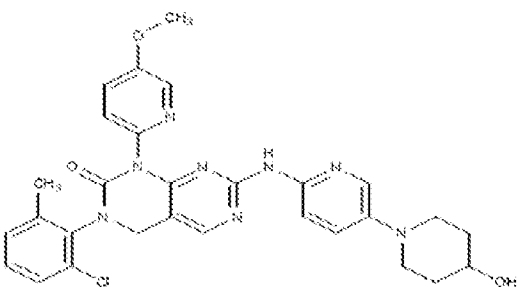

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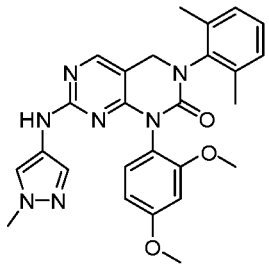
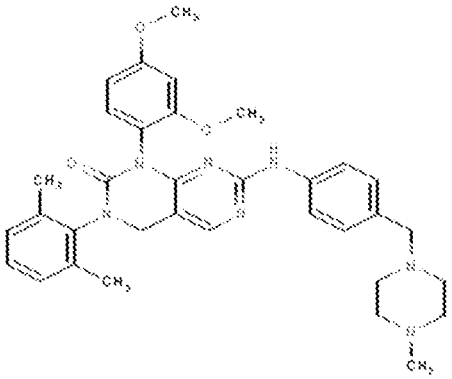
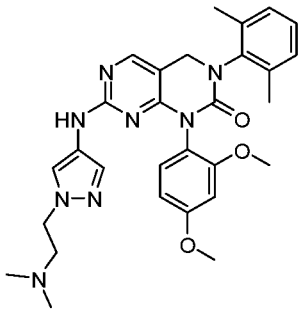


(Example 2)



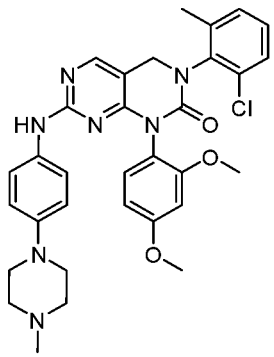
(YKL-04-136-1)

(SB1-D-01)



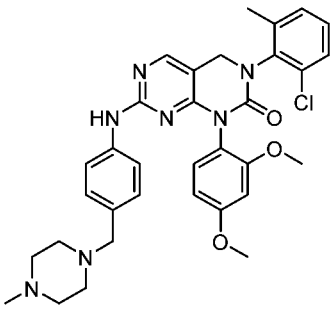
(SB1-D-02)

(YKL-04-136-2)



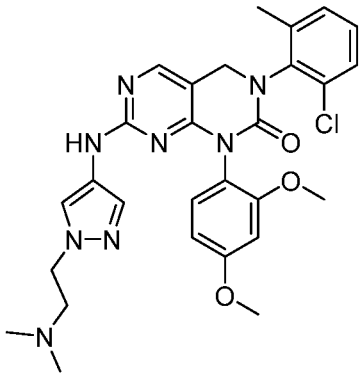
(SB1-D-03)

(YKL-04-136-3)



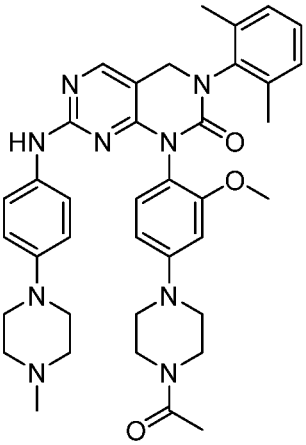
(SB1-D-04)

(YKL-04-136-9)



(SB1-D-05)

(YKL-04-136-4)



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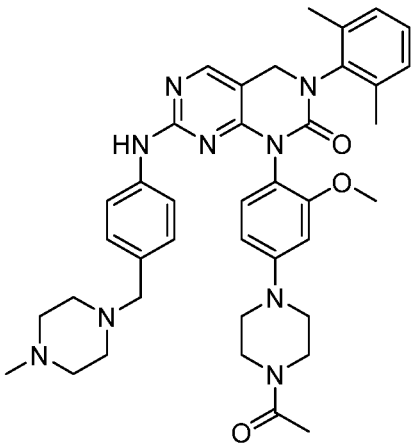
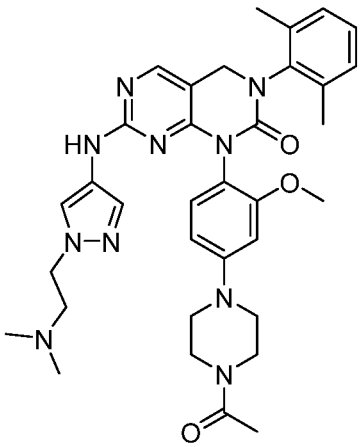
(YKL-04-136-5)



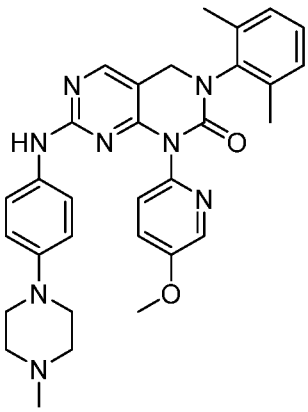
(SB1-D-07)

(YKL-04-136-11)



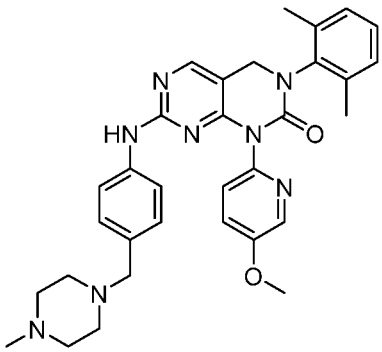
(SB1-D-08)

(YKL-04-136-7)



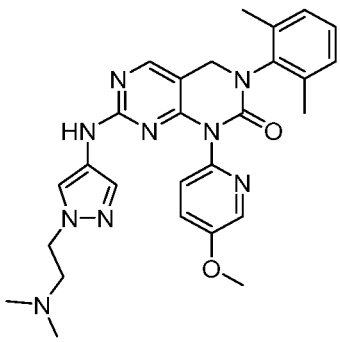
(SB1-D-09)

(YKL-04-136-6)



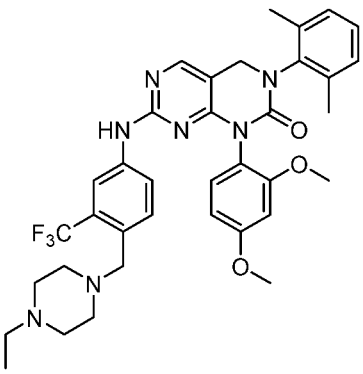
(SB1-D-10)

(YKL-04-136-10)



(SB1-D-11)

(YKL-04-136-8)



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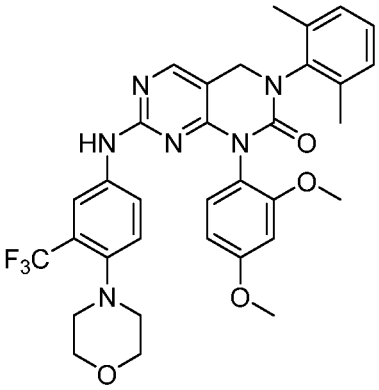

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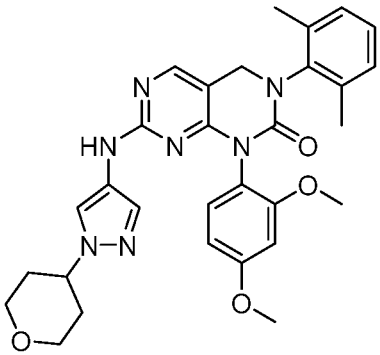

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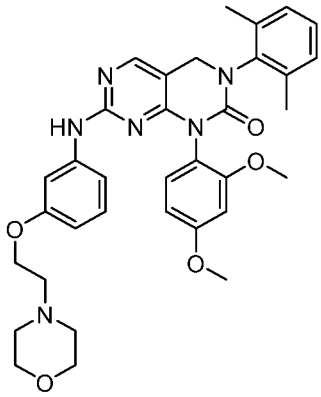
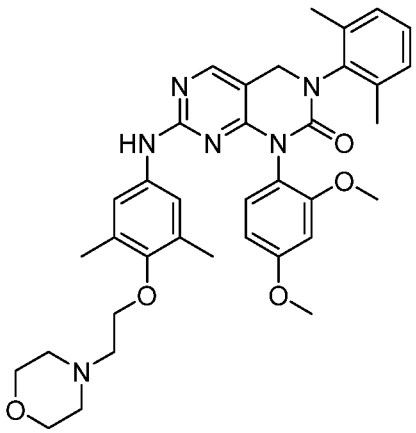
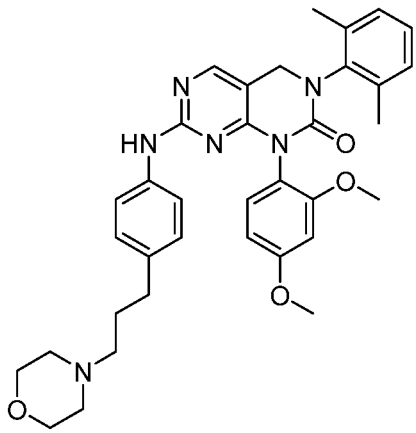


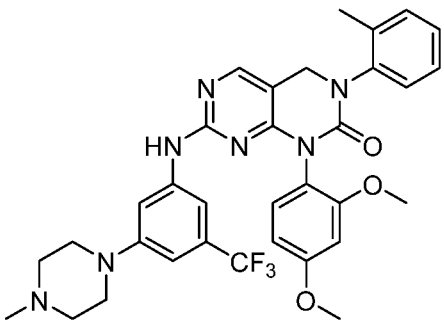
(YKL-04-106)



(YKL-04-107)



(YKL-04-108)



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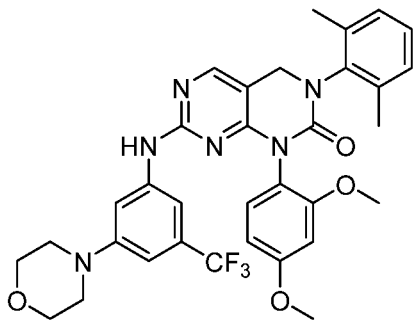
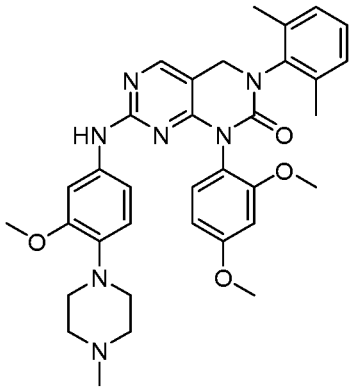
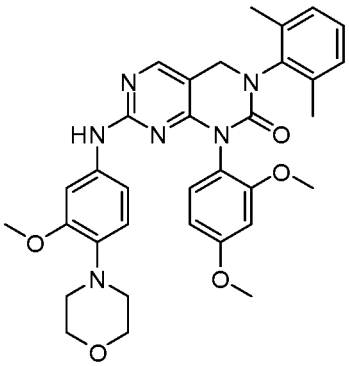


(YKL-04-113)



(YKL-04-114)



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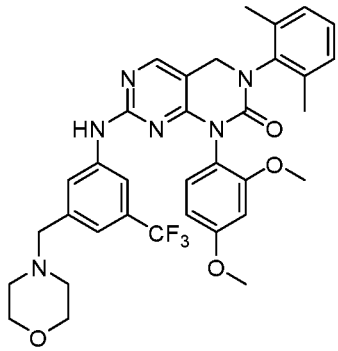

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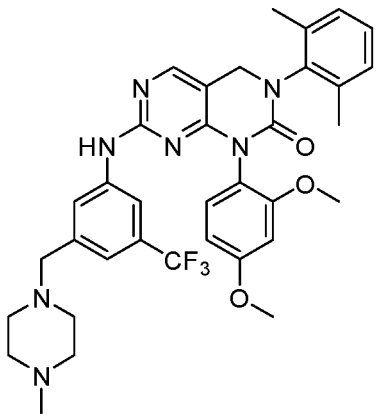
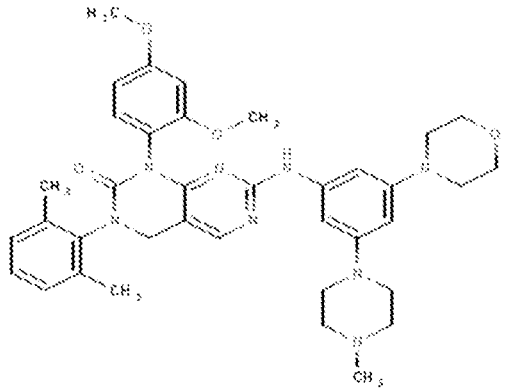
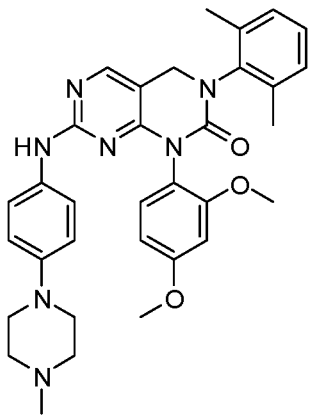


(YKL-04-125)



(HG-11-143-01)



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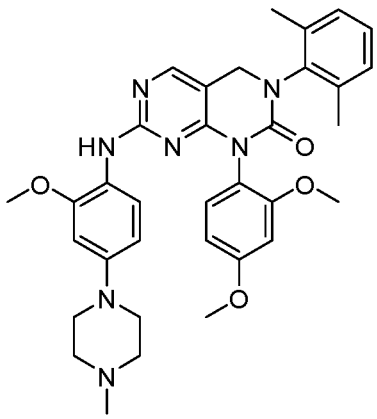

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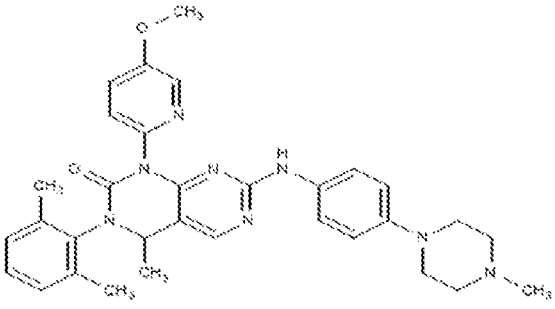
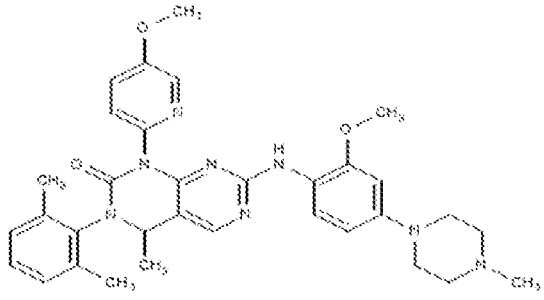


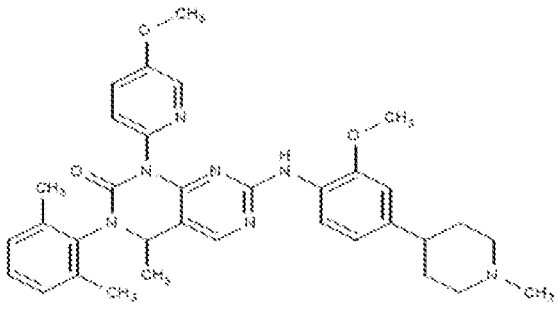
(YKL-06-038)

(SB1-D-40)



(YKL-06-039)

(SB1-D-42)



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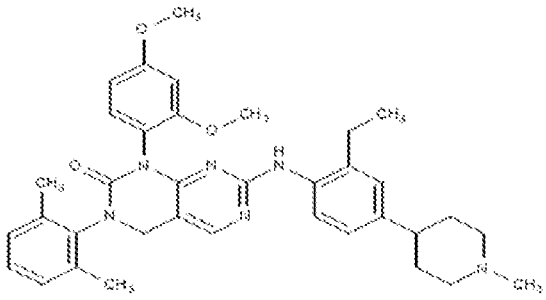

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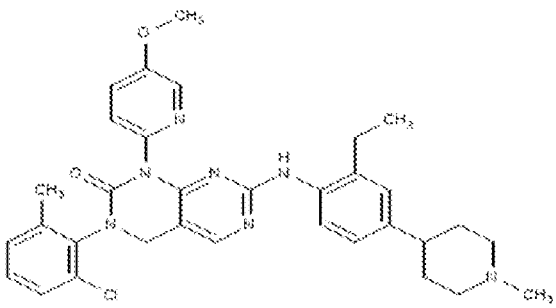

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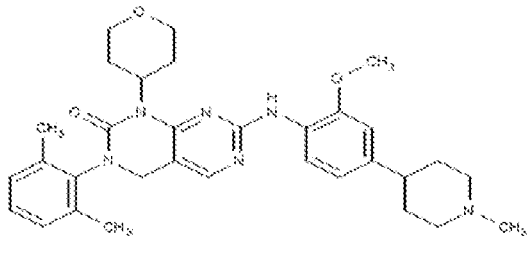

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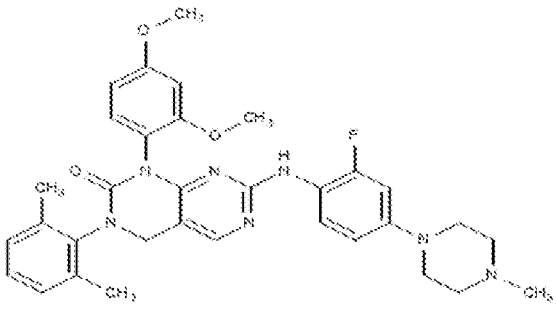

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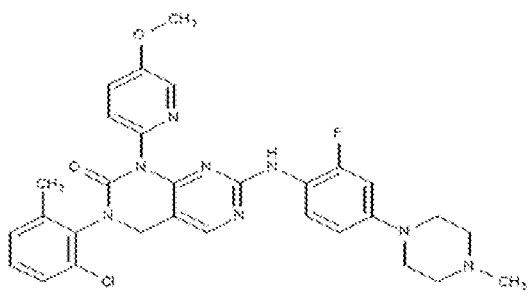

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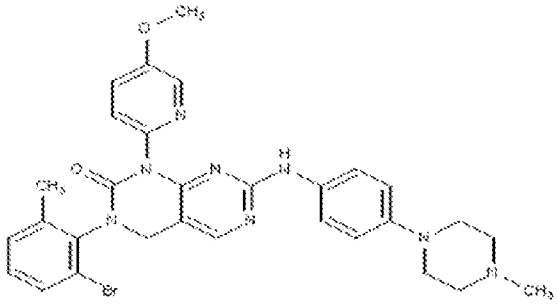
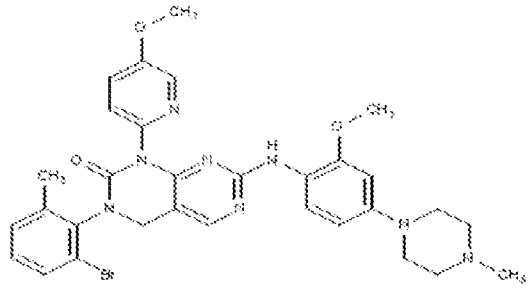
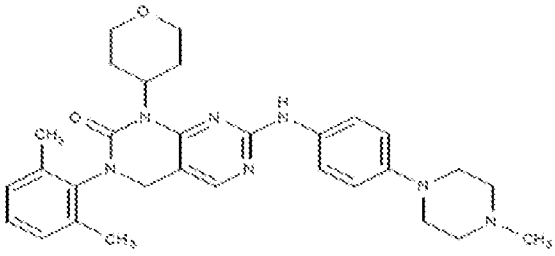


(YKL-06-056)



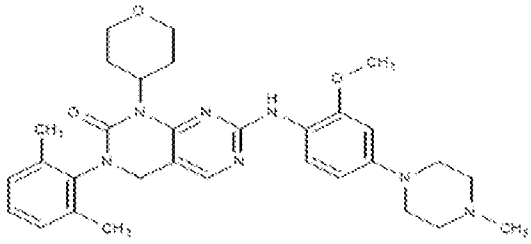
(YKL-06-057)

(SB1-D-43)



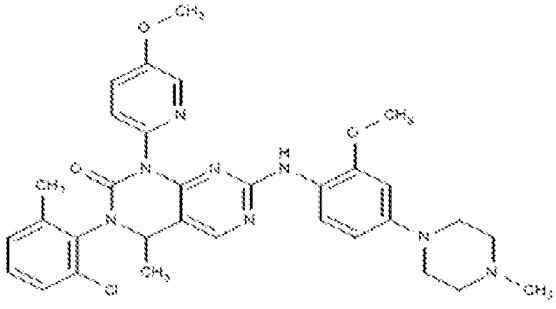
(YKL-06-077)

(SB1-D-57)



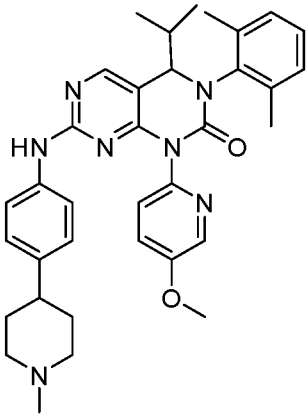
(YKL-06-078)

(SB1-D-58)



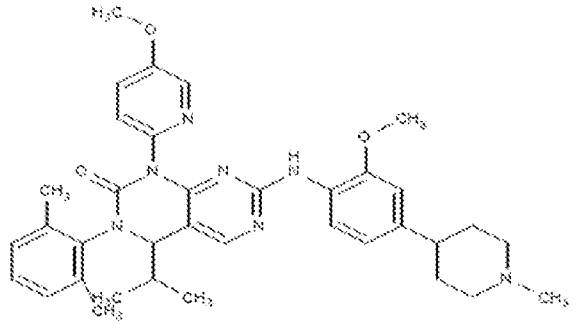
(YKL-06-080-1)

(SB1-D-60)



(YKL-06-081-1)

(SB1-D-61)

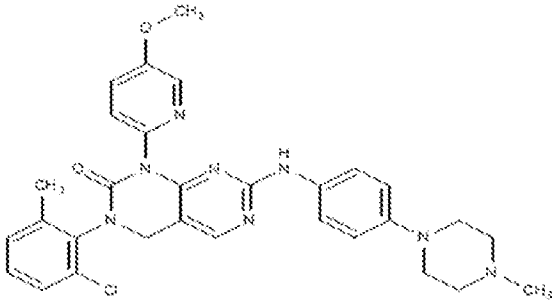


(YKL-06-082)

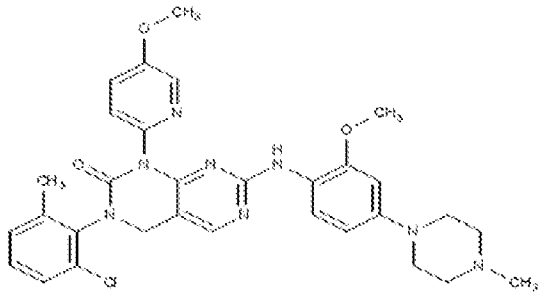
(SB1-D-62)

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

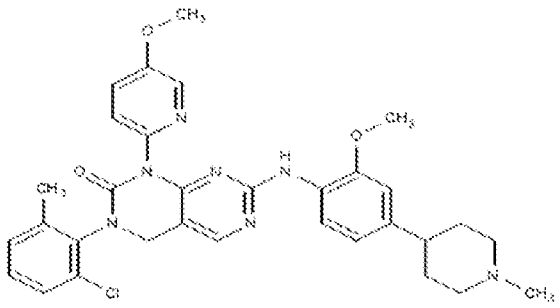
[00141] In certain embodiments, the compound of Formula (**I**) is not of the formula:



(YKL-05-95)



(YKL-05-96)

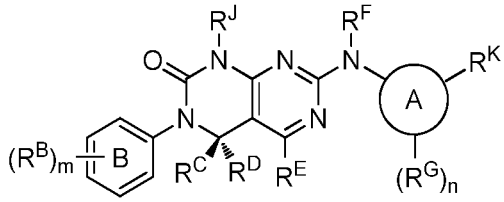


(YKL-05-99),

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

Compounds of Formula (II)

[00142] In one aspect, the present disclosure provides compounds of Formula (**II**):



(**II**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs 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, $–C(=NR^b)R^a$, $–C(=NR^b)OR^a$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^a$, $–NR^bC(=O)OR^a$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^a$, $–OC(=O)OR^a$, 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;

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;

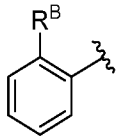
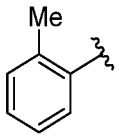
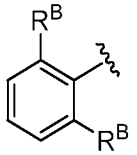
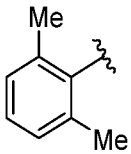
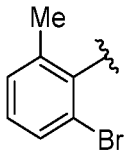
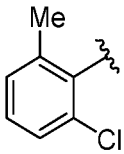
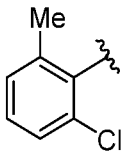
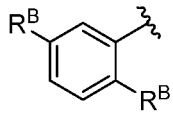
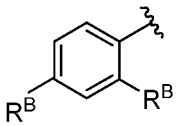
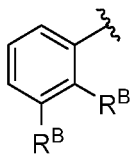
each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted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

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

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.

[00143] 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.

[00144] As generally defined herein, as applicable to Formula (**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: 
.

[00145] In certain embodiments, at least one instance of R^B is halogen (*e.g.*, F, Cl, 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 Cl. 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_{1-6} 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}

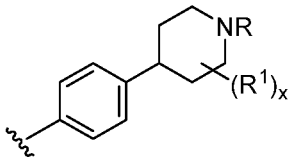
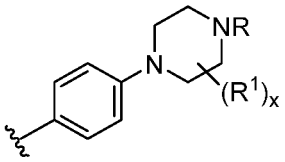
alkenyl). In certain embodiments, at least one instance of R^B is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{2-6} alkynyl). In certain embodiments, at least one instance of R^B is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 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 $-OC(=O)N(R^b)_2$.

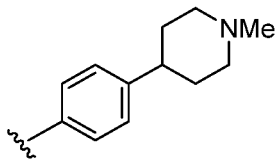
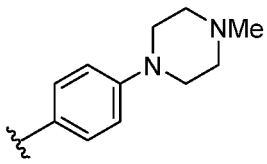
[00146] Formula (**II**) includes substituents R^C, R^D, R^E, and R^F. Substituents R^C, R^D, R^E, and R^F are described in the Detailed Description for Formula (**III**) below.

[00147] Formula (**II**) includes Ring A and one or more instances of substituent R^G. Ring A and substituent R^G are described in the Detailed Description for Formula (**III**) below.

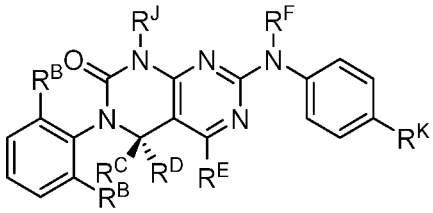
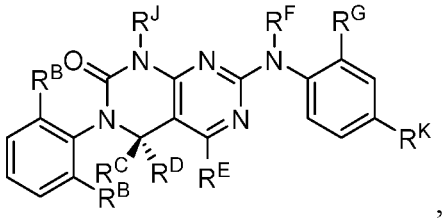
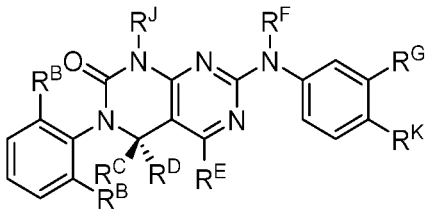
[00148] As generally defined herein, Formula (**II**) includes substituent R^K attached to Ring A. Substituent R^K is described in the Detailed Description for Formula (**III**) below.

[00149] In certain embodiments, Ring A with substituent R^K is of the formula:

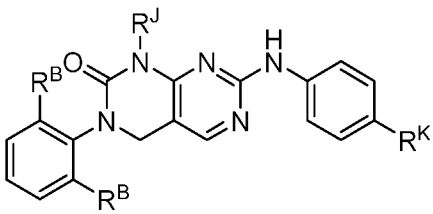
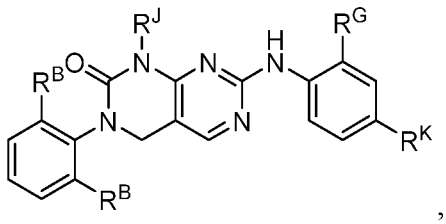
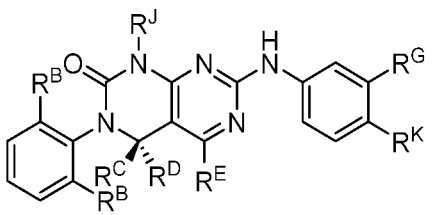
or . In certain embodiments, Ring A with substituent R^K is of the formula:  or  .

[00150] In certain embodiments, the compound of Formula (**II**) is of the formula:


,

,

,

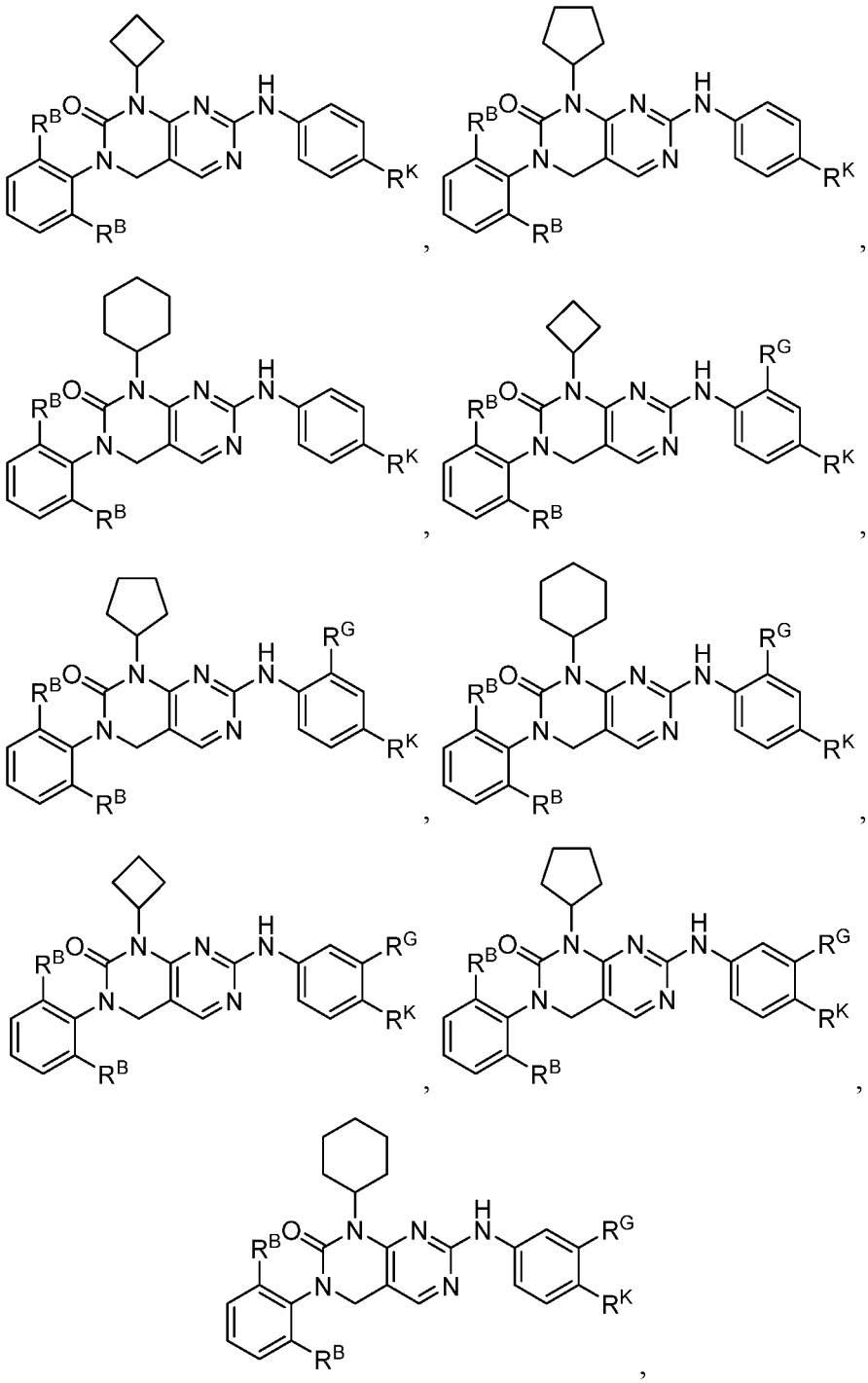
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00151] In certain embodiments, the compound of Formula (**II**) is of the formula:


,

,

,

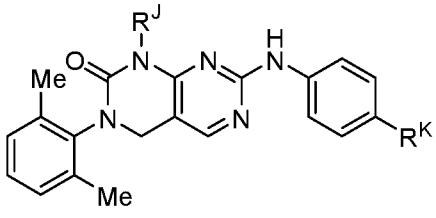
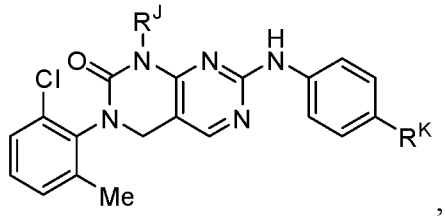
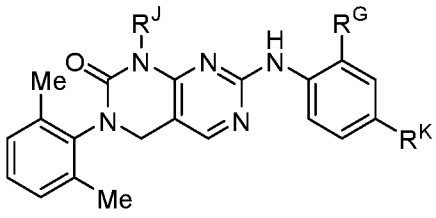
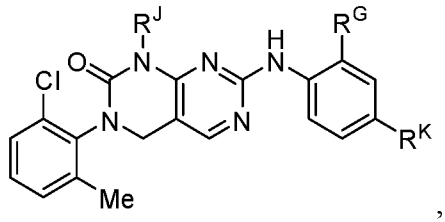
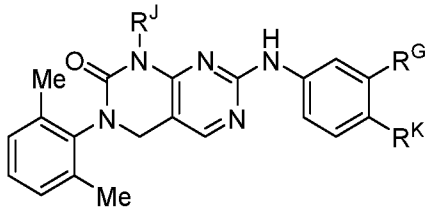
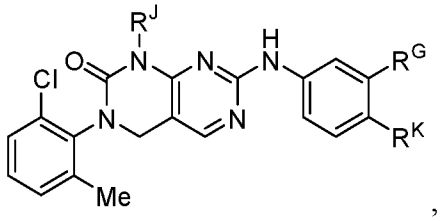
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00152] In certain embodiments, the compound of Formula (**II**) is of the formula:



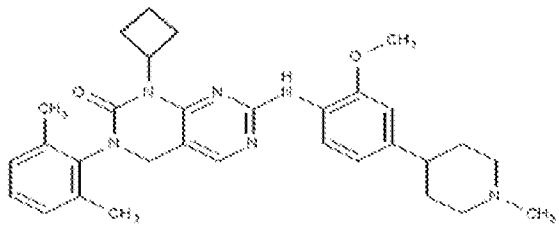
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00153] In certain embodiments, the compound of Formula (**II**) is of the formula:

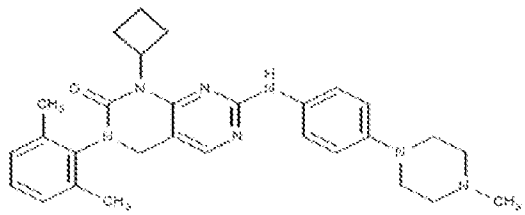

,

,

,

,

,

,

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

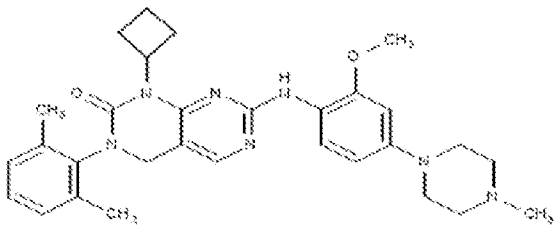
[00154] In certain embodiments, the compound of Formula (**II**) is of the formula:



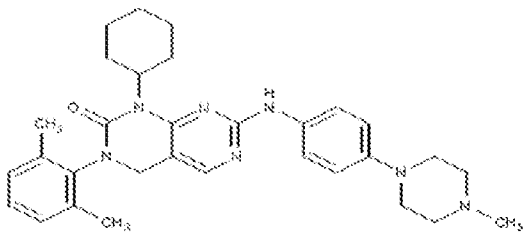
(YKL-06-050)



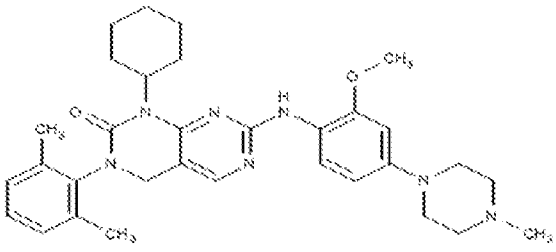
(YKL-06-060)



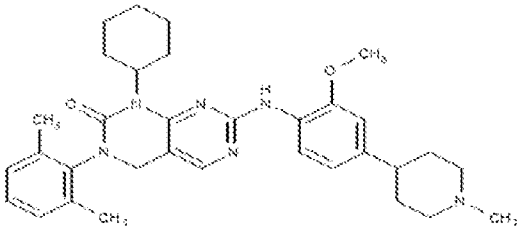
(YKL-06-061)



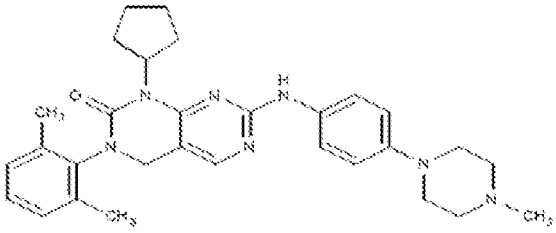
(YKL-06-062)



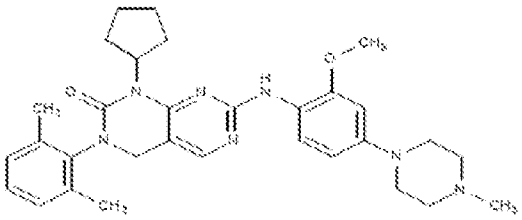
(YKL-06-063)



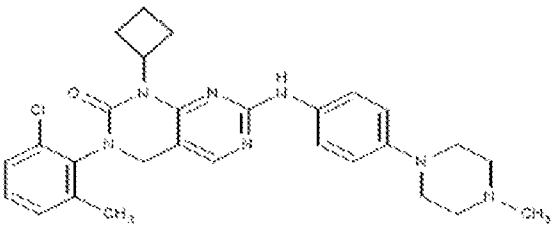
(YKL-06-064)



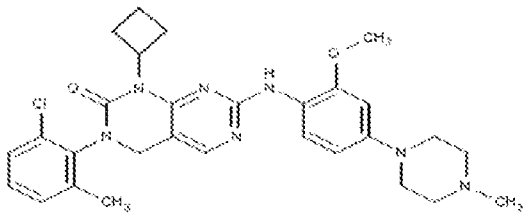
(YKL-06-075)



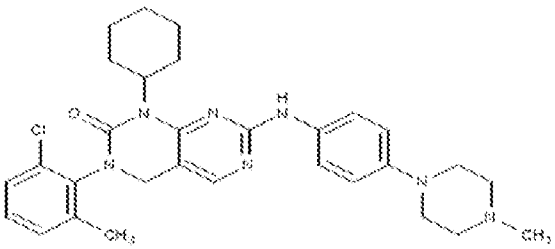
(YKL-06-076)



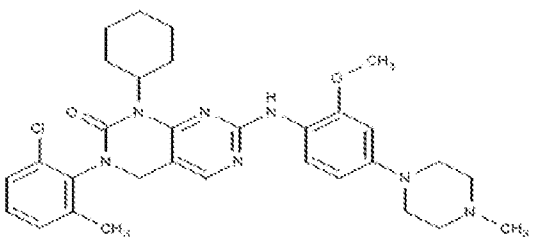
(YKL-06-088)



(YKL-06-089)



(YKL-06-090)

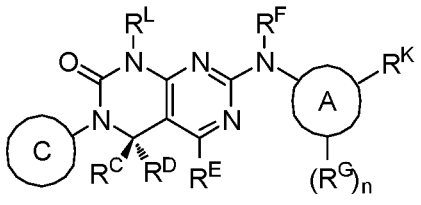


(YKL-06-091)

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

Compounds of Formula (III)

[00155] In certain embodiments, the compound is of Formula (**III**):

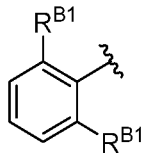
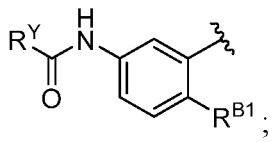


(**III**),

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, $-OR^a$, $-N(R^d)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^d)R^a$, $-C(=NR^d)OR^a$, $-C(=NR^d)N(R^d)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^d)_2$, $-NO_2$, $-NR^dC(=O)R^a$, $-NR^dC(=O)OR^a$, $-NR^dC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^d)_2$;

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, $-C(=O)R^a$, 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;

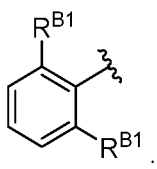
each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted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

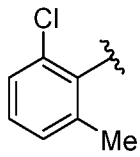
n is 0, 1, 2, 3, or 4, as valency permits;

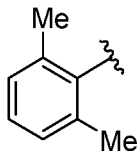
R^K is unsubstituted methyl, substituted or unsubstituted heterocyclyl, $-OR^a$, or $-N(R^c)_2$, wherein each instance of R^c is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group, or optionally two instances of R^c are taken together with their intervening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

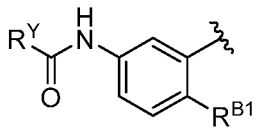
R^Y is substituted phenyl.

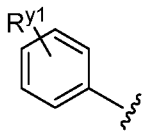
[00156] Formula (**III**) includes Ring C. In certain embodiments, Ring C is unsubstituted phenyl. In certain embodiments, Ring C is of the formula: 

. 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

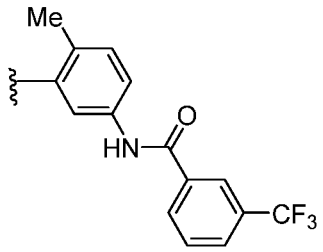
least one instance of R^{B1} is I (iodine). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted methyl. In certain embodiments, 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: 

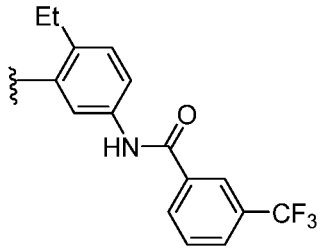
. In certain embodiments, Ring C is of the formula: 

. 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: 

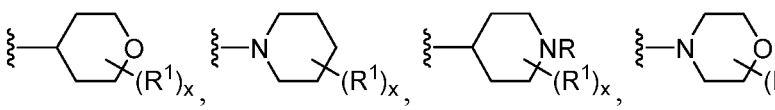
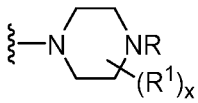
, wherein R^{y1} is halogen or substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{y1} is halogen (*e.g.*, Br, Cl, F). In certain embodiments, R^{y1} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, substituted or unsubstituted, methyl, ethyl, or propyl). In certain embodiments, 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

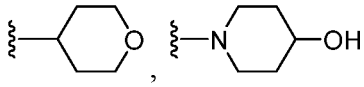
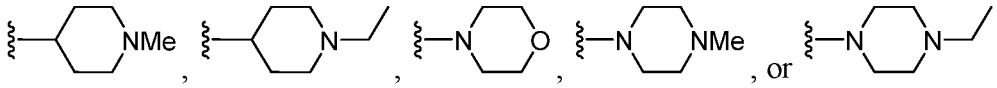
embodiments, Ring C is of the formula:  . In certain



embodiments, Ring C is of the formula: .

[00157] 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.

[00158] As generally defined herein, 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:  , 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 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 $-OR^a$ (*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 $-OC(=O)N(R^b)_2$.

[00159] As generally defined herein, Formula (**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.

[00160] As generally defined herein, Formula (**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.

[00161] As generally defined herein, Formula (**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.

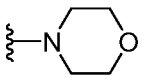
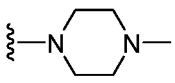
[00162] As generally defined herein, Formula (**I**), (**II**), and (**III**) include substituent R^F. In certain embodiments, R^F is hydrogen. In certain embodiments, R^E is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, R^F is substituted or unsubstituted 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 *p*-toluenesulfonamide (Ts)).

[00163] 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.

[00164] As generally defined herein, Formula (**I**), (**II**), and (**III**) 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

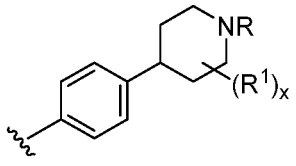
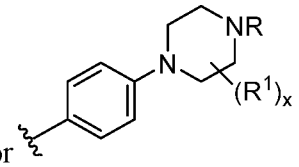
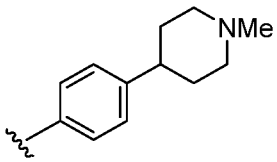
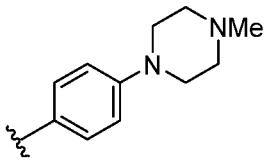
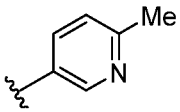
embodiments, Ring A is not substituted phenyl. In certain embodiments, Ring A is not unsubstituted phenyl. In certain embodiments, Ring A is unsubstituted phenyl. In certain embodiments, Ring A is phenyl, and includes one or more R^G substituents. In certain embodiments, Ring A includes one R^G substituent. 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).

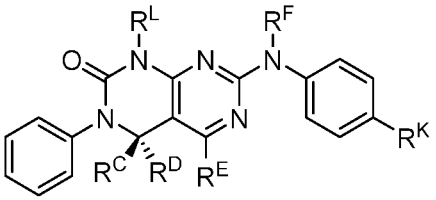
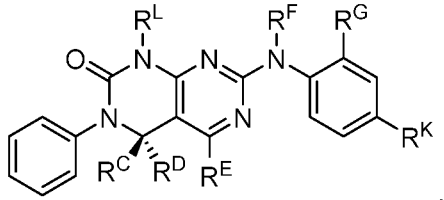
[00165] As generally defined herein, Formula (**I**), (**II**), and (**III**) include one or more instances of substituent R^G. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, at least one instance of R^G is halogen (*e.g.*, F, Cl, 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 Cl. 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

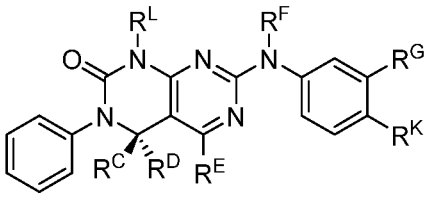
ethyl. In certain embodiments, at least one instance of R^G is unsubstituted ethyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R^G is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted 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 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^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, $-C(=NR^b)R^a$, $-C(=NR^b)OR^a$, –

$C(=NR^b)N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^b)_2$, $-NO_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^b)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^b)_2$.

[00166] In certain embodiments, Ring A with substituent R^K is of the formula:

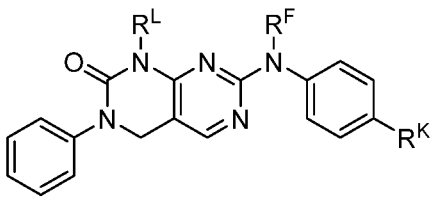
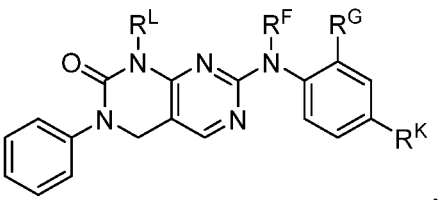
[00167]  or  . In certain embodiments, Ring A with substituent R^K is of the formula:  ,  , or  . In certain embodiments, the compound of Formula (**III**) is of the formula:

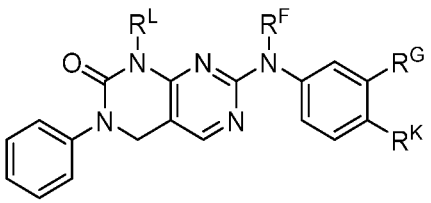
 ,  ,

 ,

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

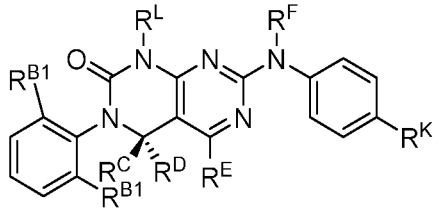
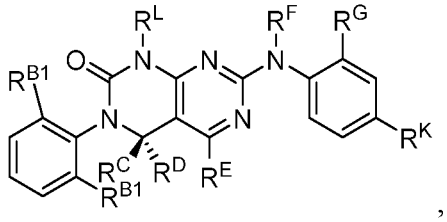
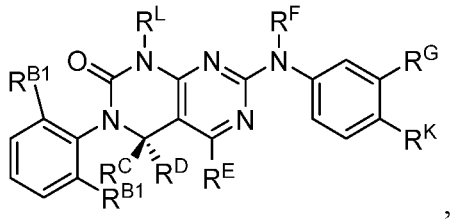
[00168] In certain embodiments, the compound of Formula (**III**) is of the formula:

 ,  ,

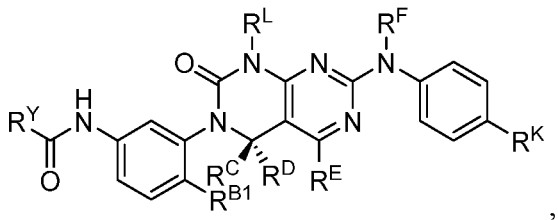
 ,

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

[00169] In certain embodiments, the compound of Formula (**III**) is of the formula:

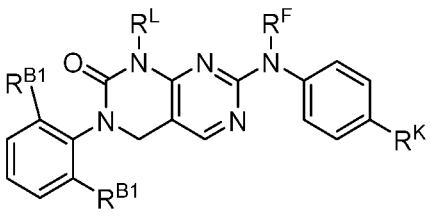

,

,

,

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

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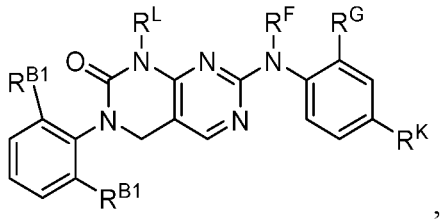
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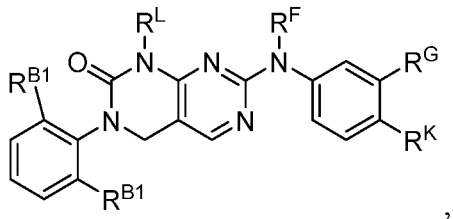
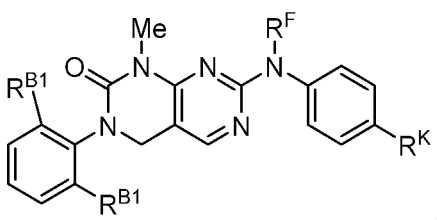

,

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

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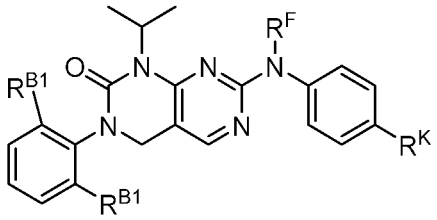
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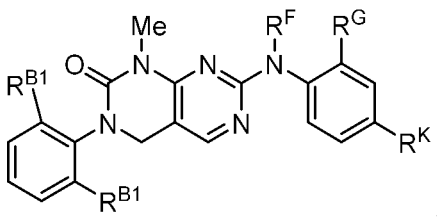
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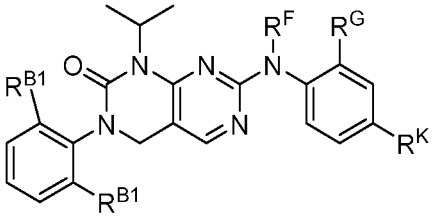
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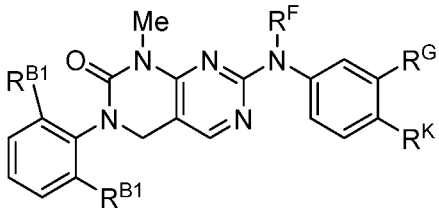
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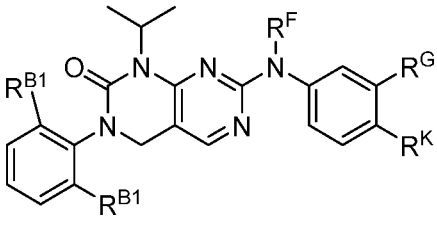
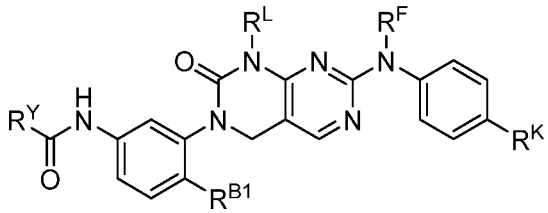

,

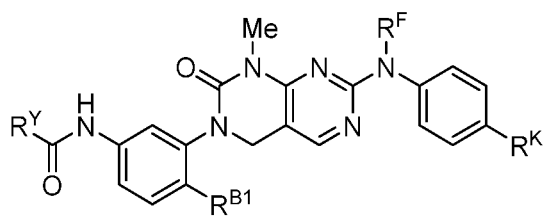
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00172] 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.

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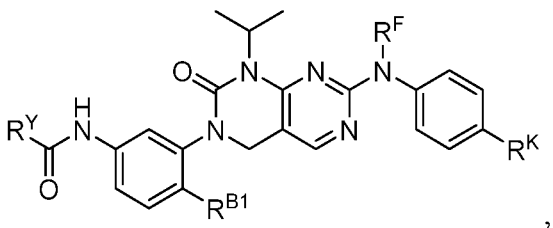
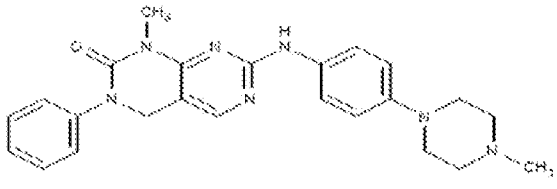
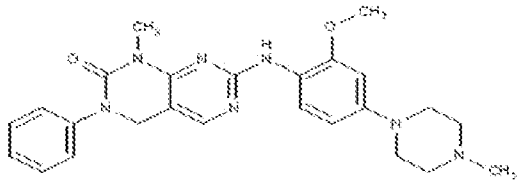

,

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

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



(HG-11-137-01)



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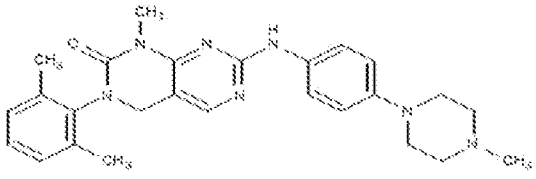
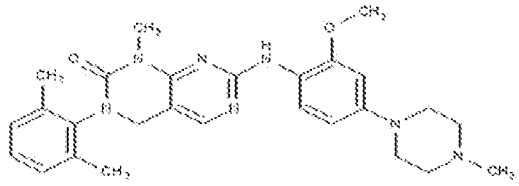


(YKL-06-029)



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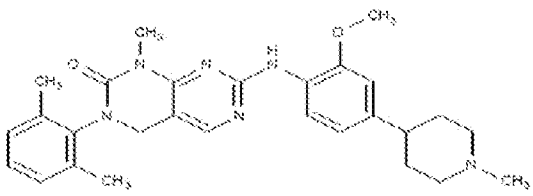

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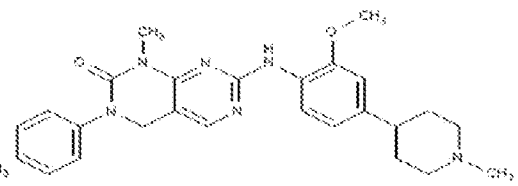

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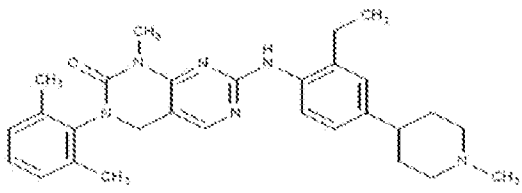

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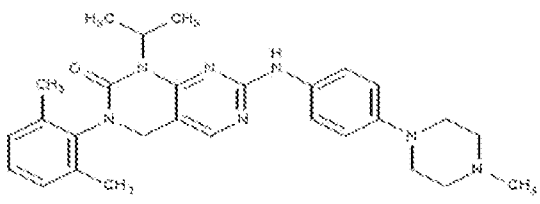

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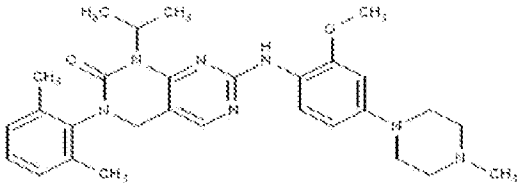

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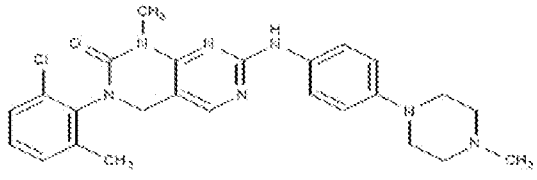

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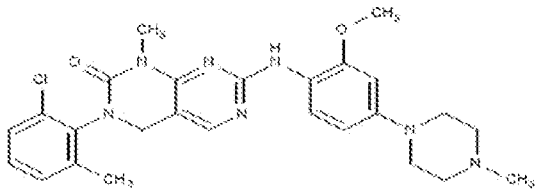

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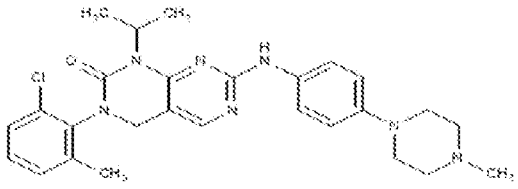

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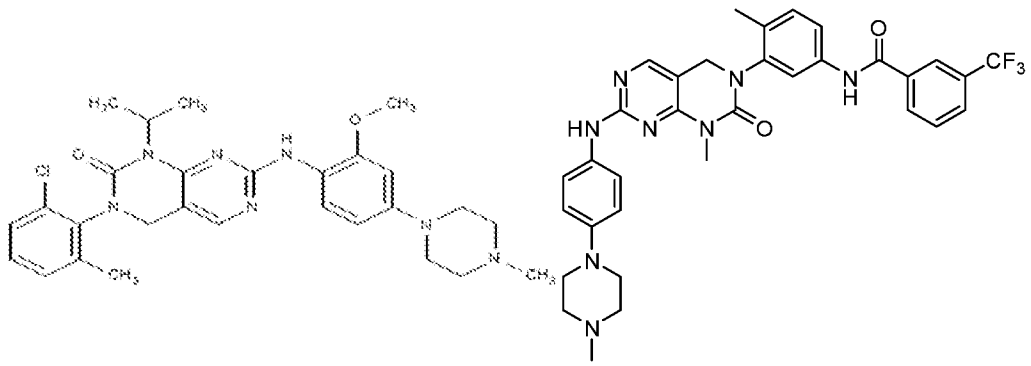

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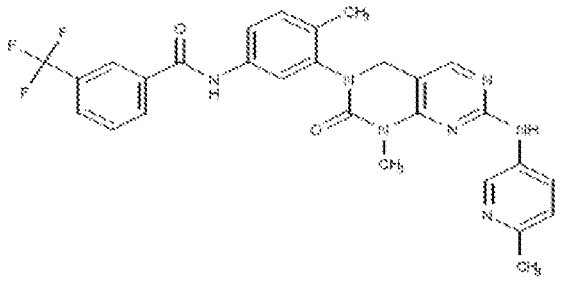
(HG-11-23-01)



(HG-4-34-01),

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

[00175] In certain embodiments, a compound described herein is a compound of Formula (**I**), (**II**), (**III**), or a pharmaceutically acceptable salt, solvate, hydrate,

polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, a compound described herein is a compound of Formula (**I**), (**II**), (**III**), or a pharmaceutically acceptable salt thereof.

[00176] Certain compounds described herein bind and/or inhibit protein kinases. In certain embodiments, the protein kinase is a SIK. In certain embodiments, the protein kinase is SIK1. In certain embodiments, the protein kinase is SIK2. In certain embodiments, the protein kinase is SIK3. In certain embodiments, the compounds described herein non-covalently bind to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds described herein reversibly bind to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds described herein non-reversibly bind to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds described herein modulate the activity of the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds described herein inhibit the activity of the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)).

[00177] The binding affinity of a compound described herein to a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) may be measured by the dissociation constant (K_d) value of an adduct of the compound and the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) using methods known in the art (*e.g.*, isothermal titration calorimetry (ITC)). In certain embodiments, the adduct comprises the compound and the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)), which are bound (*e.g.*, non-covalently) 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.

[00178] In certain embodiments, the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) is inhibited by a compound described herein. The inhibition of the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) by a compound described herein may be measured by the half maximal inhibitory concentration (IC_{50}) value of the compound when the compound, or a pharmaceutical composition thereof, is contacted, directly or indirectly, with the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). 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 compound 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.

[00179] The compounds described herein may selectively modulate the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds selectively inhibit the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds selectively increase the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the compounds inhibit the activity of two or more protein kinases (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) to the same extent. In certain embodiments, the compounds increase the activity of two or more protein kinases (*e.g.*, kinases of SIK, (*e.g.*, kinases of SIK1, SIK2, or SIK3)) to the same extent.

[00180] The selectivity of a compound described herein in inhibiting the activity of a first protein kinase (*e.g.*, SIK) over a second protein kinase may be measured by the quotient of the IC_{50} value of the compound in inhibiting the activity of the second protein kinase (*e.g.*, SIK) over the IC_{50} value of the compound in inhibiting the activity of the first protein kinase (*e.g.*, SIK). The selectivity of a compound described herein in modulating the activity of a first protein kinase (*e.g.*, SIK) over a second protein kinase may also be measured by the quotient of the K_d value of an adduct of the compound and the second protein kinase over the K_d value of an adduct of the compound and the first protein kinase (*e.g.*, SIK). In certain embodiments, the selectivity is at least about 1-fold, at least about 3-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.

[00181] It is expected that the compounds described herein may be useful in treating and/or preventing diseases associated with aberrant activity (*e.g.*, increased activity) of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). It is known in the art that protein kinases are implicated in a wide range of diseases, such as proliferative diseases, musculoskeletal diseases, genetic diseases, hematological

diseases, neurological diseases, painful conditions, psychiatric disorders, and metabolic disorders. Therefore, the compounds described herein are expected to be useful in treating and/or preventing proliferative diseases, musculoskeletal diseases, genetic diseases, hematological diseases, neurological diseases, painful conditions, psychiatric disorders, and metabolic disorders.

Pharmaceutical Compositions, Kits, and Administration

[00182] The present disclosure provides pharmaceutical compositions comprising a compound of Formula (**I**), (**II**) or, (**III**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound of Formula (**I**), (**II**), or (**III**), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00183] In certain embodiments, the compound 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, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a musculoskeletal disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a musculoskeletal disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a in a painful condition subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a painful condition in a subject in need thereof. In

certain embodiments, the effective amount is an amount effective for treating a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for inhibiting the activity (*e.g.*, aberrant activity, increased activity) of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell.

[00184] In certain embodiments, the subject being administered a compound or composition described herein is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein 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. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[00185] In certain embodiments, the cell being contacted with a compound or composition described herein is present *in vitro*. In certain embodiments, the cell being contacted with a compound or composition described herein is present *in vivo*.

[00186] An effective amount of a compound described herein may vary from about 0.001 mg/kg to about 1000 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration), wherein mg/kg is mg of compound to kg weight of the subject. In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, and from about 10.0 mg/kg to about 150 mg/kg.

[00187] In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase 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 protein kinase 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 protein kinase by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00188] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the compound 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.

[00189] 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.

[00190] 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.

[00191] 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.

[00192] 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.

[00193] 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 poly(vinyl-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.

[00194] 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.

[00195] 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.

[00196] 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.

[00197] 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.

[00198] 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.

[00199] 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.

[00200] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00201] 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.

[00202] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), 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® II, Neolone®, Kathon®, and Euxyl®.

[00203] 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.

[00204] 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.

[00205] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, 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.

[00206] 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 emulsifiers 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.

[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] Dosage forms for topical and/or transdermal administration of a compound 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.

[00215] 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 compound in powder form through the outer layers of the skin to the dermis are suitable.

[00216] 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 administrable 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.

[00217] 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.

[00218] 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).

[00219] 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 methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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.

[00224] Compounds 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.

[00225] The compounds 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 compound or pharmaceutical composition described herein is suitable for topical administration to the eye of a subject.

[00226] The exact amount of a compound 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 compound, 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.

[00227] 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.

[00228] A compound 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). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, and/or in

inhibiting the activity of a protein kinase (*e.g.*, SIK) in a subject or cell), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. 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 compound described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both.

[00229] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which are different from the compound or composition and may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. 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 a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder). 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 compound 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.

[00230] The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-musculoskeletal disease agents, anti-cancer agents, cytotoxic agents, anti-angiogenesis agents, anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, and pain-relieving agents. In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent. In certain embodiments, the additional pharmaceutical agent is an anti- musculoskeletal disease agent. In certain embodiments, the additional pharmaceutical agent is an anti-cancer agent. In certain embodiments, the additional pharmaceutical agent is an anti-viral agent. In certain embodiments, the additional pharmaceutical agent is an binder or inhibitor of a protein kinase. 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 protein kinase 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 compounds described herein or pharmaceutical compositions can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, transplantation (*e.g.*, stem cell transplantation, bone marrow transplantation), immunotherapy, and chemotherapy.

[00231] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. 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.

[00232] Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell.

[00233] In certain embodiments, a kit described herein further includes instructions for using the compound or pharmaceutical composition included in the kit. In certain embodiments, the kit comprises a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein; and instructions for using the compound, pharmaceutically acceptable salt, or pharmaceutical composition. A kit described herein 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 kits and instructions provide for treating a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for modulating (*e.g.*, inhibiting) the activity (*e.g.*, aberrant activity, such as increased activity) of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment and Uses

[00234] The present disclosure provides methods of modulating (*e.g.*, inhibiting or increasing) the activity (*e.g.*, aberrant activity, such as increased or decreased activity) of a protein kinase (*e.g.*, SIK). The present disclosure provides methods of modulating (*e.g.*, inhibiting or increasing) the activity (*e.g.*, aberrant activity, such as increased or decreased activity) of a SIK (*e.g.*, SIK1, SIK2, or SIK3) in a subject or cell. The present disclosure also provides methods for the treatment of a wide range of diseases, such as diseases associated with aberrant activity (*e.g.*, increased activity) of a protein kinase, *e.g.*, proliferative diseases, musculoskeletal diseases, genetic diseases, hematological diseases, neurological diseases, painful conditions, psychiatric disorders, and metabolic disorders in a subject in need thereof.

[00235] In another aspect, the present disclosure provides methods of modulating the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell. In certain embodiments, provided are methods of inhibiting the activity of a protein kinase in a subject. In certain embodiments, provided are methods of inhibiting the activity of a protein kinase in a cell. In certain embodiments, provided are methods of increasing the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject. In certain embodiments, provided are methods of increasing the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a cell. In certain embodiments, the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell is inhibited by a method described herein by at least about 1%, at least about 3%, 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%, or at least about 90%. In certain embodiments, the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell is increased by a method described herein by at least about 1%, at least about 3%, 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%, or at least about 90%. In some embodiments, the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell is selectively inhibited by the method. In some embodiments, the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) in a subject or cell is selectively increased by the method.

[00236] Another aspect of the present disclosure relates to methods of treating a disease in a subject in need thereof. In certain embodiments, the disease is associated with a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the disease is associated with the activity of a protein kinase. In certain embodiments, the disease is associated with the aberrant activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the disease is associated with increased activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)).

[00237] In certain embodiments, the disease is a proliferative disease. In certain embodiments, the disease is cancer. In certain embodiments, the disease is a benign neoplasm. In certain embodiments, the disease is or is associated with pathological angiogenesis. In certain embodiments, the disease is an inflammatory disease. In certain embodiments, the disease is an autoimmune disease. In certain embodiments, the disease is a musculoskeletal disease. In certain embodiments, the disease is a genetic disease. In certain embodiments, the disease is a hematological disease. In certain embodiments, the disease is a neurological disease. In certain embodiments, the disease is a painful condition. In certain embodiments, the disease is a psychiatric disorder. In certain embodiments, the disease is a metabolic disorder.

[00238] In still another aspect, the present disclosure provides methods of preventing a disease described herein in a subject in need thereof.

[00239] In certain embodiments, the methods of the disclosure include administering to a subject in need thereof an effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, the method of treating a disease in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein, wherein the disease is associated with aberrant activity of a protein kinase. In certain embodiments, the subject being administered a compound or pharmaceutical composition described herein is a human. In certain embodiments, the subject being administered a compound or pharmaceutical composition described herein is a non-human animal. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase 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 protein kinase 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 protein kinase by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00240] In certain embodiments, the methods of the disclosure include administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, the methods of the disclosure include administering to a subject in need thereof a prophylactically effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, the methods of the disclosure include contacting a cell with an effective amount of a compound or pharmaceutical composition described herein.

[00241] In another aspect, the present disclosure provides the compounds described herein for use in a method described herein (*e.g.*, method of inhibiting a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)), method of treating a disease (*e.g.*, proliferative disease, musculoskeletal disease), method of preventing a disease (*e.g.*, proliferative disease, musculoskeletal disease), or method of screening a library of compounds).

[00242] In still another aspect, the present disclosure provides the pharmaceutical compositions described herein for use in a method described herein (*e.g.*, a method of inhibiting a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)), a method of treating a disease (*e.g.*, a proliferative or musculoskeletal disease), a method of preventing a disease (*e.g.*, a proliferative or musculoskeletal disease), or a method of screening a library of compounds).

Methods of Screening a Library of Compounds

[00243] Another aspect of the disclosure relates to methods of screening a library of compounds, and pharmaceutical acceptable salts thereof, to identify a compound, or a pharmaceutical acceptable salt thereof, that is useful in a method described herein. In certain embodiments, the methods of screening a library include obtaining at least two different compounds described herein; and performing at least one assay using the

different compounds described herein. In certain embodiments, at least one assay is useful in identifying a compound that is useful in a method described herein.

[00244] Typically, the methods of screening a library of compounds involve at least one assay. In certain embodiments, the assay is performed to detect one or more characteristics associated with the treatment and/or prevention of a disease described herein or with the modulation (*e.g.*, inhibition) of the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). The characteristic may be a desired characteristic (*e.g.*, a characteristic associated with the treatment of a disease, a characteristic associated with the prevention of a disease, or a characteristic associated with the inhibition of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3))). The characteristic may be an undesired characteristic (*e.g.*, a characteristic associated with an untreated disease, a characteristic associated with a disease having not been prevented, or a characteristic associated with the non-modulation of the activity of a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). The assay may be an enzymatic activity assay, immunoassay, such as a sandwich-type assay, competitive binding assay, one-step direct test, two-step test, or blot assay. The step of performing at least one assay may be performed robotically or manually. In certain embodiments, the assay comprises (a) contacting a library of compounds with a protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)); and (b) detecting the binding of the library of compounds to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the assay comprises detecting the specific binding of the library of compounds to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)). In certain embodiments, the detected binding of the library of compounds to the protein kinase (*e.g.*, kinase of SIK, (*e.g.*, kinase of SIK1, SIK2, or SIK3)) is useful in identifying the compound that is useful in a method described herein. In certain embodiments, the step of detecting the binding comprises using differential scanning fluorimetry (DSF), isothermal titration calorimetry (ITC), and/or an amplified luminescence proximity homogeneous assay (ALPHA). The step of performing at least one assay may be performed in a cell *in vitro* or *in vivo*.

EXAMPLES

[00245] In order that the disclosure may be more fully understood, the following examples are set forth. The examples described in this application are offered to

illustrate the compounds, pharmaceutical compositions, uses, and methods provided herein and are not to be construed in any way as limiting their scope.

Experimental Procedures

Example I. Selected Compounds and Biological Activity

SIK2 Protein Production and Purification

[00246] A lentiviral expression construct encoding the human SIK2 open reading frame (Clone TRCN0000491575) was obtained from the Broad Institute Genetic Perturbation Platform. Human SIK2 was amplified by PCR and cloned into a baculovirus expression vector, pCoofy29, as described previously (Scholz, *et al.*, *BMC Biotechnol.*, 13, 12 (2013)), resulting a His6-MBP-tagged SIK2 construct for Spodoptera frugiperda (Sf9) insect cell expression. High-titer recombinant baculovirus was obtained using the Bac-to-Bac Baculovirus Expression System (Invitrogen). Sf9 cells at a cell density of 3 × 106 cells/mL were infected with P1 virus at a multiplicity of infection of 5. Cells were harvested by centrifugation at 48 h post-infection at 27 °C. The cell pellet was lysed by homogenization in lysis buffer containing 5mM Tris 7.5, 250mM NaCl, 5% Glycerol, 0.5 mM TCEP, and 1 tablet of EDTA-free protease inhibitor (Roche). The His6-MBP-tagged SIK2 protein was isolated from the cell lysate by incubating with Ni-NTA superflow resin (Qiagen) at 4 °C for 2 h. After extensive washes, the bound protein was eluted by buffered imidazole. The eluted protein was further purified by FPLC using superdex 200 gel filtration column (GE Healthcare) with buffer containing 50 mM Tris 7.5, 150 mM NaCl, 0.5 mM TCEP, and 2% Glycerol. The monomeric species was collected and analyzed by Coomassie blue stained SDS-PAGE gel indicating sample purity greater than 80%. This preparation was used for caliper assay and compound IC_{50} measurement.

SIK2 kinase activity assay

[00247] IC_{50}'s for selected compounds in Table 5 below were measured by Caliper-based mobility shift assay (PerkinElmer). For these experiments, full length His6-MBP-tagged hSIK2 (4 nM) was incubated with HG-9-91-01 derivatives in buffer 5 containing 100 mM HEPES 7.5, 10 mM MgCl2, 2.5 mM DTT, 0.004% Tween20, 0.003% Brij-35, 30 μM ATP and 1.5 μM ProfilerPro FL-Peptide 10 (5-FAMKKKVSRSGLYRSPSMPENLNRPR-COOH, PerkinElmer, Catalog No.

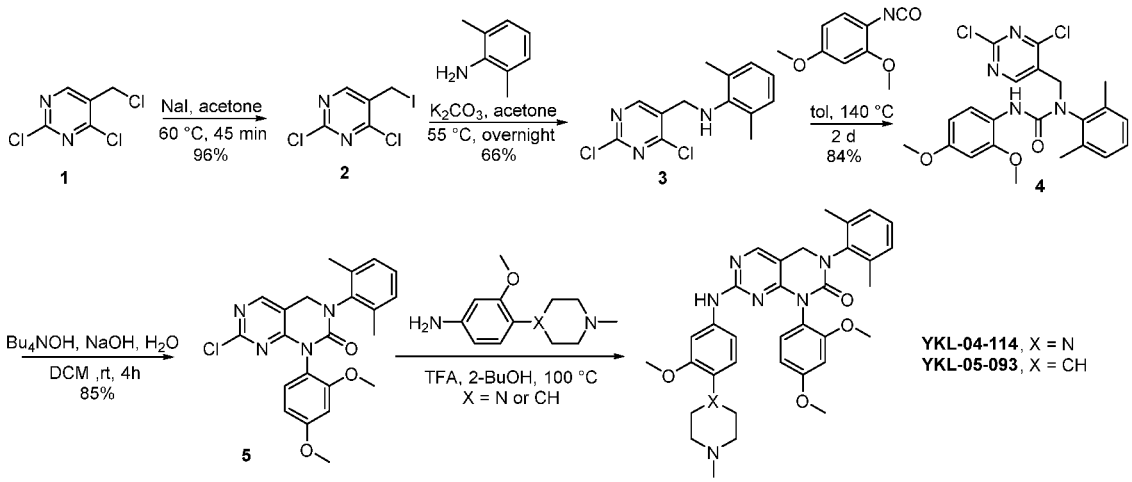
760354) at rt. Reactions were quenched by adding 20 mM EDTA (pH 8) after 1 hr, and percentage of substrate conversion was measured by LabChip EZ Reader II (PerkinElmer). IC_{50}'s for SIK2 inhibition were calculated using SmartFit nonlinear regression in Genedata Screener software suite (Genedata). The IC_{50}'s for selected compounds are listed in Table 5 below.

Compound Characterization

[00248] The urea formation was performed using a Biotage® Initiator+ Microwave Synthesizer. All reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}) and Waters LCMS system (Waters 2489 UV/Visible Detector, Waters 3100 Mass, Waters 515 HPLC pump, Waters 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFire™ C18 column (4.6 x 50 mm, 5 μm particle size) : solvent gradient = 97% A at 0 min, 0% A at 5 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in Acetonitrile; flow rate : 2.5 mL/min. Purification of reaction products was carried out by flash chromatography using CombiFlash®Rf with Teledyne Isco Redi*Sep*®Rf High Performance Gold or Silicycle Silia*Sep*™ High Performance columns (4 g, 12 g, 24 g, 40 g, 80 g or 120 g). The purity of all compounds was over 95% and was analyzed with Waters LCMS system. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Inova-600 (600 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.24) for ^{1}H NMR or dimethyl sulfoxide (δ = 2.50) for ^{1}H NMR and dimethyl sulfoxide (δ = 39.51) for ^{13}C NMR. Data are reported as (*br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet).

Example II. Preparation of YKL-04-114 and YKL-05-093

[00249] 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)

[00250] 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)**

[00251] 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_2CO_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 × 3). The combined organic phase was washed with brine (80 mL × 3), dried with Na_2SO_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 *N*-((2,4-dichloropyrimidin-5- yl)methyl)-2,6-dimethylaniline **3** as a light brown solid (4.5 g, yield 66%). LCMS (m/z): 282.3 $[M + H]^+$.

1-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-1-(2,6-dimethylphenyl)urea (4)

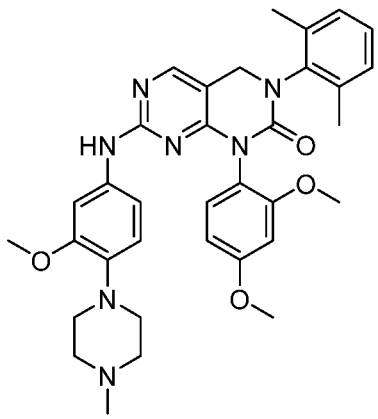
[00252] A round bottomed flask with a Dean-Stark apparatus was charged with *N*-((2,4-dichloropyrimidin-5-yl)methyl) -2,6-dimethylaniline **3** (3.0 g, 10.6 mmol), 1-isocyanato-2,4-dimethoxybenzene (2.5 g, 14.0 mmol), toluene (3 mL). The mixture was stirred at 130 °C for 2 d, cooled to rt, and concentrated. The residue was purified

by column chromatography on silica gel (petroleum ether / EtOAc = 4/1, 2/1, 1/1, EA) to get 1-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-1-(2,6-dimethylphenyl)urea **4** as a light brown solid (4.1 g, yield 84%). LCMS (m/z): 461.4 $[M + H]^+$.

7-chloro-1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1*H*)-one (5)

[00253] To the solution of 1-((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_2O, 11.8 mmol). The mixture was stirred at rt for 4 h. The final mixture was diluted with H_2O (20 mL), extracted with DCM (80 mL × 3). The combined organic phase was washed with brine (50 mL × 2), dried with Na_2SO_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%). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.37 (s, 1H), 7.16-7.19 (m, 4H), 6.68 (d, J = 2.4 Hz, 1H), 6.58 (dd, J = 8.8, 2.4 Hz, 1H), 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 $[M + H]^+$.

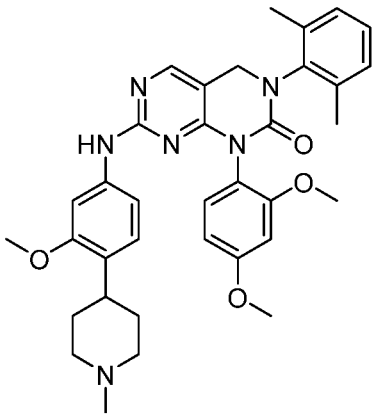
YKL-04-114



[00254] A mixture of 7-chloro-1-(2,4-dimethoxyphenyl)- 3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5- d]pyrimidin-2(1*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-BuOH (0.5 mL) was stirred at 100 °C overnight. The reaction was cooled

and concentrated. The residue was purified by prep-HPLC (MeOH/H_2O 5:95 – 100:0), followed by column chromatography on silica gel (0-10% MeOH in DCM) to afford YKL-04-114 as a white solid (8.0 mg, 56%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.21 (s, 1H), 8.20 (s, 1H), 7.25-7.22 (m, 4H), 7.03 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 8.8, 2.8 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.73 (d, J = 14.4 Hz, 1H), 4.59 (d, J = 14.4 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.94 (m, 4H), 2.58 (m, 4H), 2.34 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H); LCMS (m/z): 610.7 $[M + H]^+$.

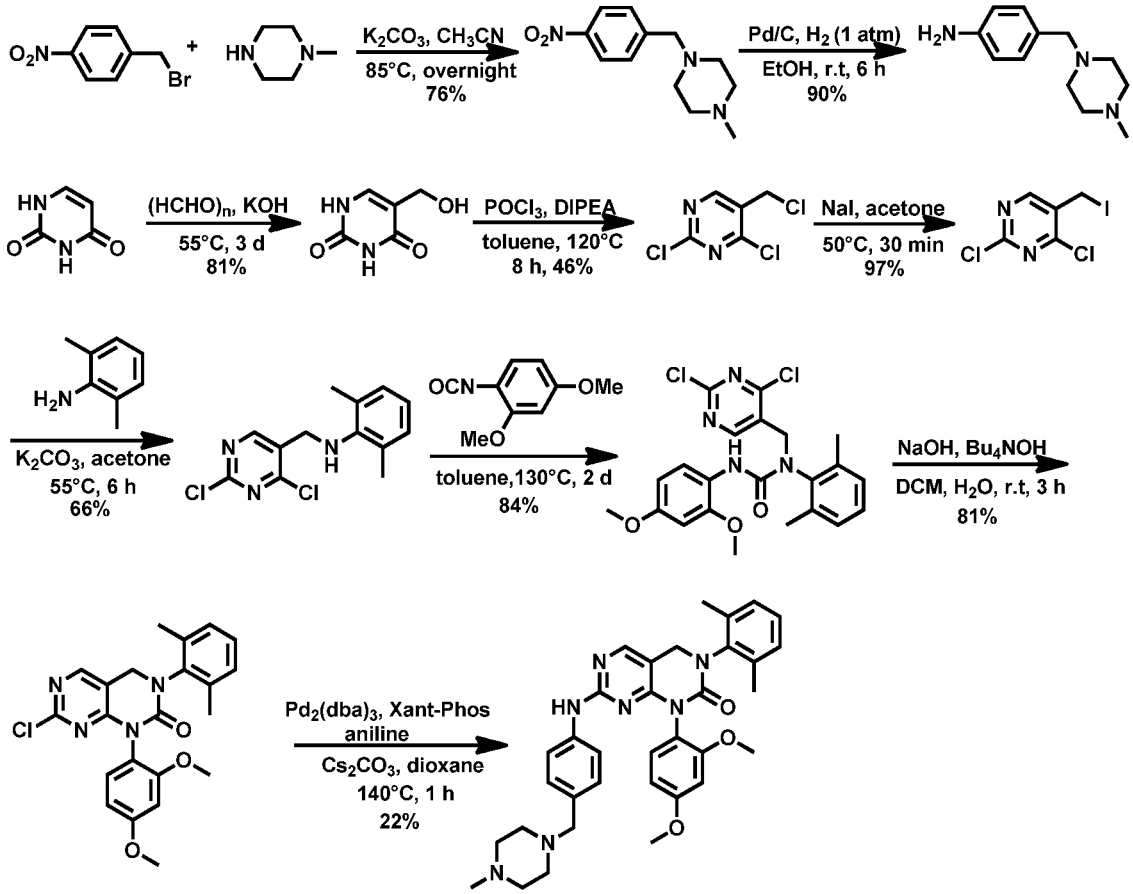
YKL-05-093



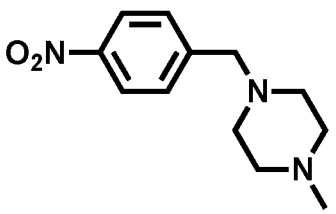
[00255] A mixture of 7-chloro-1-(2,4-dimethoxyphenyl)- 3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5- d]pyrimidin-2(1*H*)-one **5** (100 mg, 0.24 mmol), 3-methoxy-4-(1-methylpiperidin-4-yl)aniline (78 mg, 0.35 mmol), and TFA (55 mg, 0.48 mmol) in 2-BuOH (5 mL) was stirred at 100 °C overnight. The reaction was cooled and concentrated. The residue was purified by prep-HPLC (MeOH/H_2O 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 $[M + H]^+$.

Bicylic Ureas

Synthetic Scheme 1. Synthesis of YKL-04-136-1

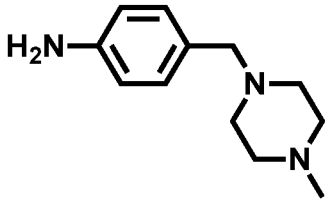


[00256] 1-methyl-4-(4-nitrobenzyl)piperazine



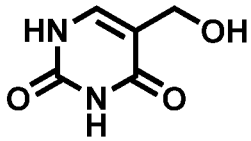
[00257] To a solution of 1-(bromomethyl)-4-nitrobenzene (4.0 g, 18.5 mmol) and 1-methylpiperazine (1.7 g, 17.0 mmol) in CH_3CN was added K_2CO_3 (3.8 g, 27.5 mmol), the mixture was stirred at 85 ^oC overnight. After completion, removed the solvent, extracted with ethyl acetate (150 mL × 3), washed with water (80 mL × 2), brine (80 mL × 2), dried with Na_2SO_4, purified by silica gel (DCM / MeOH = 50/1, 30/1), light brown solid 1-methyl-4-(4-nitrobenzyl)piperazine (3.3 g) was obtained, yield 76%. LC/MS (ESI) m/z = 236 $(M + H)^+$.

[00258] 4-((4-methylpiperazin-1-yl)methyl)aniline



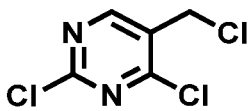
[00259] A suspension of 1-methyl-4-(4-nitrobenzyl)piperazine (1.0 g, 4.25 mmol), Pd/C (200 mg) in EtOH (20 mL) was stirred at room temperature under H_2 (1 atm) for 6 h, then filtered, removed the solvent to give 4-((4-methylpiperazin-1-yl)methyl)aniline as light brown solid (785 mg), yield 90%. LC/MS (ESI) m/z = 206 $(M + H)^+$.

[00260] 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione



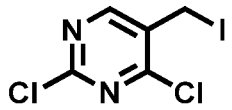
[00261] To a suspension of uracil (37.0 g, 330 mmol) and paraformaldehyde (12.3 g, 410 mmol) was added a solution of KOH (10.5 g, 187 mmol) in water (290 mL), the mixture was stirred at 55 °C for 3 d, after concentration at 60 °C under vacuum to a volume of 100 mL, the residue was diluted with acetone (200 mL), the resulting precipitate was collected by filtration, washed with acetone and dried to give 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione as white solid (38 g), yield 81%.

[00262] 2,4-dichloro-5-(chloromethyl)pyrimidine



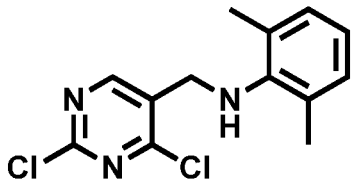
[00263] To a suspension of 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione (35.0 g, 246.3 mmol) in toluene (100 mL) was added $POCl_3$ (105 mL, 1147 mmol) followed by slow addition of DIPEA (120 mL, 689 mmol), the mixture was tirred at 110-120 °C for 8 h. Then the reaction mixture was poured to a mixture of water (100 mL) and ethyl acetate (200 mL), extracted with ethyl acetate (1 L × 2), washed with brine (200 mL × 3), died with Na_2SO_4. Purified by silica gel (DCM) to give 2,4-dichloro-5-(chloromethyl)pyrimidine as light yellow solid (22 g), yield 46%. LC/MS (ESI) m/z = 197 $(M + H)^+$.

[00264] 2,4-dichloro-5-(iodomethyl)pyrimidine



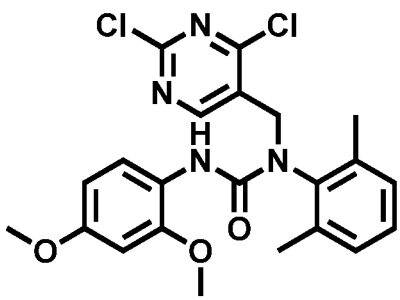
[00265] To a solution of 2,4-dichloro-5-(chloromethyl)pyrimidine (22.0 g, 111.4 mmol) in acetone (120 mL) was added NaI (20.1 g, 134.1 mmol), the mixture was stirred at 50 °C for 30 min, then filtered, the filtrate was removed the solvent, purified by silica gel (DCM) to give 2,4-dichloro-5-(iodomethyl)pyrimidine as light brown solid (31 g), yield 97%. LC/MS (ESI) m/z = 289 $(M + H)^+$.

[00266] N-((2,4-dichloropyrimidin-5-yl)methyl)-2,6-dimethylaniline



[00267] To a solution of 2,6-dimethylaniline (3.8 g, 31.4 mmol) and 2,4-dichloro-5-(iodomethyl)pyrimidine (7.0 g, 24.2 mmol) in acetone was added K_2CO_3 (5.0 g, 36.2 mmol), the mixture was stirred at 50 °C for 6 h. then removed acetone, extracted with ethyl acetate (150 mL × 3), washed with water (80 mL × 2), brine (80 mL× 2), dried with Na_2SO_4. Purified by silica gel (PE/DCM = 2/1, 1/1, DCM) to give N-((2,4-dichloropyrimidin-5-yl)methyl)-2,6-dimethylaniline as a light yellow solid (4.5 g), yield 66%. LC/MS (ESI) m/z = 282 $(M + H)^+$.

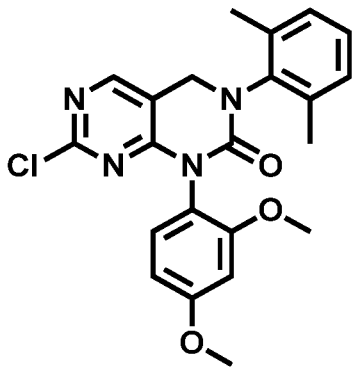
[00268] 1-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-1-(2,6-dimethylphenyl)urea



[00269] A round-bottomed flask was charged with N-((2,4-dichloropyrimidin-5-yl)methyl)-2,6-dimethylaniline (3.0 g, 10.6 mmol), 1-isocyanato-2,4-dimethoxybenzene (2.5 g, 14.0 mmol) and toluene (3 mL), the mixture was stirred at

130 °C for 2 d. then purified by silica gel (PE/ethyl acetate = 4/1, 2/1, 1/1, ethyl acetate) to give 1-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-1-(2,6-dimethylphenyl)urea as light brown solid (4.1 g), yield 84%. LC/MS (ESI) m/z = 461 $(M + H)^+$.

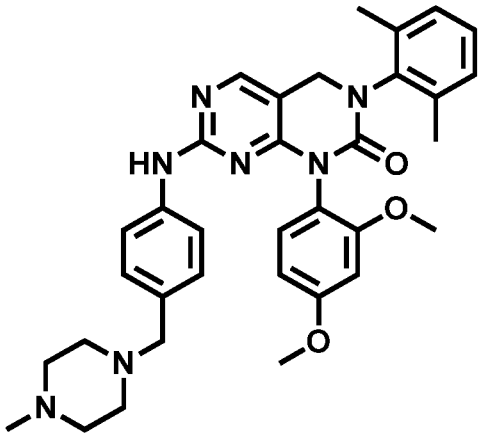
[00270] 7-chloro-1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one



[00271] To a solution of 1-((2,4-dichloropyrimidin-5-yl)methyl)-3-(2,4-dimethoxyphenyl)-1-(2,6-dimethylphenyl)urea (2.0 g, 4.34 mmol) in DCM (30 mL) was added NaOH (260 mg, 6.5 mmol) and Bu_4NOH (338 mg, 1.30 mmol), the mixture was stirred room temperature for 3 h. then extracted with DCM (80 mL × 3), washed with water (50 mL × 2), brine (50 mL × 2), dried with Na_2SO_4. Purified by silica gel (PE/ethyl acetate = 3/1, 1/1) to give 7-chloro-1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as off-white solid (1.5 g), yield 81%. LC/MS (ESI) m/z = 425 $(M + H)^+$.

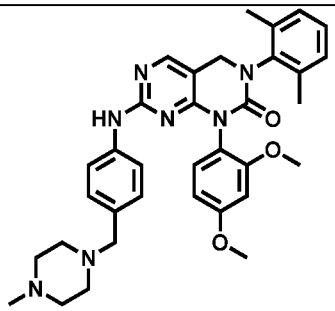
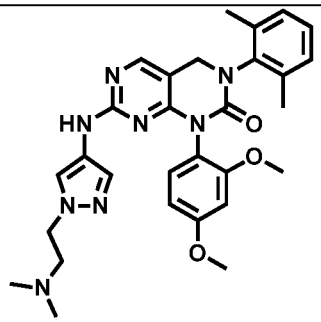
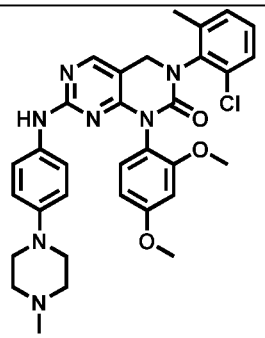
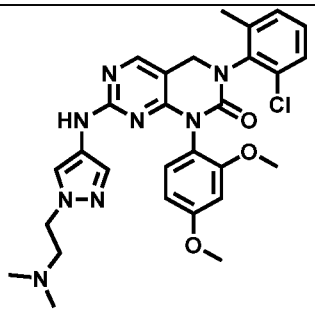
[00272] 1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-7-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one

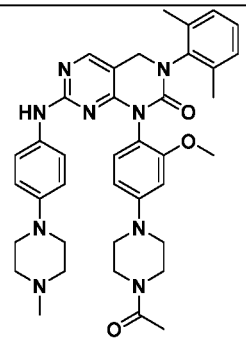
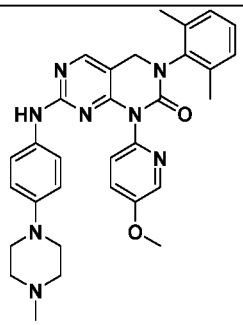
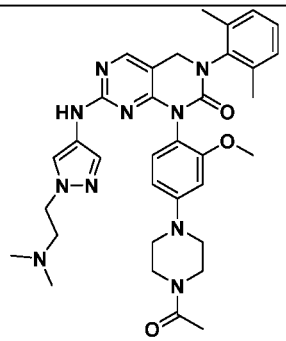
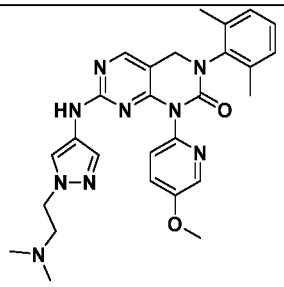
(YKL-04-136-1)

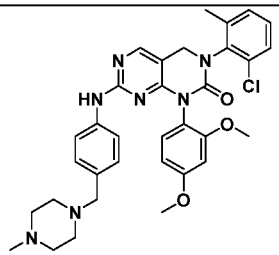
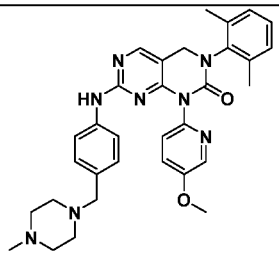
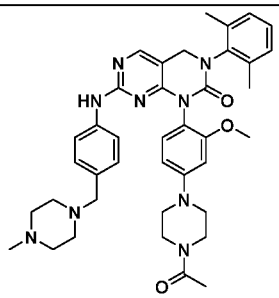
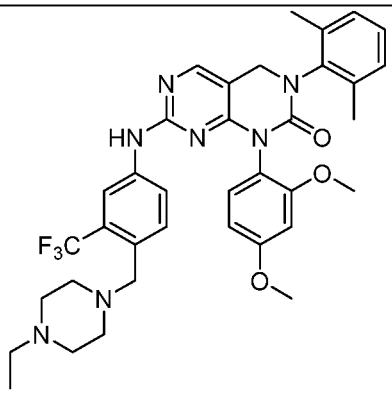


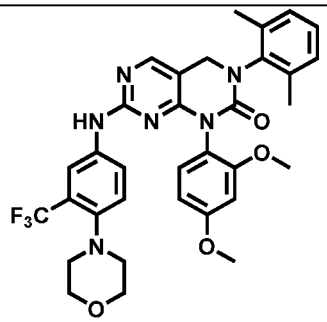
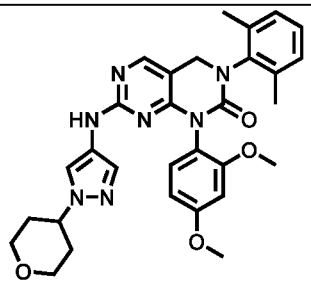
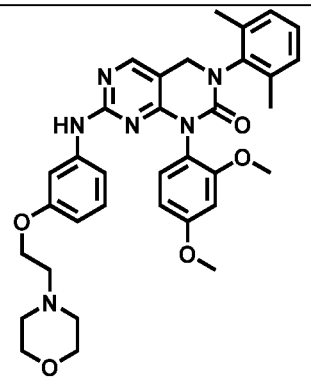
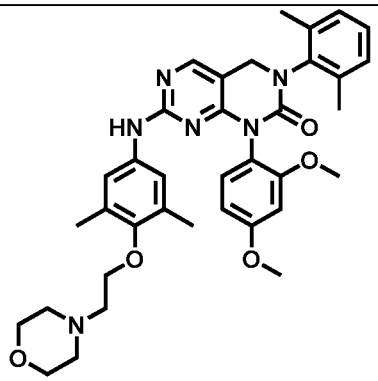
[00273] A sealed- tube was charged with 7-chloro-1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (100 mg, 0.235 mmol), 4-((4-methylpiperazin-1-yl)methyl)aniline (72 mg, 0.351 mmol), $Pd_2(dba)_3$ (22 mg, 0.0240 mmol), Xant-Phos (28 mg, 0.0484 mmol), Cs_2CO_3 (200 mg, 0.614 mmol) and dioxane (2 mL), the mixture was stirred at 150 ^oC for 1 h under microwave condition. Then filtered, removed the solvent, purified by prep-HPLC to give 1-(2,4-dimethoxyphenyl)-3-(2,6-dimethylphenyl)-7-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as white solid (30 mg), yield 22%. Rt = 2.07 min; ^1H NMR 600 MHz (DMSO-d_6) δ 9.42 (*s*, 1H), 8.16 (*s*, 1H), 7.26-7.16 (*m*, 6H), 6.90 (*d*, 2H), 6.74 (*d*, 1H), 6.65 (*dd*, 1H), 4.70 (*d*, 1H), 4.56 (*d*, 1H), 3.87 (*s*, 3H), 3.66 (*s*, 3H), 3.32 (*s*, 2H), 2.30 (*m*, 8H), 2.26 (*s*, 3H), 2.23 (*s*, 3H), 2.14 (*s*, 3H); LC/MS (ESI) m/z = 594.80 $(M + H)^+$.

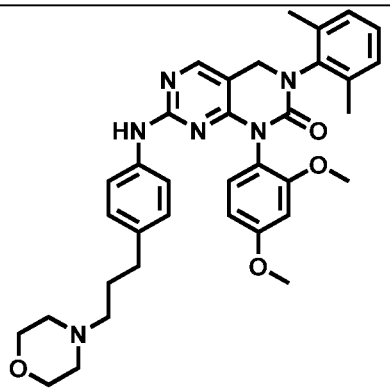
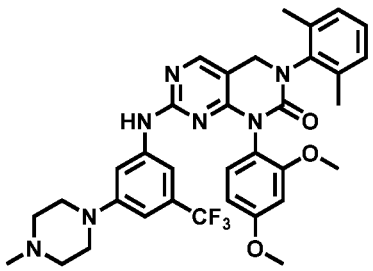
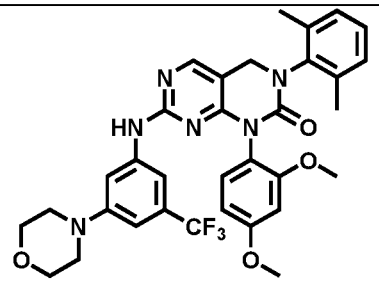
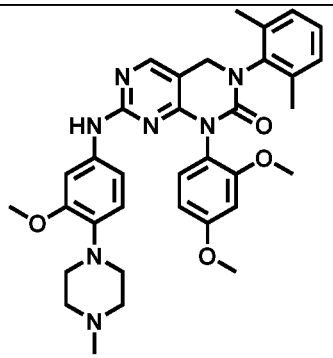
Table 1. The following compounds were produced by using the corresponding starting compounds according to a method similar to that described for YKL-04-136-1:

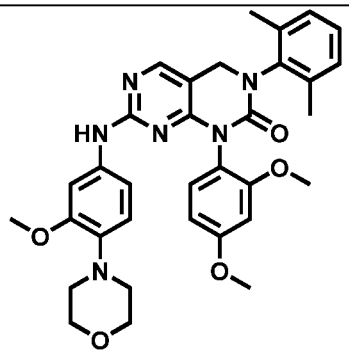
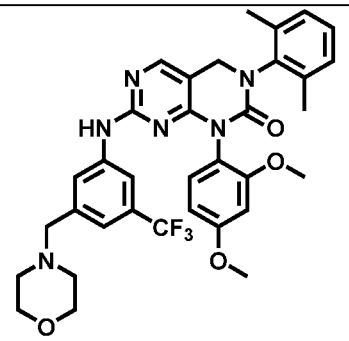
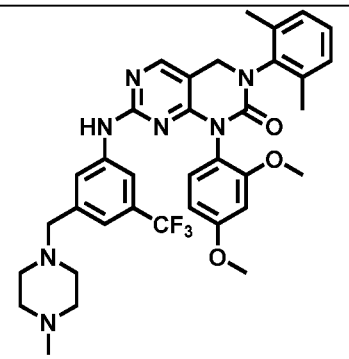
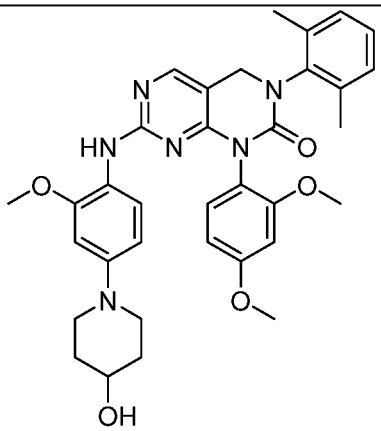
YKL-04-136-1	 **Chemical Formula:** $C_{34}H_{39}N_7O_3$ **Exact Mass: 593.31**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.42 (*s*, 1H), 8.16 (*s*, 1H), 7.26-7.16 (*m*, 6H), 6.90 (*d*, 2H), 6.74 (*d*, 1H), 6.65 (*dd*, 1H), 4.70 (*d*, 1H), 4.56 (*d*, 1H), 3.87 (*s*, 3H), 3.66 (*s*, 3H), 3.32 (*s*, 2H), 2.30 (*m*, 8H), 2.26 (*s*, 3H), 2.23 (*s*, 3H), 2.14 (*s*, 3H); MS *m/z*: 594.4 [M+1].
YKL-04-136-2	 **Chemical Formula:** $C_{29}H_{34}N_8O_3$ **Exact Mass: 542.28**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.43 (*s*, 1H), 8.10 (*s*, 1H), 7.24-7.11 (*m*, 5H), 6.78 (*d*, 2H), 6.68 (*d*, 1H), 4.68 (*d*, 1H), 4.53 (*d*, 1H), 3.84 (*m*, 4H), 3.67 (*s*, 3H), 3.32 (*s*, 2H), 2.50 (*m*, 2H), 2.25 (*s*, 3H), 2.22 (*s*, 3H), 2.12 (*s*, 6H); MS *m/z*: 543.3 [M+1].
YKL-04-136-3	 **Chemical Formula:** $C_{32}H_{34}ClN_7O_3$ **Exact Mass: 599.24**	^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.23 (s, 1H), 8.13 (s, 1H), 7.45 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.30-7.35 (m, 2H), 7.15-7.18 (m, 3H), 6.75 (d, J = 2.4 Hz, 1H), 6.64 (td, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 6.57 (d, J = 4.8 Hz, 2H), 4.55-4.78 (m, 2H), 3.86 (s, 3H), 3.67 (s, 3H), 2.98 (t, J = 4.4 Hz, 4H), 2.44 (t, J = 4.4 Hz, 4H), 2.30 (d, J = 10.8 Hz, 3H), 2.22 (s, 3H) ppm. MS *m/z*: 600.3 [M+1].
YKL-04-136-4	 **Chemical Formula:** $C_{28}H_{31}ClN_8O_3$ **Exact Mass: 562.22**	^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.48 (s, 1H), 8.12 (s, 1H), 7.43 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H),7.28-7.34 (m, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.10 (s, 1 H), 6.75 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 4.53-4.77 (m, 2H), 3.84 (s, 3H), 3.80 (s, 2H), 3.66 (d, J = 2.8 Hz, 3H), 2.51 (s, 2H), 2.28 (d, J = 12.0 Hz, 2H), 2.11 (s, 6H) ppm. MS *m/z*: 563.3 [M+1].

YKL-04-136-5	 Chemical Formula: $C_{38}H_{45}N_9O_3$ Exact Mass: 675.36	^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.08-7.19 (m, 5H), 6.82 (s, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.62 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 4.53-4.66 (m, 2H), 3.80 (t, J = 4.4 Hz, 2H), 3.73 (s, 3H), 3.65 (t, J = 4.4 Hz, 2H), 3.21-3.27 (m, 4H), 3.10 (t, J = 4.2 Hz, 4H), 2.57 (t, J = 4.8 Hz, 4H), 2.35 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H) ppm. MS *m/z*: 676.4 [M+1].
YKL-04-136-6	 Chemical Formula: $C_{31}H_{34}N_8O_2$ Exact Mass: 550.28	^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.26 (bs, 1H), 8.31 (d, J = 3.2 Hz, 1H), 8.16 (s, 1H), 7.60 (dd, J_1 = 9.2 Hz, J_2 = 3.6 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.12-7.21 (m, 3H), 7.06 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 2H), 4.61 (s, 2H), 3.92 (s, 3H), 2.97 (t, J = 4.8 Hz, 4H), 2.51 (m, 2H), 2.43 (t, J = 4.8 Hz, 4H), 2.25 (s, 6H), 2.20 (s, 3H) ppm. MS *m/z*: 551.3 [M+1].
YKL-04-136-7	 Chemical Formula: $C_{34}H_{42}N_{10}O_3$ Exact Mass: 638.34	^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.40 (s, 1H), 8.09 (s, 1H), 7.06-7.20 (m, 5H), 6.83 (s, 1H), 6.73 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.46-4.68 (m, 2H), 3.81 (bs, 2H), 3.66 (s, 2H), 3.61 (m, 4H), 3.17-3.31 (m, 5H), 2.24 (s, 3H), 2.21 (s, 3H), 2.10 (s, 6H), 2.05 (s, 3H) ppm. MS *m/z*: 639.4 [M+1].
YKL-04-136-8	 Chemical Formula: $C_{27}H_{31}N_9O_2$ Exact Mass: 513.26	^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.49 (s, 1H), 8.35 (s, 1H), 8.16 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.12-7.22 (m, 3H), 7.05 (s, 1H), 6.66 (s, 1H), 4.61 (s, 2H), 3.92 (s, 3H), 3.81 (s, 1H), 2.47 (s, 2H), 2.24 (s, 6H), 2.11 (s, 6H) ppm. MS *m/z*: 514.3 [M+1].

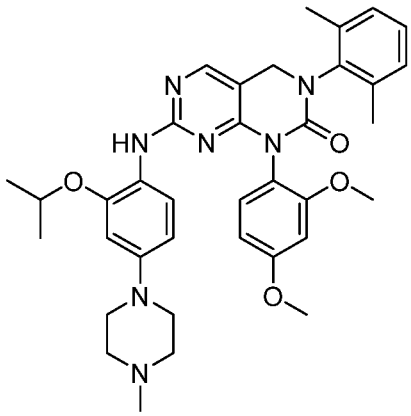
YKL-04-136-9	 Chemical Formula: $C_{33}H_{36}ClN_7O_3$ Exact Mass: 613.26	^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (m, 1H), 7.30-7.35 (m, 1H), 7.23 (d, J = 10.4 Hz, 1H), 7.18-7.20 (m, 4H), 7.00-7.05 (m, 3H), 6.59-6.62 (m, 2H), 4.48-4.91 (m, 2H), 3.89 (s, 3H), 3.73 (d, J = 6.0 Hz, 3H), 3.42 (s, 2H), 2.25-2.62 (bs, 8H), 2.37(s, 3H), 2.30 (s, 3H) ppm. MS *m/z*: 614.3 [M+1].
YKL-04-136-10	 Chemical Formula: $C_{32}H_{36}N_8O_2$ Exact Mass: 564.30	^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, J = 2.8 Hz, 1H), 8.06 (s, 1H), 7.34-7.40 (m, 2H), 7.11-7.18 (m, 5H), 7.04 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 5.6 Hz, 1H), 4.62 (s, 2H), 3.97 (s, 3H), 3.41 (s, 2H), 2.21-2.67 (bs, 4H), 2.32 (s, 6H), 2.29 (s, 3H), 1.55-1.74 (bs, 4H) ppm. MS *m/z*: 565.3 [M+1].
YKL-04-136-11	 Chemical Formula: $C_{39}H_{47}N_9O_3$ Exact Mass: 689.38	^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.20-7.23 (m, 3H), 7.11-7.14 (m, 3H), 7.04 (d, J = 8.4 Hz, 2H), 6.96 (s, 1H), 6.61 (td, J_1 = 8.8 Hz, J_2 = 2.4Hz, 2H),4.55-4.68 (m, 2H), 3.83 (t, J = 4.8 Hz, 2H), 3.74 (s, 3H), 3.67 (t, J = 4.8 Hz, 2H), 3.39 (s, 2H), 3.24-3.29 (m, 4H), 2.30-2.60 (bs, 6H),), 2.33 (s, 6H), 2.28 (s, 3H), 2.17 (s, 3H) ppm. MS *m/z*: 690.4 [M+1].
YKL-04-103	 Chemical Formula: $C_{36}H_{40}F_3N_7O_3$ Exact Mass: 675.31	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.67 (s, 1H), 8.17 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.56 (s, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 7.14-7.11 (m, 3H), 6.69 (d, J = 3.0 Hz, 1H), 6.60 (dd, J = 9.0, 3.0 Hz, 1H), 4.67 (d, J = 14.4 Hz, 1H), 4.53 (d, J = 13.8 Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.42 (s, 2H), 2.45-2.25 (m, 8H), 2.23 (s, 3H), 2.20 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H); MS *m/z*: 676.3 [M+1].

YKL-04-104	 **Chemical Formula:** $C_{33}H_{33}F_3N_6O_4$ **Exact Mass: 634.25**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.61 (s, 1H), 8.18 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.16-7.13 (m, 3H), 7.07 (d, J = 9.2 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.8, 2.4 Hz, 1H), 4.68 (d, J = 12.8 Hz, 1H), 4.54 (d, J = 12.8 Hz, 1H), 3.85 (s, 3H), 3.68-3.64 (m, 7H), 2.75-2.71 (m, 4H), 2.24 (s, 3H), 2.21 (s, 3H); MS m/z: 635.3 [M+1].
YKL-04-105	 **Chemical Formula:** $C_{30}H_{33}N_7O_4$ **Exact Mass: 555.26**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.39 (s, 1H), 8.08 (s, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.15-7.10 (m, 4H), 6.80 (s, 1H), 6.73 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 4.63 (d, J = 14.4 Hz, 1H), 4.48 (d, J = 14.4 Hz, 1H), 3.96-3.91 (m, 2H), 3.85-3.79 (m, 4H), 3.64 (s, 3H), 3.41 (q, J = 10.2 Hz, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 1.81-1.75 (m, 2H), 1.70-1.63 (m, 2H); MS m/z: 556.3 [M+1].
YKL-04-106	 **Chemical Formula:** $C_{34}H_{38}N_6O_5$ **Exact Mass: 610.29**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.35 (s, 1H), 8.12 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.11-7.08 (m, 4H), 6.90 (s, 1H), 6.80 (t, J = 8.4 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 6.56 (dd, J = 8.4, 2.8 Hz, 1H), 6.44 (dd, J = 8.4, 2.4 Hz, 1H), 4.62 (d, J = 15.2 Hz, 1H), 4.48 (d, J = 15.2 Hz, 1H), 4.16 (t, J = 8.4 Hz, 2H), 3.94-3.86 (m, 2H), 3.78 (s, 3H), 3.61 (s, 3H), 3.51-3.45 (m, 4H), 3.44-3.36 (m, 2H), 3.19-3.08 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H); MS m/z: 611.3 [M+1].
YKL-04-107	 **Chemical Formula:** $C_{36}H_{42}N_6O_5$ **Exact Mass: 638.32**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.22 (s, 1H), 8.08 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.11-7.08 (m, 3H), 6.96-6.94 (m, 2H), 6.63 (d, J = 2.8 Hz, 1H), 6.55 (dd, J = 8.4, 2.8 Hz, 1H), 4.60 (d, J = 14.4 Hz, 1H), 4.47 (d, J = 14.8 Hz, 1H), 3.90 (t, J = 5.2 Hz, 4H), 3.75 (s, 3H), 3.70-3.52 (m, 2H), 3.61 (s, 3H), 3.52-3.45 (m, 4H), 3.20-3.10 (m, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 1.97 (s, 3H), 1.97 (s, 3H); MS m/z: 639.3 [M+1].

YKL-04-108	 **Chemical Formula:** $C_{35}H_{40}N_6O_4$ **Exact Mass: 608.31**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.40 (s, 1H), 8.21 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.23-7.21 (m, 3H), 6.87 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 8.4, 2.8 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 4.59 (d, J = 15.2 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 3.66-3.62 (m, 4H), 2.52 (t, J = 7.6 Hz, 2H), 2.44-2.36 (m, 4H), 2.35-2.29 (m, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 1.71 (quit, J = 7.6 Hz, 2H); MS m/z: 609.3 [M+1].
YKL-04-112	 **Chemical Formula:** $C_{34}H_{36}F_3N_7O_3$ **Exact Mass: 647.28**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.35 (s, 1H), 8.17 (s, 1H), 7.44 (s, 1H), 7.21 (s, 1H), 7.12-7.08 (m, 4H), 6.75 (s, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8.8, 2.8 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.50 (d, J = 14.8 Hz, 1H), 3.73 (s, 3H), 3.73-3.65 (m, 2H), 3.61 (s, 3H), 3.48-3.40 (m, 2H), 3.11-3.00 (m, 2H), 2.92 (t, J = 12.0 Hz, 2H), 2.79 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H); MS m/z: 648.3 [M+1].
YKL-04-113	 **Chemical Formula:** $C_{33}H_{33}F_3N_6O_4$ **Exact Mass: 634.25**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.37 (s, 1H), 8.20 (s, 1H), 7.42 (s, 1H), 7.24 (s, 1H), 7.17-7.12 (m, 4H), 6.69 (s, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 8.4, 2.8 Hz, 1H), 4.65 (d, J = 15.2 Hz, 1H), 4.54 (d, J = 15.2 Hz, 1H), 3.78 (s, 3H), 3.72-3.67 (m, 4H), 3.65 (s, 3H), 3.06-3.01 (m, 4H), 2.23 (s, 3H), 2.20 (s, 3H); MS m/z: 635.3 [M+1].
YKL-04-114	 **Chemical Formula:** $C_{34}H_{39}N_7O_4$ **Exact Mass: 609.31**	^{1}H NMR 400 MHz (DMSO-d_6) δ 9.21 (s, 1H), 8.20 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.23-7.21 (m, 3H), 7.03 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 8.8, 2.8 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.73 (d, J = 14.8 Hz, 1H), 4.59 (d, J = 14.8 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.97-2.90 (m, 4H), 2.63-2.55 (m, 4H), 2.34 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H); MS m/z: 610.3 [M+1].

YKL-04-115	 **Chemical Formula:** $C_{33}H_{36}N_6O_5$ **Exact Mass: 596.27**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.15 (s, 1H), 8.13 (s, 1H), 7.17-7.13 (m, 4H), 6.98-6.95 (m, 1H), 6.94-6.90 (m, 1H), 6.70 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.4, 2.4 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 4.65 (d, J = 14.4 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 3.84 (s, 3H), 3.68 (t, J = 4.8 Hz, 4H), 3.67 (s, 3H), 3.61 (s, 3H), 2.82 (t, J = 4.8 Hz, 4H), 2.24 (s, 3H), 2.21 (s, 3H); MS m/z: 597.3 [M+1].
YKL-04-118	 **Chemical Formula:** $C_{34}H_{35}F_3N_6O_4$ **Exact Mass: 648.27**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.83 (s, 1H), 8.24 (s, 1H), 7.82 (s, 1H), 7.75 (s, 1H), 7.23-7.20 (m, 1H), 7.15-7.13 (m, 3H), 6.68 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 8.4, 3.0 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 14.4 Hz, 1H), 4.17-4.04 (m, 2H), 3.98-3.84 (m, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.64-3.55 (m, 4H), 3.06-2.92 (m, 2H), 2.23 (s, 3H), 2.20 (s, 3H); MS m/z: 649.3 [M+1].
YKL-04-125	 **Chemical Formula:** $C_{35}H_{38}F_3N_7O_3$ **Exact Mass: 661.30**	^{1}H NMR 600 MHz (DMSO-d_6) δ 9.77 (s, 1H), 8.21 (s, 1H), 7.63-7.60 (m, 2H), 7.20 (d, J = 9.0 Hz, 1H), 7.15-7.13 (m, 3H), 7.13 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 9.0, 3.0 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 4.55 (d, J = 15.6 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.41-3.34 (m, 4H), 3.05-2.97 (m, 2H), 2.90-2.83 (m, 2H), 2.77 (s, 3H), 2.38-2.29 (m, 2H), 2.23 (s, 3H), 2.20 (s, 3H); MS m/z: 662.3 [M+1].
YKL-05-57	 Exact Mass: 610.29 Molecular Weight: 610.72	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.48 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.19 – 7.09 (m, 4H), 6.70 (d, J = 2.7 Hz, 1H), 6.61 (dd, J = 8.6, 2.6 Hz, 1H), 6.51 (d, J = 2.6 Hz, 1H), 6.05 (d, J = 8.8 Hz, 1H), 4.71 – 4.59 (m, 2H), 4.50 (dd, J = 14.2, 0.9 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H), 3.58 (td, J = 8.9, 4.4 Hz, 1H), 3.44 – 3.34 (m, 2H), 2.73 (ddd, J = 12.6, 10.3, 2.9 Hz, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 1.80 (ddt, J = 11.3, 6.0, 3.0 Hz, 2H), 1.47 (dtd, J = 12.9, 9.7, 3.8 Hz, 2H); MS m/z: 611.3 [M+1].

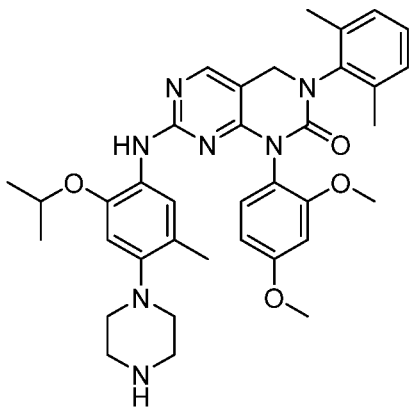
[00274] YKL-05-58



Exact Mass: 637.34
Molecular Weight: 637.78

[00275] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.42 (s, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 6.62 (dd, J = 8.6, 2.6 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 5.99 (d, J = 8.9 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.60 (p, J = 6.1 Hz, 1H), 4.51 (d, J = 14.4 Hz, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 2.99 (t, J = 5.0 Hz, 4H), 2.43 (t, J = 5.0 Hz, 4H), 2.24 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H). MS m/z: 638.4 [M+1].

[00276] YKL-05-59

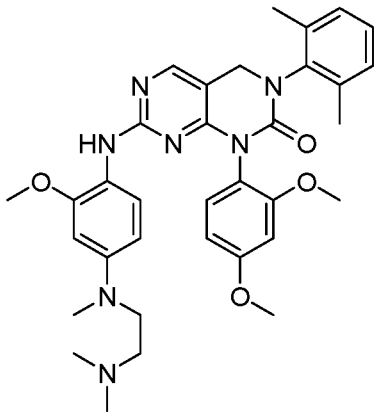


Exact Mass: 637.34
Molecular Weight: 637.78

[00277] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.14 (d, J = 0.9 Hz, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.18 – 7.11 (m, 3H), 6.72 – 6.67 (m, 2H), 6.61 (dd, J = 8.6, 2.7 Hz, 1H), 4.67 (dd, J = 14.3, 0.9 Hz, 1H), 4.57 – 4.51 (m, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.09 (d, J = 11.9 Hz, 2H), 2.71 (td, J = 11.9, 3.1 Hz, 3H), 2.24 (s, 3H),

2.20 (s, 3H), 1.93 – 1.86 (m, 3H), 1.62 – 1.48 (m, 4H), 1.28 – 1.20 (m, 7H). MS m/z: 638.4 [M+1].

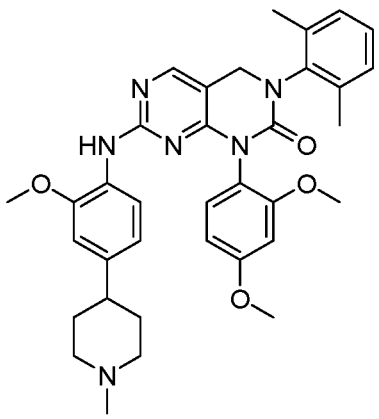
[00278] YKL-05-60



Exact Mass: 611.32
Molecular Weight: 611.75

[00279] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.43 (s, 1H), 7.24 (d, J = 8.9 Hz, 1H), 7.18 – 7.10 (m, 4H), 6.68 (d, J = 2.6 Hz, 1H), 6.60 (dd, J = 8.6, 2.6 Hz, 1H), 6.26 (d, J = 2.6 Hz, 1H), 5.85 (s, 1H), 4.63 (dd, J = 14.2, 1.0 Hz, 1H), 4.50 (d, J = 15.0 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.35 – 3.31 (m, 2H), 2.83 (s, 3H), 2.36 – 2.30 (m, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.17 (s, 6H). MS m/z: 612.4 [M+1].

[00280] YKL-05-68

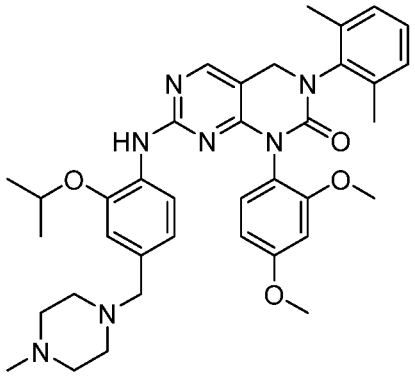


Exact Mass: 608.31
Molecular Weight: 608.74

[00281] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.59 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.21 – 7.11 (m, 4H), 6.78 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.6, 2.6 Hz, 1H), 6.41 – 6.34 (m, 1H), 4.67 (dd, J = 14.4, 1.0 Hz, 1H), 4.53

(dd, J = 14.4, 0.9 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 2.87 (d, J = 11.0 Hz, 2H), 2.40 – 2.28 (m, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.98 (t, J = 11.4 Hz, 2H), 1.68 (t, J = 7.5 Hz, 2H), 1.60 (qd, J = 12.2, 3.7 Hz, 2H). MS m/z: 609.3 [M+1].

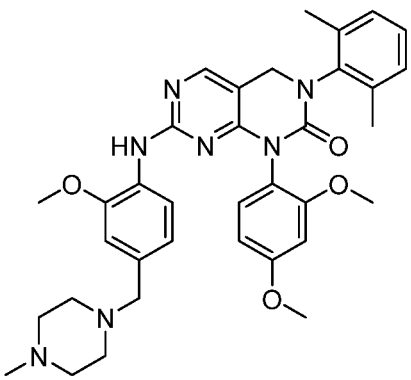
[00282] YKL-05-69



Exact Mass: 651.35
Molecular Weight: 651.81

[00283] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.57 (s, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.15 (s, 2H), 6.83 (d, J = 1.7 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 6.63 (dd, J = 8.6, 2.6 Hz, 1H), 6.38 (dd, J = 8.4, 1.7 Hz, 1H), 4.69 (dd, J = 14.4, 1.0 Hz, 1H), 4.63 – 4.49 (m, 2H), 3.86 (s, 3H), 3.64 (s, 3H), 3.32 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H). MS m/z: 652.4 [M+1].

[00284] YKL-05-70

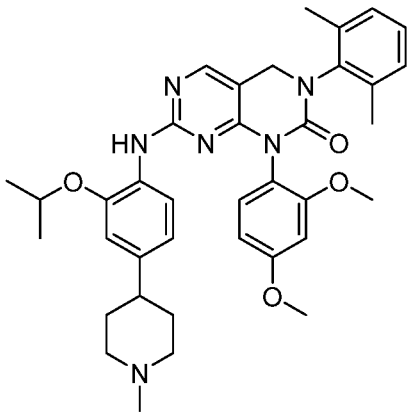


Exact Mass: 623.32
Molecular Weight: 623.76

[00285] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.63 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.14 (s, 3H), 6.82 (d, J = 1.7 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.6, 2.6 Hz, 1H), 6.44 (dd, J = 8.4, 1.7 Hz, 1H), 4.68 (dd, J

= 14.4, 1.0 Hz, 1H), 4.57 – 4.47 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 3.33 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H). MS m/z: 624.3 [M+1].

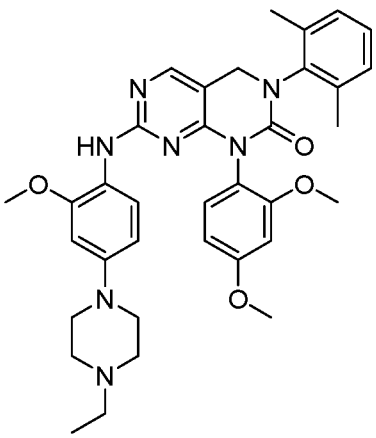
[00286] YKL-05-74



Exact Mass: 636.34
Molecular Weight: 636.80

[00287] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.63 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.24 (s, 2H), 6.88 (d, J = 1.9 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.72 (dd, J = 8.6, 2.6 Hz, 1H), 6.40 (dd, J = 8.4, 1.9 Hz, 1H), 4.77 (dd, J = 14.4, 1.0 Hz, 1H), 4.70 (p, J = 6.1 Hz, 1H), 4.66 – 4.59 (m, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.58 – 3.46 (m, 1H), 2.98 (d, J = 11.0 Hz, 2H), 2.48 – 2.38 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 2.19 – 2.06 (m, 2H), 1.78 (d, J = 12.7 Hz, 2H), 1.68 (qd, J = 12.3, 3.7 Hz, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 1.31 (s, 2H), 1.11 (dd, J = 6.1, 1.4 Hz, 3H). MS m/z: 637.4 [M+1].

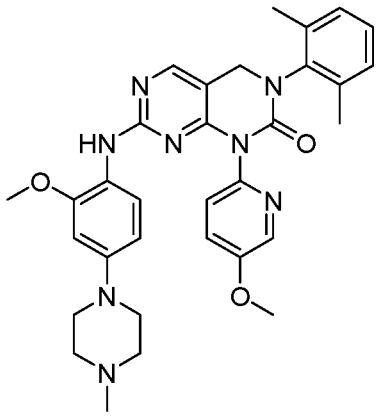
[00288] YKL-05-76



Exact Mass: 623.32
Molecular Weight: 623.76

[00289] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.44 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.3 Hz, 4H), 6.65 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.6, 2.6 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H), 5.99 (d, J = 8.5 Hz, 1H), 4.60 (dd, J = 14.3, 1.0 Hz, 1H), 4.50 – 4.40 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.60 (s, 3H), 2.97 (dd, J = 6.3, 3.7 Hz, 4H), 2.30 (q, J = 7.2 Hz, 2H), 2.17 (d, J = 11.6 Hz, 6H), 0.97 (t, J = 7.2 Hz, 3H). MS m/z: 624.3 [M+1].

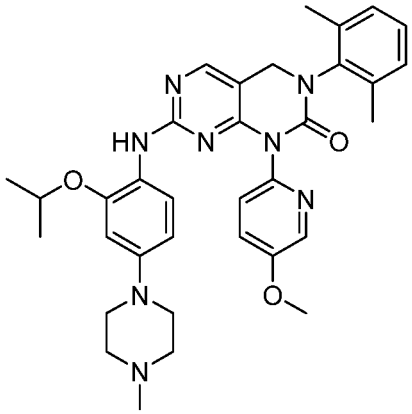
[00290] YKL-05-77



Exact Mass: 580.29
Molecular Weight: 580.69

[00291] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.29 (d, J = 3.5 Hz, 1H), 8.14 (s, 1H), 7.61 (s, 1H), 7.57 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.15-7.18 (m, 4H), 6.53 (d, J = 2.5 Hz, 1H), 6.04 (s, 1H), 4.62 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 3.04 (t, J = 5.0 Hz, 4H), 2.45 (t, J = 5.0 Hz, 4H), 2.25 (s, 6H), 2.22 (s, 3H) ppm. MS m/z: 581.3 [M+1].

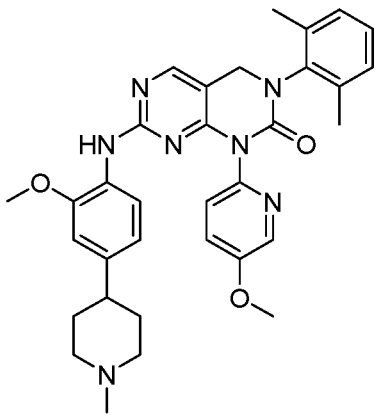
[00292] YKL-05-88



Exact Mass: 608.32
Molecular Weight: 608.75

[00293] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (dd, J = 3.2, 0.5 Hz, 1H), 8.09 (s, 1H), 7.53 (dd, J = 8.7, 3.1 Hz, 1H), 7.42 (s, 1H), 7.34 (dd, J = 8.6, 0.5 Hz, 1H), 7.15 – 7.01 (m, 4H), 6.49 (d, J = 2.6 Hz, 1H), 5.92 (d, J = 8.8 Hz, 1H), 4.62 – 4.48 (m, 3H), 3.87 (s, 3H), 3.01 – 2.89 (m, 4H), 2.41 – 2.35 (m, 4H), 2.19 (s, 6H), 2.16 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H). MS m/z: 609.3 [M+1].

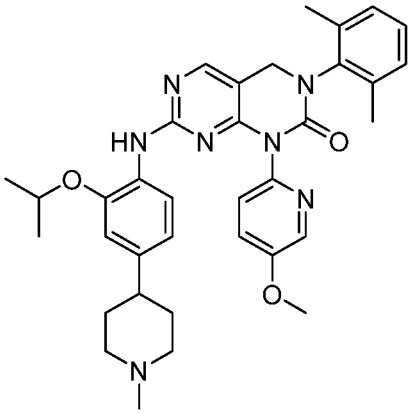
[00294] YKL-05-89



Exact Mass: 579.30
Molecular Weight: 579.70

[00295] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (dd, J = 3.2, 0.5 Hz, 1H), 8.13 (d, J = 0.9 Hz, 1H), 7.62 (s, 1H), 7.52 (dd, J = 8.7, 3.1 Hz, 1H), 7.35 (dd, J = 8.7, 0.5 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.15 – 7.06 (m, 3H), 6.74 (d, J = 1.9 Hz, 1H), 6.36 – 6.24 (m, 1H), 4.58 (d, J = 0.9 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.84 (d, J = 11.1 Hz, 2H), 2.30 (tt, J = 11.5, 4.0 Hz, 1H), 2.19 (s, 6H), 2.17 (s, 3H), 2.02 – 1.91 (m, 2H), 1.69 – 1.61 (m, 2H), 1.56 (qd, J = 12.2, 3.7 Hz, 2H). MS m/z: 580.3 [M+1].

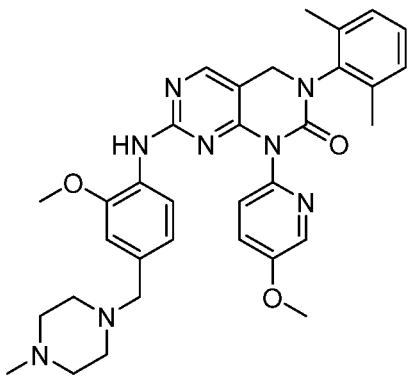
[00296] YKL-05-90



Exact Mass: 607.33
Molecular Weight: 607.76

[00297] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (dd, J = 3.1, 0.6 Hz, 1H), 8.13 (d, J = 0.9 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.39 – 7.33 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.14 – 7.05 (m, 3H), 6.74 (d, J = 1.9 Hz, 1H), 6.23 (dd, J = 8.4, 1.8 Hz, 1H), 4.62 – 4.50 (m, 3H), 3.88 (s, 3H), 2.81 (d, J = 10.8 Hz, 2H), 2.27 (tt, J = 11.6, 3.8 Hz, 1H), 2.19 (s, 6H), 2.15 (s, 3H), 1.93 (t, J = 11.4 Hz, 2H), 1.63 (d, J = 12.2 Hz, 2H), 1.52 (qd, J = 12.3, 3.7 Hz, 2H), 1.21 (s, 3H), 1.19 (s, 3H). MS m/z: 608.3 [M+1].

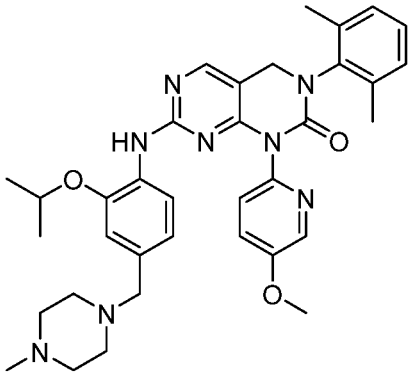
[00298] YKL-05-91



Exact Mass: 594.31
Molecular Weight: 594.72

[00299] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 3.3 Hz, 1H), 8.14 (d, J = 1.0 Hz, 1H), 7.65 (s, 1H), 7.52 (dd, J = 8.7, 3.1 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.16 – 7.06 (m, 3H), 6.77 (d, J = 1.7 Hz, 1H), 6.37 (dd, J = 8.3, 1.7 Hz, 1H), 4.62 – 4.54 (m, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.24 (s, 3H), 2.19 (s, 6H), 2.09 (s, 3H). MS m/z: 595.3 [M+1].

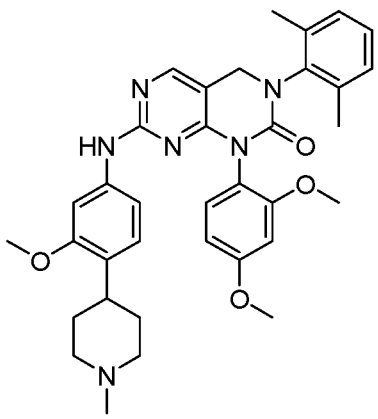
[00300] YKL-05-92



Exact Mass: 622.34
Molecular Weight: 622.77

[00301] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 3.1 Hz, 1H), 8.15 (s, 1H), 7.57 (s, 1H), 7.54 (dd, J = 8.7, 3.1 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.15 – 7.06 (m, 3H), 6.79 (d, J = 1.7 Hz, 1H), 6.30 (dd, J = 8.3, 1.7 Hz, 1H), 4.59 (s, 2H), 4.52 (p, J = 6.1 Hz, 1H), 3.89 (s, 3H), 3.24 (s, 3H), 2.19 (s, 6H), 2.10 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H). MS m/z: 623.4 [M+1].

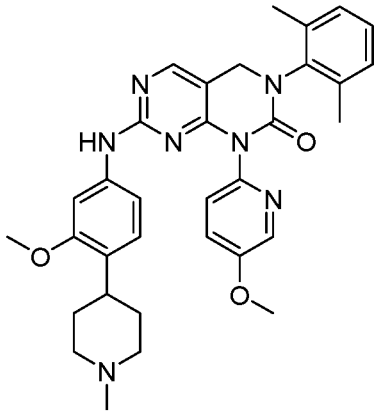
[00302] YKL-05-93



Exact Mass: 608.31
Molecular Weight: 608.74

[00303] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.09 (s, 1H), 7.14 – 7.06 (m, 4H), 7.00 – 6.91 (m, 1H), 6.86 (s, 1H), 6.68 – 6.60 (m, 2H), 6.55 (dd, J = 8.6, 2.7 Hz, 1H), 4.60 (dd, J = 14.3, 1.0 Hz, 1H), 4.52 – 4.42 (m, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 2.86 – 2.75 (m, 2H), 2.61 (tt, J = 11.5, 4.1 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 1.92 (td, J = 11.4, 3.0 Hz, 2H), 1.59 – 1.41 (m, 4H). MS m/z: 609.3 [M+1].

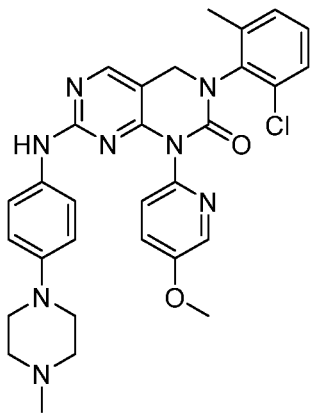
[00304] YKL-05-94



Exact Mass: 579.30
Molecular Weight: 579.70

[00305] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.23 (d, J = 3.1 Hz, 1H), 8.14 (s, 1H), 7.51 (dd, J = 8.7, 3.1 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.14 – 7.05 (m, 3H), 6.89 – 6.76 (m, 2H), 6.62 (d, J = 8.3 Hz, 1H), 4.57 (s, 2H), 3.86 (s, 3H), 3.55 (s, 3H), 2.89 – 2.73 (m, 2H), 2.61 (tt, J = 11.7, 4.4 Hz, 1H), 2.19 (s, 6H), 2.14 (s, 3H), 1.91 (td, J = 11.4, 3.0 Hz, 2H), 1.60 – 1.38 (m, 4H). MS m/z: 580.3 [M+1].

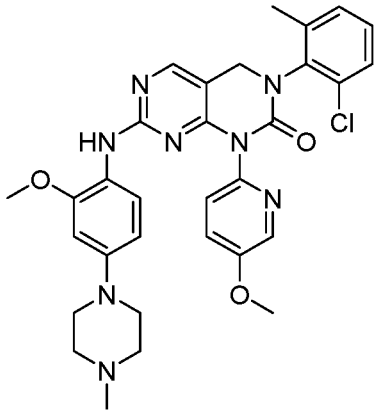
[00306] YKL-05-95



Exact Mass: 570.23
Molecular Weight: 571.08

[00307] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.29 (s, 1H), 8.32 (d, J = 3.0 Hz, 1H), 8.20 (s, 1H), 7.61 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 7.46 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 7.40 (d, J = 10.5 Hz, 1H), 7.31-7.36 (m, 2H), 7.06 (s, 2H), 6.56 (d, J = 6.5 Hz, 2H), 4.64-4.71 (m, 2H), 3.94 (s, 3H), 2.98 (t, J = 5.0 Hz, 4H), 2.44 (t, J = 5.0 Hz, 4H),2.32 (s, 3H), 2.21 (s, 3H) ppm. MS m/z: 571.3 [M+1].

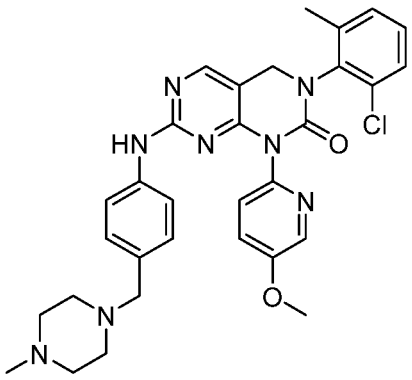
[00308] YKL-05-96



Exact Mass: 600.24
Molecular Weight: 601.11

[00309] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.29 (d, J = 3.0 Hz, 1H), 8.17 (s, 1H), 7.67 (s, 1H), 7.58 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 1H), 7.46 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.31-7.35 (m, 2H), 7.12 (bs, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.04 (bs, 1H), 4.64-4.71 (m, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 3.05 (s, 4H), 2.48 (s, 4H), 2.32 (s, 3H), 2.24 (s, 3H) ppm. MS m/z: 601.3 [M+1].

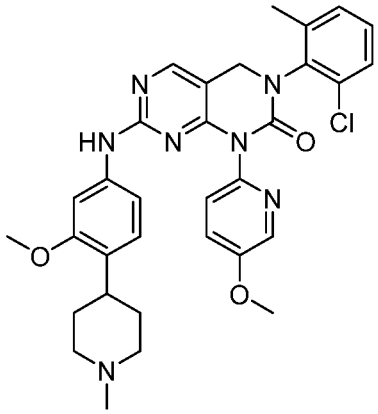
[00310] YKL-05-97



Exact Mass: 584.24
Molecular Weight: 585.11

[00311] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.52 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.25 (s, 1H), 7.61 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 1H), 7.46 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.32-7.36 (m, 2H), 7.15 (d, J = 6.5 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 4.67-4.74 (m, 2H), 3.96 (s, 3H), 3.34 (s, 4H), 2.25-2.46 (bs, 8H), 2.18 (s, 4H) ppm. MS m/z: 585.3 [M+1].

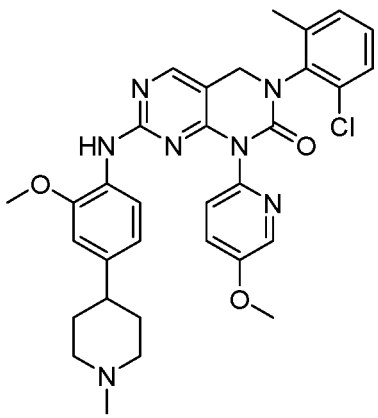
[00312] YKL-05-98



Exact Mass: 599.24
Molecular Weight: 600.12

[00313] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.37 (d, J = 3.1 Hz, 1H), 8.30 (s, 1H), 7.65 (dd, J = 8.7, 3.1 Hz, 1H), 7.52 (dd, J = 7.1, 2.4 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.04 – 6.89 (m, 2H), 6.76 – 6.66 (m, 1H), 4.83 – 4.70 (m, 2H), 3.99 (s, 3H), 3.83 – 3.76 (m, 1H), 3.69 (s, 3H), 3.24 (d, J = 11.3 Hz, 2H), 2.95 – 2.81 (m, 1H), 2.38 (s, 3H), 1.86 – 1.65 (m, 4H). MS m/z: 600.3 [M+1].

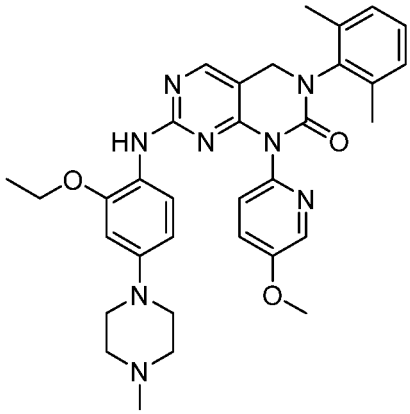
[00314] YKL-05-99



Exact Mass: 599.24
Molecular Weight: 600.12

[00315] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (d, J = 3.1 Hz, 1H), 8.15 (s, 1H), 7.67 (s, 1H), 7.53 (dd, J = 8.7, 3.1 Hz, 1H), 7.39 (dd, J = 7.1, 2.3 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.19 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 4.69 – 4.57 (m, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.87 (d, J = 11.0 Hz, 2H), 2.37 – 2.28 (m, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.09 – 1.95 (m, 2H), 1.71 – 1.62 (m, 2H), 1.57 (qd, J = 12.3, 3.7 Hz, 2H). MS m/z: 600.3 [M+1].

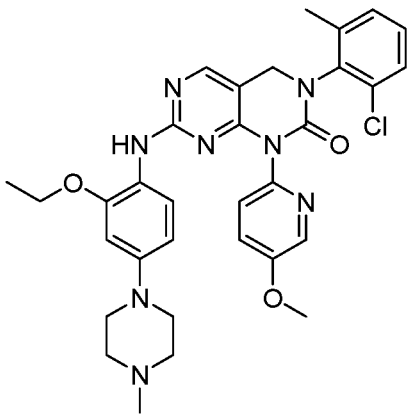
[00316] YKL-05-151



Exact Mass: 594.31
Molecular Weight: 594.72

[00317] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 3.1 Hz, 1H), 8.10 (s, 1H), 7.58 – 7.47 (m, 2H), 7.34 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 3.5 Hz, 4H), 6.51 (d, J = 2.6 Hz, 1H), 5.96 (d, J = 8.1 Hz, 1H), 4.56 (s, 2H), 3.98 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.16 – 3.00 (m, 4H), 2.93 – 2.75 (m, 4H), 2.55 – 2.45 (m, 3H), 2.19 (s, 6H), 1.25 (t, J = 7.0 Hz, 3H). MS m/z: 595.3 [M+1].

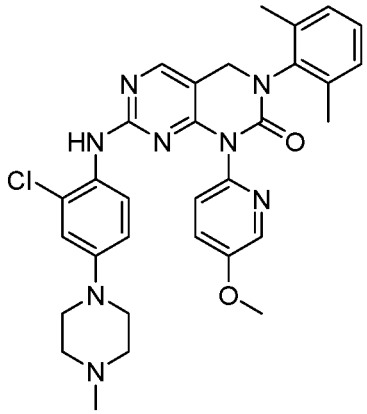
[00318] YKL-05-152



Exact Mass: 614.25
Molecular Weight: 615.13

[00319] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 3.1 Hz, 1H), 8.12 (s, 1H), 7.55 – 7.50 (m, 2H), 7.39 (dd, J = 6.7, 2.8 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 2.6 Hz, 1H), 5.95 (d, J = 9.5 Hz, 1H), 4.71 – 4.54 (m, 2H), 3.97 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.10 – 2.94 (m, 4H), 2.67 – 2.49 (m, 4H), 2.30 (s, 3H), 2.25 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H). MS m/z: 615.3 [M+1].

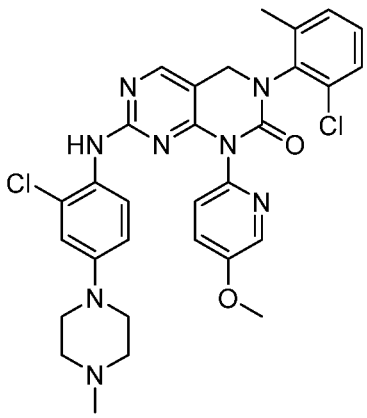
[00320] YKL-05-153



Exact Mass: 584.24
Molecular Weight: 585.11

[00321] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.22 (d, J = 3.2 Hz, 1H), 8.10 (s, 1H), 7.48 (dd, J = 8.7, 3.1 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.15 – 7.12 (m, 3H), 6.89 (d, J = 2.8 Hz, 1H), 6.63 – 6.58 (m, 1H), 4.59 (d, J = 0.9 Hz, 2H), 3.86 (s, 3H), 3.21 – 3.03 (m, 4H), 2.71 – 2.54 (m, 4H), 2.43 – 2.27 (m, 3H), 2.23 (s, 6H). MS m/z: 585.3 [M+1].

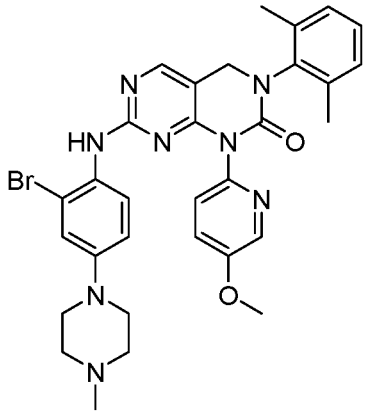
[00322] YKL-05-154



Exact Mass: 604.19
Molecular Weight: 605.52

[00323] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.22 (d, J = 3.1 Hz, 1H), 8.13 (s, 1H), 7.49 (dd, J = 8.7, 3.1 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.35 – 7.27 (m, 3H), 7.12 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.60 (d, J = 9.0 Hz, 1H), 4.71 – 4.58 (m, 2H), 3.86 (s, 3H), 3.20 – 3.03 (m, 4H), 2.70 – 2.51 (m, 4H), 2.37 – 2.30 (m, 4H), 2.29 (s, 3H). MS m/z: 605.2 [M+1].

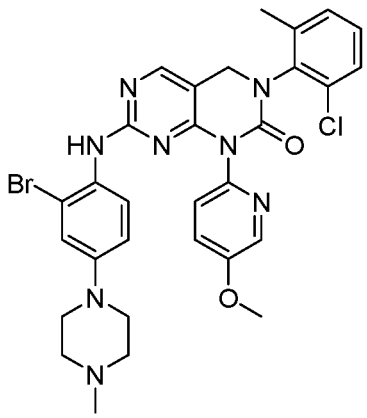
[00324] YKL-05-155



Exact Mass: 628.19
Molecular Weight: 629.56

[00325] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22 (d, J = 3.2 Hz, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.48 (dd, J = 8.7, 3.1 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.17 – 7.10 (m, 4H), 7.04 (d, J = 2.8 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 4.59 (d, J = 0.9 Hz, 2H), 3.86 (s, 3H), 3.19 – 3.01 (m, 4H), 2.70 – 2.55 (m, 4H), 2.42 – 2.30 (m, 3H), 2.22 (s, 6H). MS m/z: 629.2 [M+1].

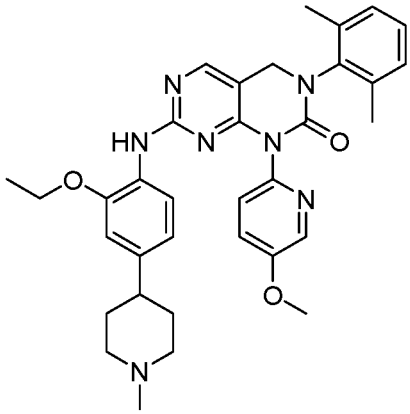
[00326] YKL-05-156



Exact Mass: 648.14
Molecular Weight: 649.98

[00327] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.22 (d, J = 3.1 Hz, 1H), 8.12 (s, 1H), 7.48 (dd, J = 8.7, 3.1 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.34 – 7.27 (m, 3H), 7.10 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 4.73 – 4.58 (m, 2H), 3.86 (s, 3H), 3.17 – 3.00 (m, 4H), 2.57 – 2.49 (m, 4H), 2.29 (s, 3H), 2.28 – 2.23 (m, 3H). MS m/z: 649.2 [M+1].

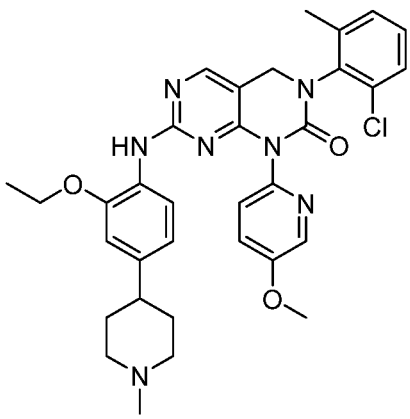
[00328] YKL-05-163



Exact Mass: 593.31
Molecular Weight: 593.73

[00329] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 – 8.23 (m, 1H), 8.14 (s, 1H), 7.62 (s, 1H), 7.54 (dd, J = 8.7, 3.1 Hz, 1H), 7.37 (dd, J = 8.6, 0.5 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.15 – 7.07 (m, 3H), 6.73 (d, J = 1.8 Hz, 1H), 6.25 (dd, J = 8.2, 1.8 Hz, 1H), 4.59 (d, J = 0.9 Hz, 2H), 4.00 (q, J = 6.9 Hz, 2H), 3.88 (s, 3H), 3.28 – 3.20 (m, 4H), 2.78 – 2.46 (m, 5H), 2.19 (s, 6H), 1.81 (d, J = 13.4 Hz, 2H), 1.74 – 1.57 (m, 2H), 1.28 (t, J = 6.9 Hz, 3H). MS m/z: 594.3 [M+1].

[00330] YKL-05-164

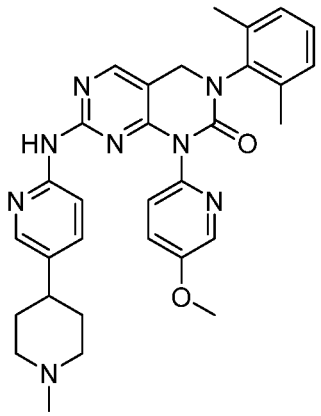


Exact Mass: 613.26
Molecular Weight: 614.15

[00331] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 – 8.27 (m, 1H), 8.21 (d, J = 0.9 Hz, 1H), 7.67 (s, 1H), 7.59 (dd, J = 8.7, 3.1 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.41 – 7.36 (m, 1H), 7.35 – 7.28 (m, 2H), 7.21 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 1.9 Hz, 1H), 6.34 – 6.26 (m, 1H), 4.75 – 4.62 (m, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 2.86 (d, J = 10.9 Hz, 2H), 2.38 – 2.31 (m, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 2.03 – 1.90 (m, 2H),

1.73 – 1.64 (m, 2H), 1.58 (qd, *J* = 12.4, 3.8 Hz, 2H), 1.32 (t, *J* = 6.9 Hz, 3H). MS m/z: 614.3 [M+1].

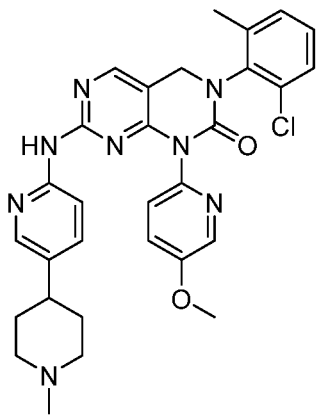
[00332] YKL-05-165



Exact Mass: 550.28
Molecular Weight: 550.67

[00333] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.33 (dd, *J* = 3.1, 0.6 Hz, 1H), 8.25 (d, *J* = 0.9 Hz, 1H), 8.08 – 8.00 (m, 1H), 7.61 (dd, *J* = 8.7, 3.1 Hz, 1H), 7.43 (dd, *J* = 8.7, 0.6 Hz, 1H), 7.21 – 7.12 (m, 4H), 7.07 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.66 (d, *J* = 0.9 Hz, 2H), 3.93 (s, 3H), 3.00 – 2.85 (m, 2H), 2.46 – 2.35 (m, 1H), 2.25 (s, 6H), 2.15 – 1.95 (m, 2H), 1.70 (d, *J* = 12.7 Hz, 2H), 1.63 – 1.54 (m, 2H). MS m/z: 551.3 [M+1].

[00334] YKL-05-166

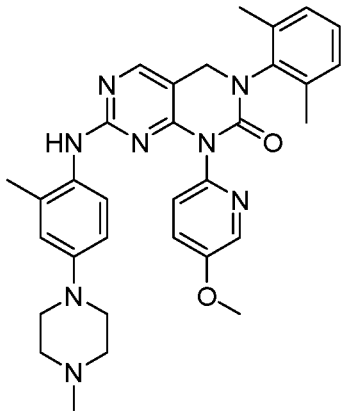


Exact Mass: 570.23
Molecular Weight: 571.08

[00335] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.34 (d, *J* = 3.1 Hz, 1H), 8.27 (d, *J* = 1.0 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.16 (d, *J* = 8.6 Hz,

1H), 7.07 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.79 – 4.64 (m, 2H), 3.93 (s, 3H), 3.00 – 2.82 (m, 2H), 2.45 – 2.34 (m, 1H), 2.31 (s, 3H), 2.29 – 2.19 (m, 2H), 1.69 (d, *J* = 12.7 Hz, 3H), 1.64 – 1.53 (m, 2H). MS m/z: 571.3 [M+1].

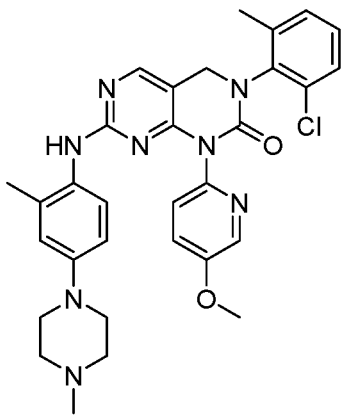
[00336] YKL-05-178



Exact Mass: 564.30
Molecular Weight: 564.69

[00337] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.20 (d, *J* = 3.1 Hz, 1H), 8.06 (s, 1H), 7.45 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.49 – 6.39 (m, 1H), 4.56 (s, 2H), 3.85 (s, 3H), 3.09 – 2.96 (m, 4H), 2.29 – 2.23 (m, 3H), 2.22 (s, 6H), 2.04 (s, 3H). MS m/z: 565.3 [M+1].

[00338] YKL-05-179

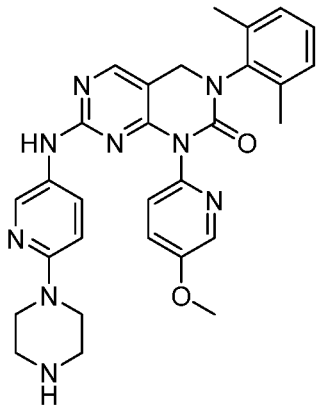


Exact Mass: 584.24
Molecular Weight: 585.11

[00339] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.20 (d, *J* = 3.1 Hz, 1H), 8.08 (s, 1H), 7.45 (dd, *J* = 8.7, 3.1 Hz, 1H), 7.43 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.35 – 7.26 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.48 – 6.40 (m, 1H),

4.70 – 4.54 (m, 2H), 3.85 (s, 4H), 3.08 – 2.96 (m, 4H), 2.29 (s, 3H), 2.27 – 2.22 (m, 4H), 2.04 (s, 3H). MS m/z: 585.3 [M+1].

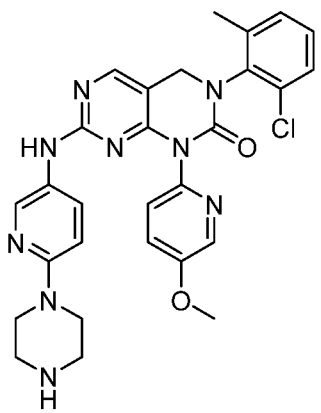
[00340] YKL-05-180



Exact Mass: 537.26
Molecular Weight: 537.63

[00341] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.75 (s, 2H), 8.27 (d, J = 3.1 Hz, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.55 (dd, J = 8.7, 3.1 Hz, 1H), 7.50 (s, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.20 – 7.12 (m, 3H), 6.60 (s, 1H), 4.62 (s, 2H), 3.90 (s, 3H), 3.22 – 3.13 (m, 4H), 2.24 (s, 6H). MS m/z: 538.3 [M+1].

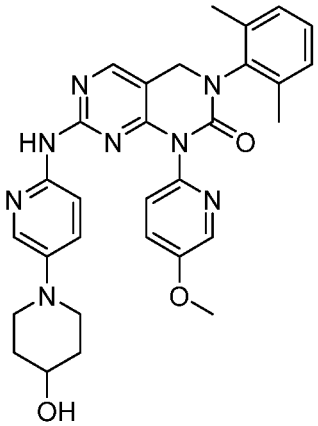
[00342] YKL-05-181



Exact Mass: 557.21
Molecular Weight: 558.04

[00343] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.77 (s, 2H), 8.28 (d, J = 3.1 Hz, 1H), 8.20 (s, 1H), 8.05 (s, 1H), 7.55 (dd, J = 8.7, 3.1 Hz, 1H), 7.48 (s, 1H), 7.44 (dd, J = 7.4, 2.1 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.36 – 7.27 (m, 2H), 6.59 (s, 1H), 4.72 – 4.62 (m, 2H), 3.90 (s, 3H), 3.18 (s, 4H), 2.30 (s, 3H). MS m/z: 558.2 [M+1].

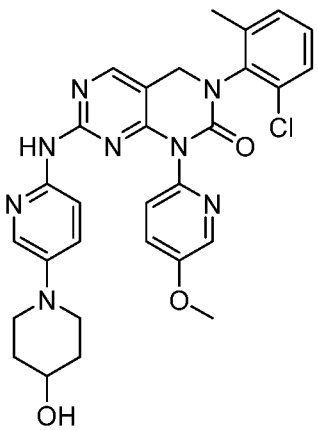
[00344] YKL-05-182



Exact Mass: 552.26
Molecular Weight: 552.64

[00345] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.32 (d, J = 3.2 Hz, 1H), 8.21 (s, 1H), 7.87 (d, J = 3.1 Hz, 1H), 7.60 (dd, J = 8.7, 3.1 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.21 – 7.12 (m, 3H), 7.07 (d, J = 9.1 Hz, 1H), 6.81 (dd, J = 9.3, 3.1 Hz, 1H), 4.66 (d, J = 4.2 Hz, 1H), 4.64 (s, 2H), 3.92 (s, 3H), 3.60 (tq, J = 8.4, 4.0 Hz, 1H), 3.37 (dt, J = 12.5, 4.4 Hz, 2H), 2.75 (ddd, J = 12.8, 10.0, 3.0 Hz, 2H), 2.24 (s, 6H), 1.86 – 1.74 (m, 2H), 1.46 (dtd, J = 12.9, 9.4, 3.8 Hz, 2H). MS m/z: 553.3 [M+1].

[00346] YKL-05-183

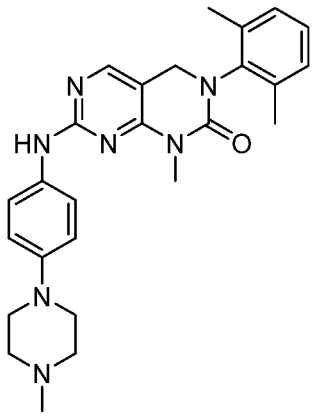


Exact Mass: 572.21
Molecular Weight: 573.05

[00347] ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.33 (d, J = 3.1 Hz, 1H), 8.24 (s, 1H), 7.87 (d, J = 3.0 Hz, 1H), 7.60 (dd, J = 8.7, 3.1 Hz, 1H), 7.44 (dd, J = 7.4, 2.1 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.06 (d, J = 9.1 Hz, 1H), 6.81 (d, J = 8.9 Hz, 1H), 4.75 – 4.62 (m, 3H), 3.92 (s, 3H), 3.60 (tt, J = 8.9, 4.2 Hz, 1H), 3.37 (dt, J = 12.6, 4.6 Hz, 2H), 2.76 (ddd, J = 12.8, 10.1, 3.0 Hz, 2H), 2.31

(s, 3H), 1.86 – 1.75 (m, 2H), 1.46 (dtd, *J* = 12.9, 9.3, 3.8 Hz, 2H). MS m/z: 573.2 [M+1].

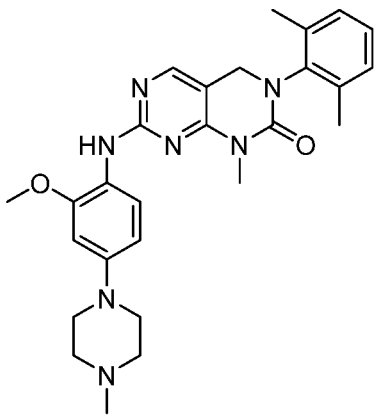
[00348] YKL-06-029



Exact Mass: 457.26
Molecular Weight: 457.58

[00349] ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.08 (d, *J* = 1.0 Hz, 1H), 7.59 (d, *J* = 9.1 Hz, 2H), 7.26 – 7.08 (m, 3H), 6.89 (d, *J* = 9.1 Hz, 2H), 4.55 – 4.40 (m, 2H), 3.14 – 2.96 (m, 4H), 2.49 – 2.41 (m, 4H), 2.23 (s, 3H), 2.18 (s, 6H). MS m/z: 458.3 [M+1].

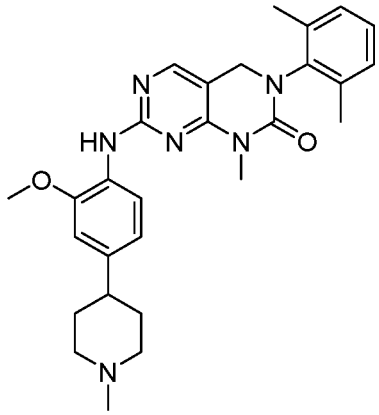
[00350] YKL-06-030



Exact Mass: 487.27
Molecular Weight: 487.61

[00351] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.10 (m, 3H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.50 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.53 – 4.41 (m, 2H), 3.83 (s, 3H), 3.27 (s, 3H), 3.18 – 3.06 (m, 4H), 2.49 – 2.42 (m, 4H), 2.23 (s, 3H), 2.17 (s, 6H). MS m/z: 488.3 [M+1].

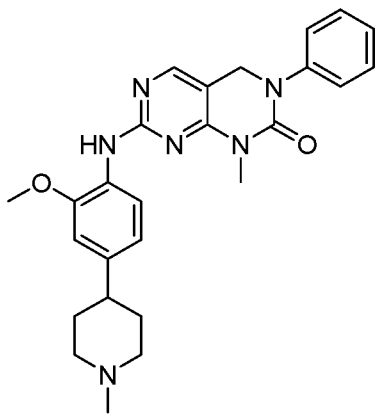
[00352] YKL-06-031



Exact Mass: 486.27
Molecular Weight: 486.62

[00353] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.26 – 7.11 (m, 3H), 6.93 (d, J = 1.8 Hz, 1H), 6.82 (dd, J = 8.3, 1.8 Hz, 1H), 4.49 (s, 2H), 3.87 (s, 3H), 3.31 (s, 3H), 2.88 (dt, J = 11.8, 3.2 Hz, 2H), 2.51 (p, J = 1.9 Hz, 6H), 2.44 (tt, J = 11.6, 4.1 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 6H), 1.98 (td, J = 11.6, 2.8 Hz, 2H), 1.81 – 1.62 (m, 4H). MS m/z: 487.3 [M+1].

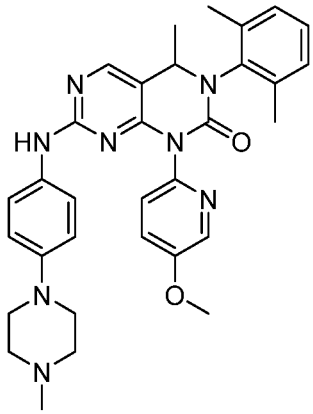
[00354] YKL-06-033



Exact Mass: 458.24
Molecular Weight: 458.57

[00355] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.47 – 7.34 (m, 4H), 7.27 (td, J = 7.1, 1.5 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H), 6.82 (dd, J = 8.3, 1.9 Hz, 1H), 4.72 (s, 2H), 3.87 (s, 3H), 2.89 (dt, J = 12.0, 3.1 Hz, 2H), 2.44 (ddt, J = 11.7, 8.1, 4.1 Hz, 1H), 2.22 (s, 3H), 2.00 (t, J = 11.4 Hz, 2H), 1.82 – 1.63 (m, 4H). MS m/z: 459.3 [M+1].

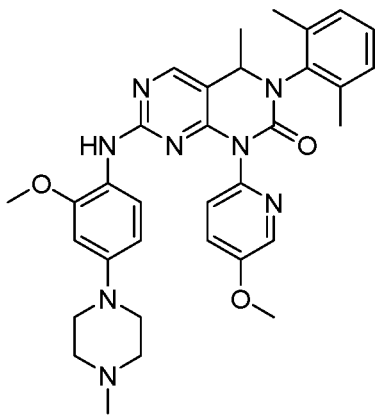
[00356] YKL-06-038



Exact Mass: 564.30
Molecular Weight: 564.69

[00357] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, J = 2.1 Hz, 1H), 8.04 (s, 1H), 7.32-7.38 (m, 2H), 7.08-7.15 (m, 5H), 6.93 (s, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.73 (q, J = 6.4 Hz, 1H), 3.93 (s, 1H), 3.12 (t, J = 5.2 Hz, 4H), 2.58 (t, J = 5.2 Hz, 4H), 2.35 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H) ppm. MS m/z: 565.3 [M+1].

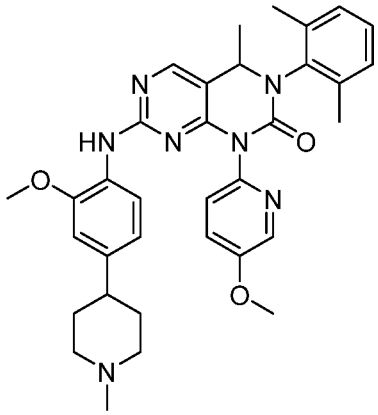
[00358] YKL-06-039



Exact Mass: 594.31
Molecular Weight: 594.72

[00359] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 2.8 Hz, 1H), 8.06 (s, 1H), 7.34-7.43 (m, 4H), 7.10-7.16 (m, 3H), 6.45 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 6.4 Hz, 1H), 4.71-4.76 (q, J = 6.4 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.22 (t, J = 5.2 Hz, 4H), 2.82 (s, 4H), 2.52 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H). MS m/z: 595.3 [M+1].

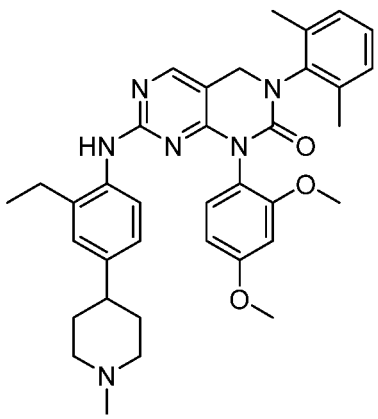
[00360] YKL-06-040



Exact Mass: 593.31
Molecular Weight: 593.73

[00361] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (d, J = 3.1 Hz, 1H), 8.29 (s, 1H), 7.73 (s, 1H), 7.61 (dd, J = 8.7, 3.1 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.23 – 7.14 (m, 3H), 6.81 (d, J = 1.9 Hz, 1H), 6.38 (d, J = 8.3 Hz, 1H), 4.86 (q, J = 6.5 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.04 – 2.89 (m, 2H), 2.47 – 2.36 (m, 1H), 2.35 – 2.27 (m, 2H), 2.20 – 2.05 (m, 1H), 1.80 – 1.71 (m, 2H), 1.65 (qd, J = 12.5, 3.7 Hz, 2H), 1.41 (d, J = 6.5 Hz, 3H). MS m/z: 594.3 [M+1].

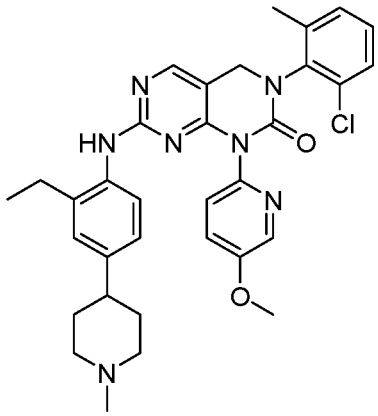
[00362] YKL-06-044



Exact Mass: 606.33
Molecular Weight: 606.77

[00363] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.98 (s, 1H), 7.10 – 7.02 (m, 5H), 6.87 (d, J = 2.2 Hz, 1H), 6.71 (dd, J = 8.2, 2.2 Hz, 1H), 6.56 (d, J = 2.7 Hz, 1H), 6.46 (dd, J = 8.6, 2.6 Hz, 1H), 4.55 (d, J = 14.5 Hz, 1H), 4.43 (d, J = 14.5 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 3H), 3.04 – 2.90 (m, 2H), 2.35 – 2.26 (m, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.74 – 1.66 (m, 2H), 1.65 – 1.53 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H). MS m/z: 607.4 [M+1].

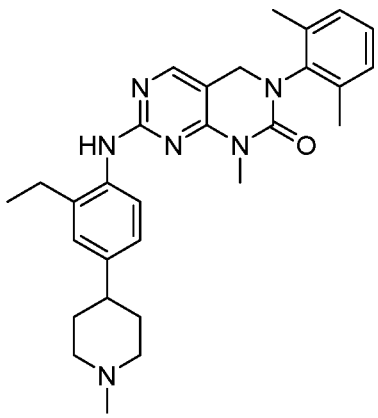
[00364] YKL-06-045



Exact Mass: 597.26
Molecular Weight: 598.15

[00365] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.16 (d, J = 3.1 Hz, 1H), 8.05 (s, 1H), 7.41 (dd, J = 8.7, 3.1 Hz, 1H), 7.38 (dd, J = 7.2, 2.3 Hz, 1H), 7.29 – 7.21 (m, 4H), 6.97 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.64 – 4.51 (m, 2H), 3.81 (s, 3H), 2.86 (d, J = 11.0 Hz, 2H), 2.35 – 2.26 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 2.07 – 1.92 (m, 2H), 1.63 (t, J = 7.7 Hz, 2H), 1.55 (qd, J = 12.4, 3.7 Hz, 2H), 0.97 (t, J = 7.5 Hz, 3H). MS m/z: 598.3 [M+1].

[00366] YKL-06-046

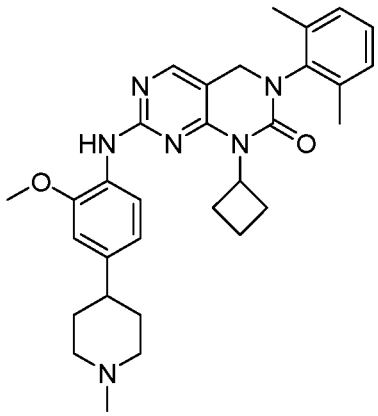


Exact Mass: 484.30
Molecular Weight: 484.65

[00367] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.90 (s, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.12 – 7.05 (m, 3H), 7.02 (d, J = 2.1 Hz, 1H), 6.96 (dd, J = 8.2, 2.2 Hz, 1H), 4.43 – 4.32 (m, 2H), 3.16 (s, 3H), 2.85 (d, J = 11.0 Hz, 2H), 2.54 (q, J = 7.6 Hz, 2H), 2.40 – 2.34 (m, 1H), 2.18 (s, 3H), 2.09 (s, 6H), 2.04 – 1.93 (m, 2H), 1.73 – 1.66

(m, 2H), 1.60 (qd, *J* = 12.3, 3.8 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 3H). MS m/z: 485.3 [M+1].

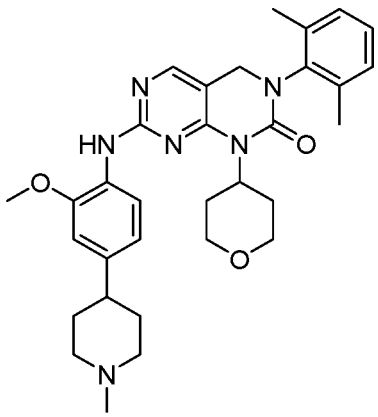
[00368] YKL-06-050



Exact Mass: 526.31
Molecular Weight: 526.69

[00369] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.02 (m, 3H), 6.85 (d, *J* = 1.8 Hz, 1H), 6.76 (dd, *J* = 8.3, 1.8 Hz, 1H), 4.80 – 4.64 (m, 1H), 4.33 (s, 2H), 3.78 (s, 3H), 3.10 – 2.92 (m, 2H), 2.53 – 2.45 (m, 2H), 2.39 – 2.16 (m, 5H), 2.07 (s, 6H), 1.77 (d, *J* = 11.7 Hz, 2H), 1.68 (qd, *J* = 12.5, 3.3 Hz, 2H), 1.59 (tt, *J* = 10.0, 4.3 Hz, 2H). MS m/z: 527.3 [M+1].

[00370] YKL-06-051

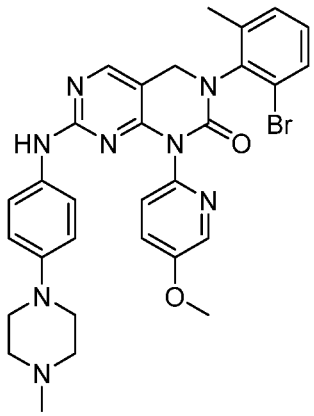


Exact Mass: 556.32
Molecular Weight: 556.71

[00371] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.97 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.16 – 7.01 (m, 3H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.75 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.69 (tt, *J* = 12.0, 3.9 Hz, 1H), 4.35 (s, 2H), 3.87 (dd, *J* = 11.2, 4.4 Hz, 2H),

3.79 (s, 3H), 3.01 – 2.84 (m, 2H), 2.56 (qd, J = 12.3, 4.6 Hz, 2H), 2.25 (s, 3H), 2.08 (s, 6H), 1.79 – 1.61 (m, 4H), 1.57 – 1.45 (m, 2H). MS m/z: 557.3 [M+1].

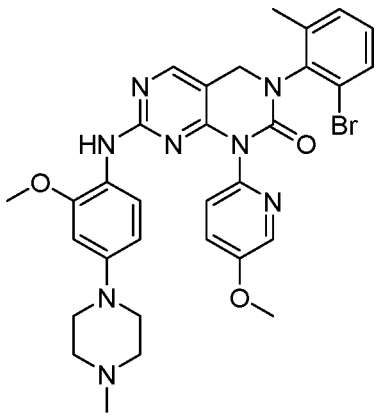
[00372] YKL-06-056



Exact Mass: 614.18
Molecular Weight: 615.54

[00373] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.33-7.38 (m, 2H), 7.24 (d, J = 6.8 Hz, 1H), 7.07-7.14 (m, 3H), 6.96 (s, 1H), 6.69 (d, J = 8.2 Hz, 2H), 4.79 (d, J = 13.6 Hz, 1H), 4.57 (d, J = 14 Hz, 1H), 3.93 (s, 3H), 3.11 (t, J = 5.2 Hz, 4H), 2.58 (t, J = 5.2 Hz, 4H), 2.38 (s, 3H), 2.35 (s, 3H), 1.80 (s, 3H). MS m/z: 615.2 [M+1].

[00374] YKL-06-057

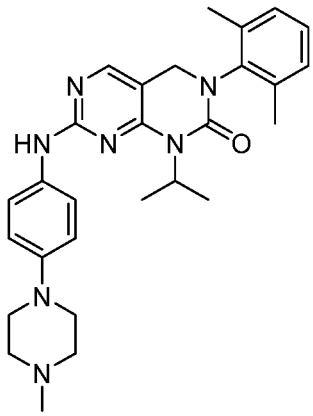


Exact Mass: 644.19
Molecular Weight: 645.56

[00375] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.35-7.40 (m, 2H), 7.23 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 3H), 6.46 (d, J = 2.0 Hz, 1H), 6.13 (d, J = 6 Hz, 2H), 4.79(d, J = 14.0 Hz, 1H), 4.58

(d, J = 13.6 Hz, 1H), 3.95 (s, 3H), 3.81(s, 3H), 3.12 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.39 (s, 3 H), 2.36 (s, 3 H). MS m/z: 645.2 [M+1].

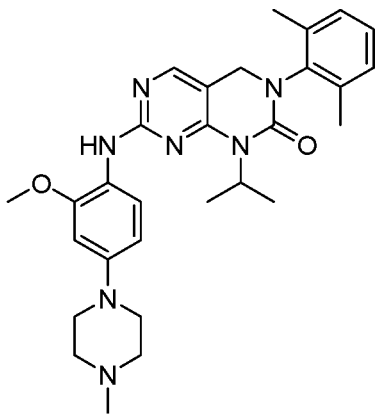
[00376] YKL-06-058



Exact Mass: 485.29
Molecular Weight: 485.64

[00377] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 1H), 7.44-7.48 (m, 2H), 7.08-7.15 (m, 3H), 7.02 (s, 1H), 6.92 -6.96 (m, 2H), 5.02-5.13 (m, 1H), 4.37 (d, J = 0.4 Hz, 2H), 3.19 (t, J = 5.2 Hz, 4H), 2.60 (t, J = 5.2 Hz, 4H), 2.36 (s, 3H), 2.23 (s, 6H), 1.55 (s, 3H), 1.53 (s, 3H). MS m/z: 486.3 [M+1].

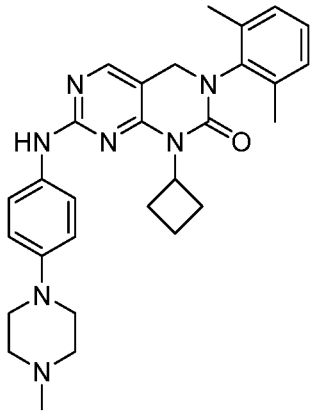
[00378] YKL-06-059



Exact Mass: 515.30
Molecular Weight: 515.66

[00379] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 9.6 Hz, 1H), 7.94 (s, 1H), 7.39 (s, 1H), 7.09-7.15 (m, 3H)， 6.55-6.58 (m, 2H), 5.06-5.17 (m, 1H), 4.38 (s, 2H), 3.90 (s, 3H), 3.20 (t, J = 5.2 Hz, 4H), 2.62 (t, J = 5.2Hz, 4H), 2.37 (s, 3H), 2.23 (s, 6H), 1.58 (s, 3H), 1.56 (s, 3H). MS m/z: 516.3 [M+1].

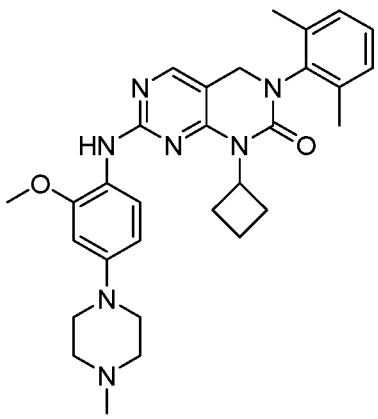
[00380] YKL-06-060



Exact Mass: 497.29
Molecular Weight: 497.65

[00381] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 1H), 7.44-7.48 (m, 2H), 7.09-7.16 (m, 3H), 6.93 -6.97 (m, 3H)， 4.84-4.93 (m, 1H), 4.36 (s, 2H), 3.19 (t, J = 4.8 Hz, 4H), 2.55-2.65 (m, 6H), 2.42-2.50 (m, 2H), 2.36 (s, 3H), 2.22 (s, 6H), 1.71-1.85 (m, 2H). MS m/z: 498.3 [M+1].

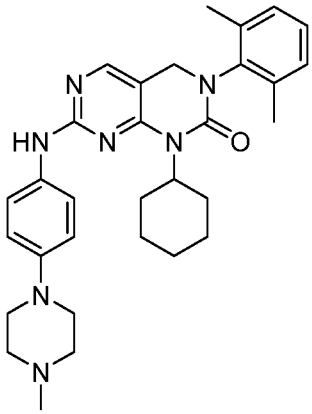
[00382] YKL-06-061



Exact Mass: 527.30
Molecular Weight: 527.67

[00383] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.36 (s, 1H), 7.09-7.15 (m, 3H), 6.56-6.60 (m, 2H), 4.90-4.98 (m, 1H), 4.36 (s, 2H), 3.90 (s, 3H), 3.20 (t, J = 5.2 Hz, 4H), 2.57- 2.67 (m, 6H), 2.46-2.53 (m, 2H), 2.38 (s, 3H), 2.23 (s, 6H), 1.74-1.88 (m, 2H). MS m/z: 528.3 [M+1].

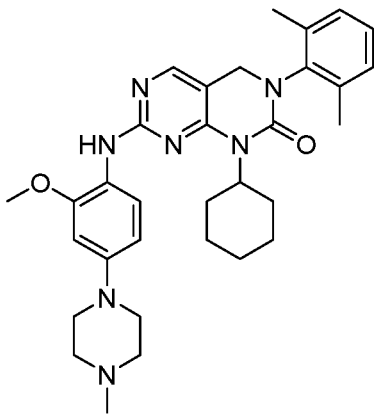
[00384] YKL-06-062



Exact Mass: 525.32
Molecular Weight: 525.70

[00385] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 1H), 7.46-7.50 (m, 2H), 7.08-7.15 (m, 3H), 7.01 (s, 1H), 6.92-6.96 (m, 2H), 4.61-4.69 (m, 1H), 4.37 (s, 2H), 3.18 (t, J = 5.2 Hz, 4H), 2.60 (t, J = 5.2 Hz, 4H), 2.43-2.53 (m, 2H), 2.36 (s, 3H), 2.22 (s, 6H), 1.76-1.85 (m, 4H), 1.65 (d, J = 12.4 Hz, 1H), 1.31-1.43 (m, 2H), 1.13-1.23 (m, 1H). MS m/z: 526.3 [M+1].

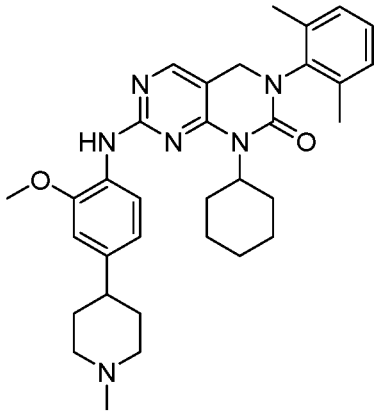
[00386] YKL-06-063



Exact Mass: 555.33
Molecular Weight: 555.73

[00387] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.24(d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.42 (s, 1H), 7.08-7.15 (m, 3H），7.54-7.57 (m, 2H), 4.65-4.73 (m, 1H), 4.37 (s, 2H), 3.90 (m, 3H), 3.19 (t, J = 5.2 Hz, 4H), 2.61 (t, J = 5.2 Hz, 4H), 2.45-2.54 (m, 2H), 2.37 (s, 3H), 2.22 (s, 6H), 1.80-1.88 (m, 4H), 1.69 (d, 1H), 1.35-1.45 (m, 2H), 1.17-1.27 (m, 1H). MS m/z: 556.3 [M+1].

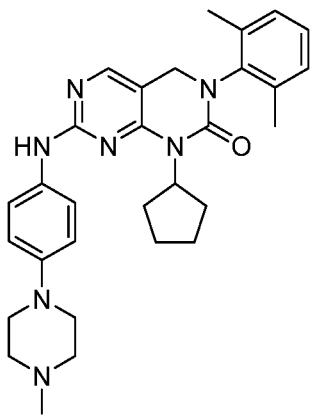
[00388] YKL-06-064



Exact Mass: 554.34
Molecular Weight: 554.74

[00389] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 1H), 8.05 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.93 (d, J = 1.9 Hz, 1H), 6.81 (dd, J = 8.2, 1.9 Hz, 1H), 4.48 (tt, J = 11.9, 3.5 Hz, 1H), 4.40 (s, 2H), 3.84 (s, 3H), 2.91 (d, J = 10.8 Hz, 2H), 2.49 – 2.41 (m, 1H), 2.32 (qd, J = 12.6, 3.7 Hz, 2H), 2.24 (s, 3H), 2.14 (s, 6H), 2.08 – 1.94 (m, 2H), 1.81 – 1.67 (m, 6H), 1.67 – 1.61 (m, 2H), 1.58 (d, J = 12.9 Hz, 1H), 1.25 (d, J = 12.8 Hz, 4H), 1.07 – 0.95 (m, 2H). MS m/z: 555.3 [M+1].

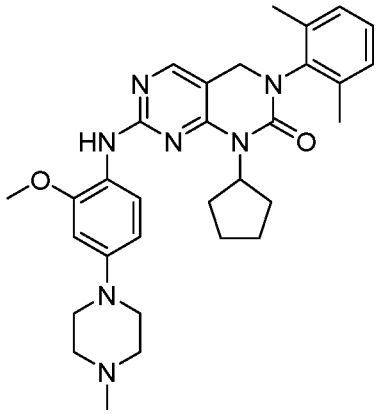
[00390] YKL-06-075



Exact Mass: 511.31
Molecular Weight: 511.67

[00391] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 1H), 7.44-7.47 (m, 2H), 7.08-7.15 (m, 3H), 6.99 (m, 3H），6.91-6.95 (m, 2H), 5.17-5.26 (m, 1H), 4.38 (s, 2H), 3.19 (t, J = 5.2 Hz, 4H), 2.60 (t, J =5.2 Hz, 4H), 2.36 (s, 3H), 2.23 (s, 6H), 2.17-2.21 (m, 2H), 1.88-1.91 (m, 4H), 1.52-1.57 (m, 2H). MS m/z: 512.3 [M+1].

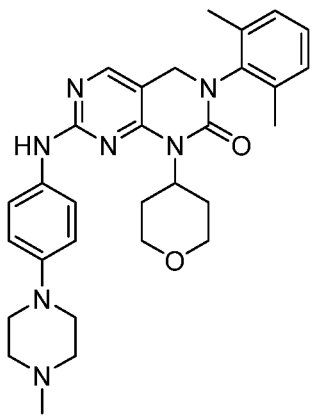
[00392] YKL-06-076



Exact Mass: 541.32
Molecular Weight: 541.70

[00393] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.8 Hz, 1H), 7.94 (s, 1H), 7.38 (s, 1H), 7.08-7.15 (m, 3H), 6.56 (t, 2H), 5.22-5.31 (m, 1H), 4.39 (s, 2H), 3.90 (s, 3H), 3.19 (t, J = 5.2 Hz, 4H), 2.60 (t, J = 5.2 Hz, 4H), 2.36 (s, 3H), 2.23 (s, 6H), 2.19-2.27 (m, 2H), 1.92-2.00 (m, 4H), 1.74-1.88 (m, 2H). MS m/z: 542.3 [M+1].

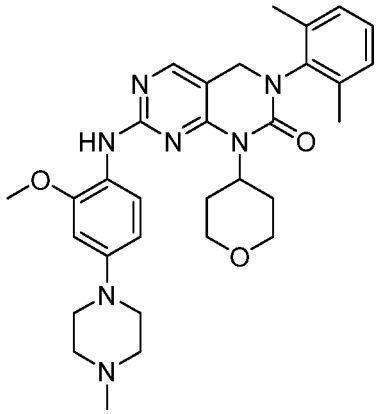
[00394] YKL-06-077



Exact Mass: 527.30
Molecular Weight: 527.67

[00395] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H)， 7.10-7.16 (m, 4H), 6.95 (d, J = 8.8 Hz, 2H), 4.87-4.95 (m, 1H), 4.39 (s, 2H), 4.07-4.11 (q, 2H), 3.50 (t, J = 11.2 Hz, 2H), 3.19 (t, J = 4.8 Hz, 4H), 2.90-3.00 (m, 2H), 2.60 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 2.22 (s, 6H), 1.67 (d, J = 10.4 Hz, 2H). MS m/z: 528.3 [M+1].

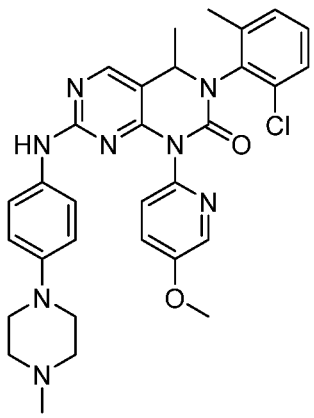
[00396] YKL-06-078



Exact Mass: 557.31
Molecular Weight: 557.70

[00397] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.23 (t, 1H), 7.96 (s, 1H), 7.44 (s, 1H), 7.09-7.16 (m, 3H), 6.58 (t, 2H), 4.90-4.98 (m, 1H), 4.39 (s, 2H),4.11 (dd, J = 4.0 Hz, J = 11.2 Hz, 2H), 3.91 (s, 3H), 3.53 (t, J = 11.2 Hz, 2H), 3.19 (t, J = 5.2 Hz, 4H), 2.90-3.01 (m, 2H),2.61 (t, J = 5.2 Hz, 4H), 2.37 (s, 3H), 2.23 (s, 6H), 1.68-1.72 (m, 2H). MS m/z: 558.3 [M+1].

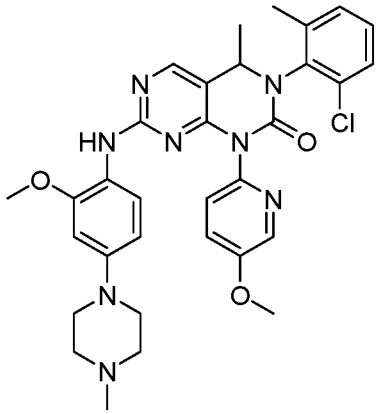
[00398] YKL-06-79



Exact Mass: 584.24
Molecular Weight: 585.11

[00399] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, J = 2.8 Hz, 1H), 8.06 (d, 1H), 7.32-7.38 (m, 3H), 7.19-7.21 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.94 (s, 1H), 6.69 (d, J = 8.8 Hz, 2H), 4.97-5.02 (q, J = 6.8 Hz, 0.73H), 4.76-4.81 (q, J = 6.8 Hz, 0.27H), 3.93 (s, 3H), 3.12 (t, J = 4.8 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.35 (t, 6H), 1.56 (d, J = 6.4 Hz, 1H), 1.50 (d, J = 6.8 Hz, 2H). MS m/z: 585.3 [M+1].

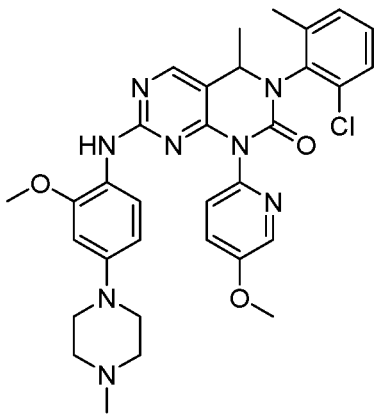
[00400] YKL-06-080



Exact Mass: 614.25
Molecular Weight: 615.13

[00401] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 2.8 Hz, 1H), 8.07 (s, 1H), 7.32-7.41 (m, 5H), 7.19-7.22 (m, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 6.4 Hz, 1H), 4.98-5.03 (q, J = 6.4 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.11 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H), 2.36 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H). MS m/z: 615.3 [M+1].

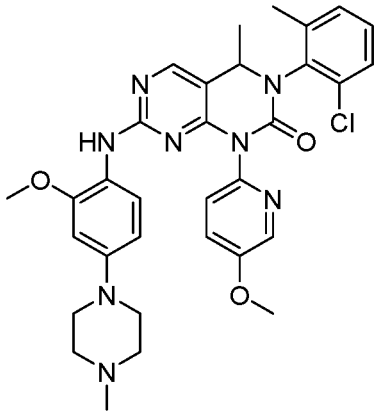
[00402] YKL-06-080-1



Exact Mass: 614.25
Molecular Weight: 615.13

[00403] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 2.4 Hz, 1H), 8.06 (s, 1H), 7.32-7.41 (m, 5H), 7.19 -7.22 (m, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 6.0 Hz, 1H), 4.80 (q, J = 6.4 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.11 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 2.34 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H). MS m/z: 615.3 [M+1].

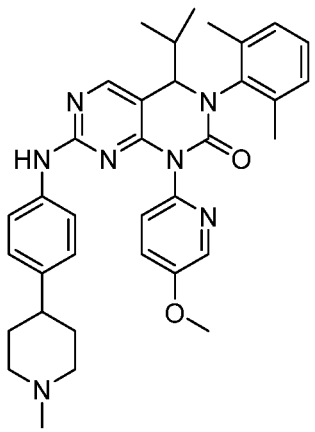
[00404] YKL-06-080-2



Exact Mass: 614.25
Molecular Weight: 615.13

[00405] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 2.4 Hz, 1H), 8.07 (s, 1H), 7.31-7.40 (m, 5H), 7.20 (t, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 6.8 Hz, 1H), 4.98-5.03 (q, J = 6.4 Hz, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.12 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H), 2.36 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H). MS m/z: 615.3 [M+1].

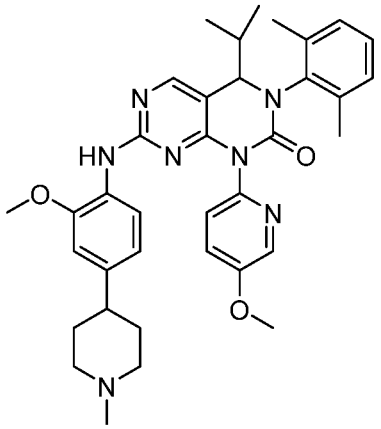
[00406] YKL-06-081



Exact Mass: 591.33
Molecular Weight: 591.76

[00407] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, J = 2.8 Hz, 1H), 7.99 (s, 1H), 7.29-7.36 (m, 2H), 7.11-7.17 (m, 5H), 6.98 (s, 1H), 6.71 (d, J = 8.4 Hz, 2H), 4.28 (d, J = 2.8 Hz, 1H), 3.92 (s, 3H), 3.11 (t, J = 4.8 Hz, 4H), 2.57 (t, J = 4.8 Hz, 4H), 2.39 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H), 2.16-2.20 (m, 1H), 1.17 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 7.2 Hz, 3H). MS m/z: 592.4 [M+1].

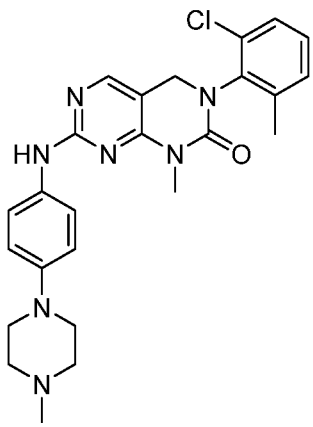
[00408] YKL-06-082



Exact Mass: 621.34
Molecular Weight: 621.79

[00409] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 2.8 Hz, 1H), 8.00 (s, 1H), 7.30-7.41 (m, 4H), 7.11-7.17 (m, 3H), 6.46 (d, J = 2.4 Hz, 1H), 6.14 (s, 1H), 4.28 (d, J = 3.2 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.11 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.40 (s, 3H), 2.36 (s, 3H), 2.24 (s, 3H), 2.14-2.22 (m, 1H), 1.17 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H). MS m/z: 622.4 [M+1].

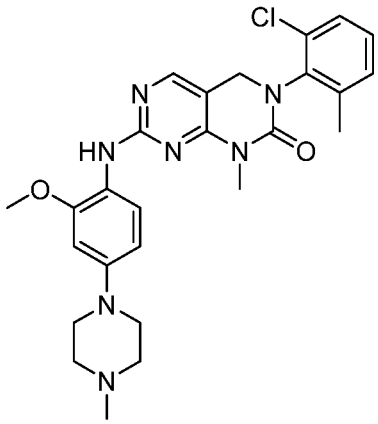
[00410] YKL-06-084



Exact Mass: 477.20
Molecular Weight: 478.00

[00411] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 4.8 Hz, 1H), 7.19 (t, 3H), 6.95 (d, J = 8.8 Hz, 2H), 4.69 (d, J = 13.6 Hz, 1H), 4.35 (d, J = 13.6 Hz, 1H), 3.44 (s, 3H), 3.19 (t, J = 4.8 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 2.29 (s, 3H). MS m/z: 478.2 [M+1].

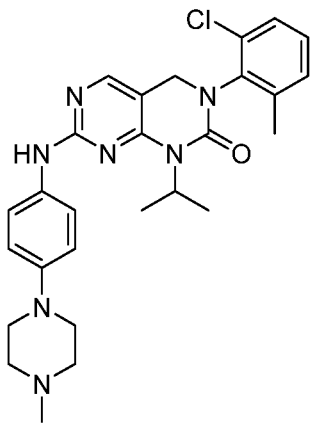
[00412] YKL-06-085



Exact Mass: 507.21
Molecular Weight: 508.02

[00413] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 7.47 (s, 1H), 7.31-7.35 (m, 1H), 7.20 (d, J = 4.8 Hz, 2H), 6.58 (t, 2H),4.70 (d, J = 14 Hz, 1H), 4.36 (d, J = 14.0 Hz, 1H), 3.90 (s, 3H), 3.47 (s, 3H), 3.19 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 2.29 (s, 3H). MS m/z: 508.2 [M+1].

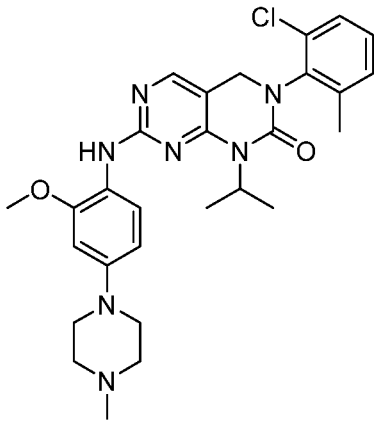
[00414] YKL-06-086



Exact Mass: 505.24
Molecular Weight: 506.05

[00415] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.30-7.33 (m, 1H), 7.18 (d, 2H), 6.95 (t, 3H), 5.04-5.150 (m, 1H), 4.62 (d, J = 13.6 Hz, 1H), 4.27 (d, J = 13.6 Hz, 1H), 3.19(t, J = 4.8 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 2.27 (s, 3H),1.53-1.56 (m, 6H). MS m/z: 506.2 [M+1].

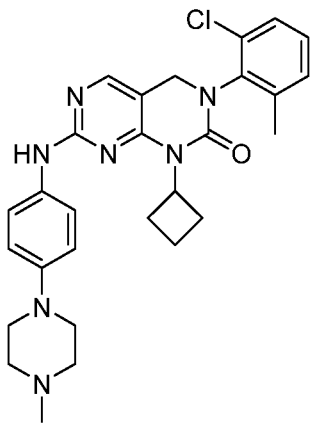
[00416] YKL-06-087



Exact Mass: 535.25
Molecular Weight: 536.08

[00417] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.21 (t, 1H), 7.95 (s, 1H), 7.39 (s, 1H),7.30-7.33 (q, 1H), 7.18 (t, 2H), 6.57 (t, 2H), 5.09-5.19 (m, 1H), 4.62 (d, J = 13.6 Hz, 1H), 4.27 (d, J = 13.6 Hz, 1H), 3.90 (m, 3H), 3.19 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 2.37 (s, 3H), 2.27 (s, 3H),1.56-1.59 (m, 6H). MS m/z: 536.3 [M+1].

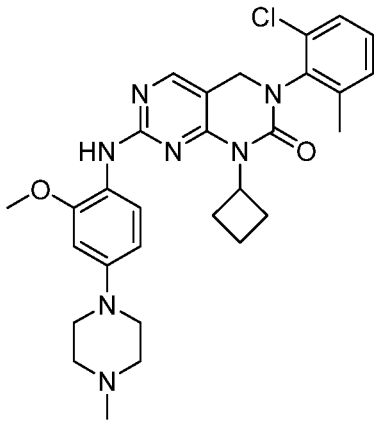
[00418] YKL-06-088



Exact Mass: 517.24
Molecular Weight: 518.06

[00419] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H), 7.46 (d, J = 9.2 Hz, 2H), 7.30-7.34 (m, 1H), 7.18 (q, 2H), 6.96 (t, 3H), 4.86-4.95 (m, 1H), 4.61 (d, J = 13.6 Hz, 1H), 4.25 (d, J = 14 Hz, 1H), 3.19 (t, J = 4.8 Hz, 4H), 2.55-2.68 (m, 6H), 2.42-2.48 (m, 2H), 2.36 (s, 3H), 2.26 (s, 3H),1.68-1.85 (m, 2H). MS m/z: 518.3 [M+1].

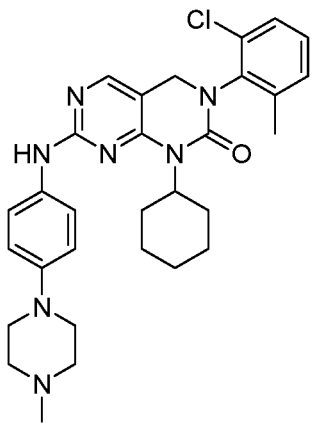
[00420] YKL-06-089



Exact Mass: 547.25
Molecular Weight: 548.09

[00421] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, J = 8.8 Hz, 1H), 7.97 (s, 1H), 7.36 (s, 1H), 7.30-7.34 (m, 1H), 7.17 (q, 2H), 6.59 (t, 2H), 4.91-5.00 (m, 1H), 4.62 (d, J = 13.6 Hz, 1H), 4.25 (d, J = 14.0 Hz, 1H), 3.90 (s, 3H), 3.20 (t, J = 4.8 Hz, 4H), 2.60-2.71 (m, 6H), 2.46-2.53 (m, 2H), 2.37 (s, 3H), 2.26 (s, 3H), 1.72-1.86 (m, 2H). MS m/z: 548.3 [M+1].

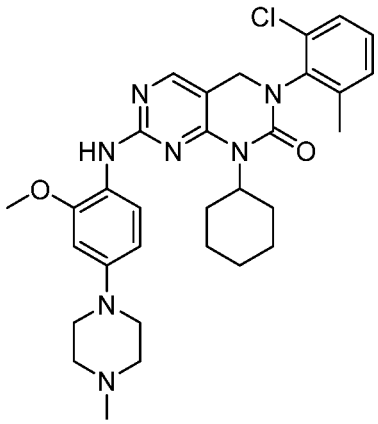
[00422] YKL-06-090



Exact Mass: 545.27
Molecular Weight: 546.12

[00423] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 1H), 7.48 (d, J = 9.2 Hz, 2H), 7.30-7.33 (m, 1H), 7.18 (d, 2H), 7.04 (s, 1H), 6.94 (d, J = 9.2 Hz, 2H), 4.60-4.71 (m, 2H), 4.27 (d, J = 14 Hz, 1H), 3.19 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 2.40-2.53 (m, 2H), 2.36 (s, 3H), 2.27 (s, 3H),1.77-1.85 (m, 4H), 1.65 (d, 1H), 1.30-1.42 (m, 2H), 1.13-1.23 (m, 1H). MS m/z: 546.3 [M+1].

[00424] YKL-06-091



Exact Mass: 575.28
Molecular Weight: 576.14

[00425] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.42 (s, 1H), 7.30-7.33 (m, 1H), 7.17 (d, 2H), 6.56 (d, 2H), 4.68-4.75 (m, 1H), 4.62 (d, *J* = 13.6 Hz, 1H), 4.27 (d, *J* = 13.6 Hz, 1H), 3.90 (s, 3H), 3.19 (t, *J* = 4.8 Hz, 4H), 2.61 (t, *J* = 4.8 Hz, 4H), 2.42-2.56 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H),1.80-1.88 (m, 4H), 1.68 (d, 1H), 1.34-1.46 (m, 2H), 1.18-1.27 (m, 1H). MS m/z: 576.3 [M+1].

Table 2. Percent activity of selected compounds against SIK1, SIK2, and SIK3 (all compounds assayed at 1μM; all assays conducted at approximate K_m for ATP)

	SIK1		SIK2	
COMPOUND	% ACTIVITY	S.D.	% ACTIVITY	S.D.
HG-11-143-01	**7.9**	7.9	**4.3**	4.3
HG-11-23-01	**12.5**	10.5	**7.0**	1.5
HG-11-139-02	**36.0**	5.5	**32.8**	3.0
HG-11-139-01	**15.3**	13.0	**2.1**	0.6
HG-11-137-01	**12.9**	10.1	**1.4**	0.7
HG-11-136-01	**19.1**	18.2	**2.8**	1.4
GNF-7	**12.0**	9.7	**27.4**	0.7

	SIK3	
COMPOUND	% ACTIVITY	S.D.
HG-11-143-01	**9.3**	0.2
HG-11-139-01	**7.5**	1.1
HG-11-137-01	**8.6**	1.8
HG-11-136-01	**9**	0.5

Table 3. Selectivity of selected compounds against different classes of kinases

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
Compound Concentration (uM)	1 uM
AAK1	13
ABL1(E255K)-phosphorylated	0.4
ABL1(F317I)-nonphosphorylated	0
ABL1(F317I)-phosphorylated	1.3
ABL1(F317L)-nonphosphorylated	0
ABL1(F317L)-phosphorylated	1.8
ABL1(H396P)-nonphosphorylated	0
ABL1(H396P)-phosphorylated	0
ABL1(M351T)-phosphorylated	0.55
ABL1(Q252H)-nonphosphorylated	0
ABL1(Q252H)-phosphorylated	0.25
ABL1(T315I)-nonphosphorylated	0
ABL1(T315I)-phosphorylated	1.2
ABL1(Y253F)-phosphorylated	0.15
ABL1-nonphosphorylated	0
ABL1-phosphorylated	0
ABL2	0.35
ACVR1	2.8
ACVR1B	9.6
ACVR2A	5
ACVR2B	3.2
ACVRL1	16
ADCK3	38
ADCK4	44
AKT1	100
AKT2	100
AKT3	100
ALK	1.6
ALK(C1156Y)	12
ALK(L1196M)	8.2
AMPK-alpha1	33
AMPK-alpha2	30
ANKK1	68
ARK5	8.2
ASK1	100
ASK2	46
AURKA	0
AURKB	26

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
AURKC	33
AXL	25
BIKE	8.8
BLK	0.1
BMPR1A	4.6
BMPR1B	0
BMPR2	77
BMX	3
BRAF	26
BRAF(V600E)	13
BRK	0.45
BRSK1	100
BRSK2	91
BTK	0.05
BUB1	100
CAMK1	82
CAMK1D	68
CAMK1G	95
CAMK2A	93
CAMK2B	90
CAMK2D	100
CAMK2G	100
CAMK4	100
CAMKK1	94
CAMKK2	100
CASK	54
CDC2L1	79
CDC2L2	83
CDC2L5	65
CDK11	89
CDK2	97
CDK3	100
CDK4-cyclinD1	9
CDK4-cyclinD3	26
CDK5	100
CDK7	60
CDK8	100
CDK9	91
CDKL1	84
CDKL2	14

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
CDKL3	58
CDKL5	98
CHEK1	82
CHEK2	46
CIT	58
CLK1	19
CLK2	35
CLK3	78
CLK4	33
CSF1R	0.35
CSF1R-autoinhibited	1
CSK	0.3
CSNK1A1	100
CSNK1A1L	97
CSNK1D	100
CSNK1E	59
CSNK1G1	92
CSNK1G2	100
CSNK1G3	84
CSNK2A1	1.9
CSNK2A2	0.05
CTK	33
DAPK1	63
DAPK2	88
DAPK3	63
DCAMKL1	51
DCAMKL2	88
DCAMKL3	77
DDR1	0.3
DDR2	1.6
DLK	6.6
DMPK	88
DMPK2	1.6
DRAK1	96
DRAK2	100
DYRK1A	30
DYRK1B	60
DYRK2	5
EGFR	0.7
EGFR(E746-A750del)	1.8

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
EGFR(G719C)	0.1
EGFR(G719S)	0.2
EGFR(L747-E749del, A750P)	0.35
EGFR(L747-S752del, P753S)	0.95
EGFR(L747-T751del,Sins)	0.3
EGFR(L858R)	0.1
EGFR(L858R,T790M)	1.7
EGFR(L861Q)	0
EGFR(S752-I759del)	4.2
EGFR(T790M)	0.7
EIF2AK1	93
EPHA1	0
EPHA2	0.6
EPHA3	0.8
EPHA4	0
EPHA5	0.6
EPHA6	0.2
EPHA7	72
EPHA8	0.9
EPHB1	0.3
EPHB2	0
EPHB3	0
EPHB4	0
EPHB6	0.7
ERBB2	0
ERBB3	0
ERBB4	0.2
ERK1	100
ERK2	96
ERK3	81
ERK4	95
ERK5	84
ERK8	88
ERN1	13
FAK	24
FER	0.1
FES	0
FGFR1	0.15
FGFR2	0.8
FGFR3	0.95

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
FGFR3(G697C)	1.4
FGFR4	2
FGR	0
FLT1	5.2
FLT3	34
FLT3(D835H)	16
FLT3(D835Y)	14
FLT3(ITD)	57
FLT3(K663Q)	31
FLT3(N841I)	11
FLT3(R834Q)	48
FLT3-autoinhibited	66
FLT4	6.6
FRK	0.05
FYN	0.35
GAK	6.8
GCN2(Kin.Dom.2,S808G)	0.75
GRK1	77
GRK4	26
GRK7	96
αK3A	100
GSK3B	100
HASPIN	92
HCK	0.05
HIPK1	3.8
HIPK2	0.95
HIPK3	2.6
HIPK4	51
HPK1	0.95
HUNK	28
ICK	61
IGF1R	100
IKK-alpha	99
IKK-beta	80
IKK-epsilon	47
INSR	48
INSRR	100
IRAK1	4.4
IRAK3	38
IRAK4	49

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
ITK	66
JAK1(JH1domain-catalytic)	57
JAK1(JH2domain-pseudokinase)	8.1
JAK2(JH1domain-catalytic)	0.75
JAK3(JH1domain-catalytic)	0
JNK1	23
JNK2	20
JNK3	32
KIT	0
KIT(A829P)	3.6
KIT(D816H)	6
KIT(D816V)	0.2
KIT(L576P)	0
KIT(V559D)	0
KIT(V559D,T670I)	55
KIT(V559D,V654A)	2.2
KIT-autoinhibited	0.35
LATS1	100
LATS2	60
LCK	0.05
LIMK1	0.05
LIMK2	0
LKB1	69
LOK	0
LRRK2	21
LRRK2(G2019S)	6.6
LTK	18
LYN	0
LZK	4
MAK	100
MAP3K1	73
MAP3K15	40
MAP3K2	0.05
MAP3K3	0.1
MAP3K4	16
MAP4K2	0.3
MAP4K3	1.8
MAP4K4	17
MAP4K5	0.3
MAPKAPK2	100

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
MAPKAPK5	96
MARK1	5.1
MARK2	3.7
MARK3	1.6
MARK4	32
MAST1	62
MEK1	0.55
MEK2	0.2
MEK3	6.4
MEK4	48
MEK5	0.1
MEK6	30
MELK	36
MERTK	5.6
MET	66
MET(M1250T)	46
MET(Y1235D)	61
MINK	2.8
MKK7	80
MKNK1	85
MKNK2	99
MLCK	100
MLK1	6
MLK2	11
MLK3	28
MRCKA	99
MRCKB	38
MST1	2.1
MST1R	100
MST2	0.75
MST3	4.6
MST4	2.8
MTOR	83
MUSK	86
MYLK	86
MYLK2	81
MYLK4	60
MYO3A	40
MYO3B	29
NDR1	46

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
NDR2	28
NEK1	88
NEK10	9.6
NEK11	21
NEK2	75
NEK3	39
NEK4	100
NEK5	98
NEK6	100
NEK7	100
NEK9	81
NIK	36
NIM1	42
NLK	7.6
OSR1	49
p38-alpha	1
p38-beta	3.1
p38-delta	100
p38-gamma	91
PAK1	3.7
PAK2	61
PAK3	11
PAK4	34
PAK6	37
PAK7	1.3
PCTK1	73
PCTK2	91
PCTK3	100
PDGFRA	0.5
PDGFRB	0
PDPK1	100
PFCDPK1(P.falciparum)	0.1
PFPK5(P.falciparum)	96
PFTAIRE2	78
PFTK1	100
PHKG1	100
PHKG2	93
PIK3C2B	0.55
PIK3C2G	87
PIK3CA	100

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
PIK3CA(C420R)	69
PIK3CA(E542K)	88
PIK3CA(E545A)	69
PIK3CA(E545K)	98
PIK3CA(H1047L)	96
PIK3CA(H1047Y)	63
PIK3CA(I800L)	94
PIK3CA(M1043I)	64
PIK3CA(Q546K)	94
PIK3CB	92
PIK3CD	72
PIK3CG	77
PIK4CB	63
PIM1	100
PIM2	100
PIM3	90
PIP5K1A	14
PIP5K1C	70
PIP5K2B	27
PIP5K2C	100
PKAC-alpha	85
PKAC-beta	66
PKMYT1	42
PKN1	95
PKN2	94
PKNB(M.tuberculosis)	6.6
PLK1	60
PLK2	21
PLK3	31
PLK4	18
PRKCD	94
PRKCE	61
PRKCH	100
PRKCI	63
PRKCQ	80
PRKD1	3.6
PRKD2	3.6
PRKD3	5.4
PRKG1	100
PRKG2	92

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
PRKR	73
PRKX	100
PRP4	100
PYK2	15
QSK	0.25
RAF1	93
RET	0
RET(M918T)	0.05
RET(V804L)	24
RET(V804M)	7.6
RIOK1	9.2
RIOK2	87
RIOK3	25
RIPK1	35
RIPK2	0.1
RIPK4	55
RIPK5	2.8
ROCK1	81
ROCK2	89
ROS1	63
RPS6KA4(Kin.Dom.1-N-terminal)	79
RPS6KA4(Kin.Dom.2-C-terminal)	90
RPS6KA5(Kin.Dom.1-N-terminal)	100
RPS6KA5(Kin.Dom.2-C-terminal)	80
RSK1(Kin.Dom.1-N-terminal)	48
RSK1(Kin.Dom.2-C-terminal)	9.7
RSK2(Kin.Dom.1-N-terminal)	12
RSK2(Kin.Dom.2-C-terminal)	51
RSK3(Kin.Dom.1-N-terminal)	40
RSK3(Kin.Dom.2-C-terminal)	67
RSK4(Kin.Dom.1-N-terminal)	39
RSK4(Kin.Dom.2-C-terminal)	4
S6K1	72
SBK1	6.6
SGK	63
SgK110	8.6
SGK2	76
SGK3	77
SIK	0.9
SIK2	6.1

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
SLK	0.1
SNARK	0.4
SNRK	91
SRC	0.15
SRMS	0
SRPK1	16
SRPK2	93
SRPK3	70
STK16	5.6
STK33	24
STK35	49
STK36	0
STK39	28
SYK	1.2
TAK1	11
TAOK1	1
TAOK2	0
TAOK3	1.8
TBK1	37
TEC	2.6
TESK1	0
TGFBR1	33
TGFBR2	38
TIE1	30
TIE2	0.75
TLK1	76
TLK2	92
TNIK	2.8
TNK1	0.9
TNK2	0.15
TNNI3K	3.6
TRKA	41
TRKB	63
TRKC	71
TRPM6	69
TSSK1B	50
TTK	47
TXK	0.25
TYK2(JH1domain-catalytic)	5.6
TYK2(JH2domain-pseudokinase)	1.2

KINOMEscan Gene Symbol	HG-11-136-01 GRAY779
TYRO3	1.6
ULK1	3.2
ULK2	2.2
ULK3	2
VEGFR2	1.8
VRK2	86
WEE1	69
WEE2	82
WNK1	89
WNK3	50
YANK1	0.2
YANK2	1.8
YANK3	32
YES	0.05
YSK1	19
YSK4	0.4
ZAK	1.2
ZAP70	25

Table 4. Selected Compounds and Biological Assay Data

Com-pound							Enzyme (μM)			Enzyme at 1μM (%) activity		
	Data Mode	qAC 50 Mode	qAC50 (M)	Viability loss data mode	Viability loss AC 50 mode	Viability loss AC40 (M)	SIK 1	SIK 2	SIK 3	SIK1	SIK2	SIK3
HG-11-23-01	decreasing (super-active)	<	5.00E-08	decreasing	=	1.06E-07				12.5	7	
HG-11-136-01	decreasing	=	1.71E-07	decreasing	=	9.70E-08				19.1	2.8	9
HG-11-137-01	increasing	=	4.66E-07	decreasing	=	6.96E-06				12.9	1.4	8.6
HG-11-139-01	increasing (super-active)	<	5.00E-08	decreasing	=	8.91E-06				15.3	2.1	7.5
HG-11-139-02	increasing (weakly active)	>	2.60E-05	inactive	>	1.00E-05						
HG-11-143-01	decreasing	=	4.69E-07	undefined	-	-				7.9	4.3	9.3

Table 5. IC_{50} values of exemplary compounds described herein in the SIK2 inhibition assay

Compound	**SIK2 IC_{50} (nM)**
YKL-05-95	6 ± 3
YKL-05-96	34 ± 14
YKL-05-99	40 ± 25

REFERENCES

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2. Patel, K., Foretz, M., Marion, A., Campbell, D. G., Gourlay, R., Boudaba, N., Tournier, E., Titchenell, P., Peggie, M., Deak, M., Wan, M., Kaestner, K. H., Goransson, O., Viollet, B., Gray, N. S., Birnbaum, M. J., Sutherland, C., and Sakamoto, K. (2014) The LKB1-salt-inducible kinase pathway functions as a key gluconeogenic suppressor in the liver, *Nat. Commun.*, 5.

3. Park, J., Yoon, Y. S., Han, H. S., Kim, Y. H., Ogawa, Y., Park, K. G., Lee, C. H., Kim, S. T., and Koo, S. H. (2014) SIK2 Is Critical in the Regulation of Lipid Homeostasis and Adipogenesis In Vivo. *Diabetes*, 63, 3659−3673.

4. Henriksson, E., Sall, J., Gormand, A., Wasserstrom, S., Morrice, N. A., Fritzen, A. M., Foretz, M., Campbell, D. G., Sakamoto, K., Ekelund, M., Degerman, E., Stenkula, K. G., and Goransson, O. (2015) SIK2 regulates CRTCs, HDAC4 and glucose uptake in adipocytes. *J. Cell Sci.*, 128, 472−486.

EQUIVALENTS AND SCOPE

[00426] 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.

[00427] 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.

[00428] 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.

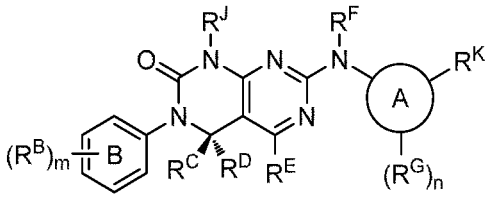
[00429] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be

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 compound of Formula (**II**):



(**II**),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug 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, $–C(=NR^b)R^a$, $–C(=NR^b)OR^a$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^a$, $–NR^bC(=O)OR^a$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^a$, $–OC(=O)OR^a$, 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;

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, $–C(=NR^b)R^a$, $–C(=NR^b)OR^a$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^a$, $–NR^bC(=O)OR^a$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^b)_2$;

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

R^K is substituted or unsubstituted heterocyclyl or $–N(R^c)_2$, wherein each instance of R^c is independently substituted or unsubstituted C_{1-6} alkyl or a nitrogen protecting group, or 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.

2. The compound of claim 1, wherein R^J is substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

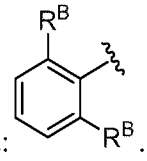
3. The compound of claim 1 or 2, wherein R^K is substituted or unsubstituted heterocyclyl, or R^K is $–N(R^c)_2$, preferably wherein each instance of R^c is substituted or unsubstituted C_{1-6} alkyl.

4. The compound of claim 3, wherein R^K is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

5. The compound of any one of claims 1-4, wherein at least one instance of R^G is $–OR^a$, wherein R^a is substituted or unsubstituted C_{1-6} alkyl, and/or

a) m is 2, or

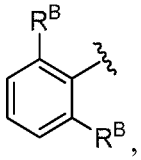
b) m is 0.

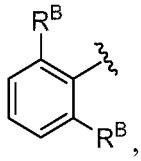
6. The compound of claim 5 part a), wherein at least one instance of R^G is –OMe, and/or Ring B is of the formula:  .

7. The compound of any one of claims 1-6, wherein at least one instance of R^B is halogen or substituted or unsubstituted C_{1-6} alkyl.

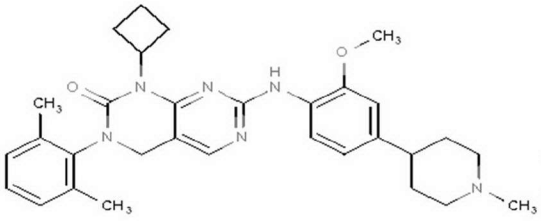
8. The compound of any one of claims 1-7, wherein R^C is hydrogen, and/or
R^D is hydrogen, and/or
R^E is hydrogen, and/or
R^f is hydrogen.

9. The compound of any one of claims 1-4 and 7-8, wherein n is 0.

10. The compound of claim 1, wherein 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, or

wherein 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.

11. The compound of claim 1, wherein the compound is of the formula:



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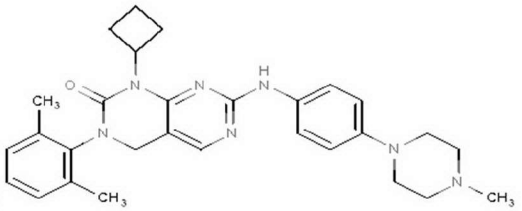

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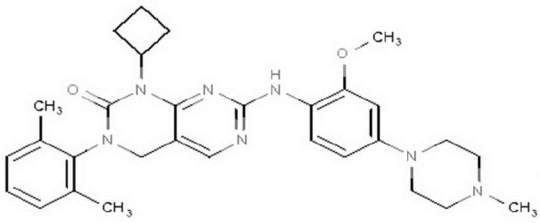

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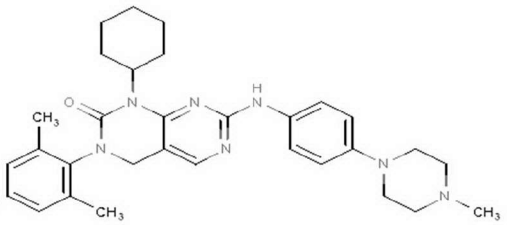

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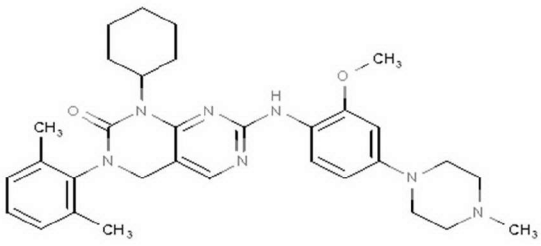
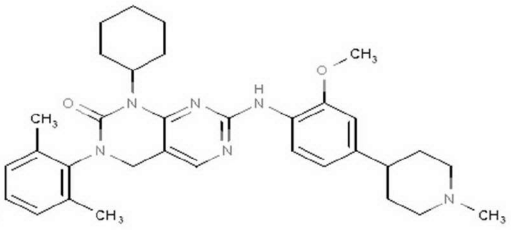
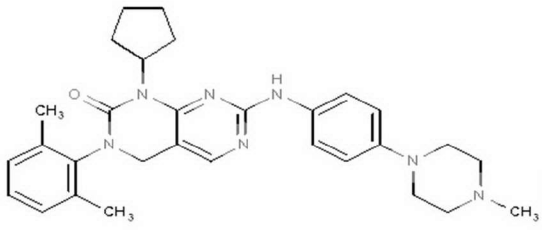


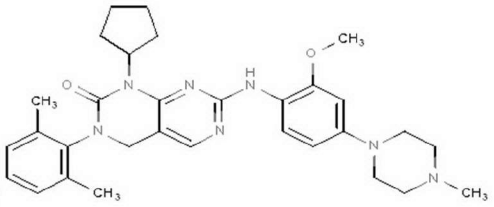
(YKL-06-063)



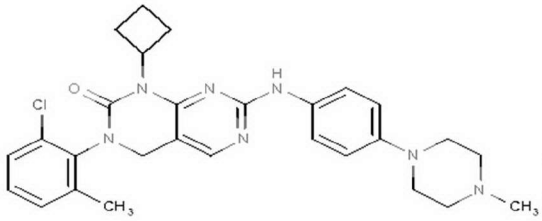
(YKL-06-064)



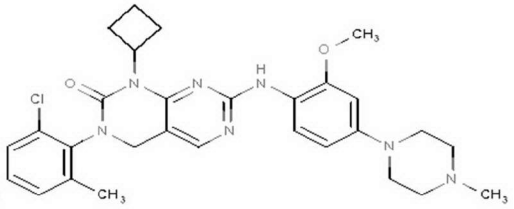
(YKL-06-075)



(YKL-06-076)



(YKL-06-088)



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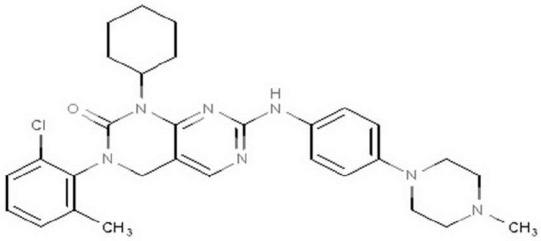

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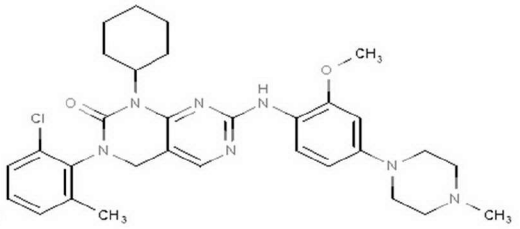
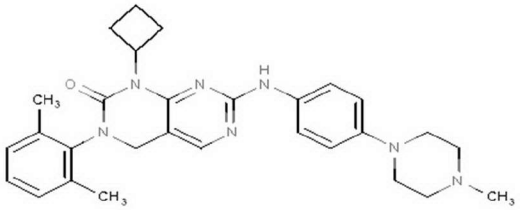


(YKL-06-091)

,

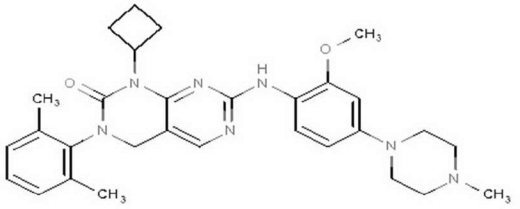
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

12. The compound of claim 11, wherein the compound is of the formula:



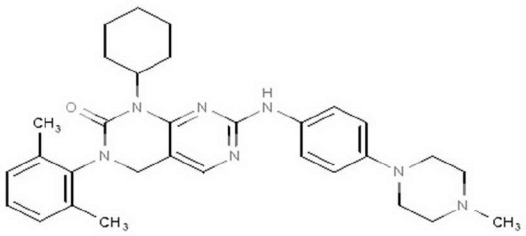
(YKL-06-060), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or

wherein the compound is of the formula:



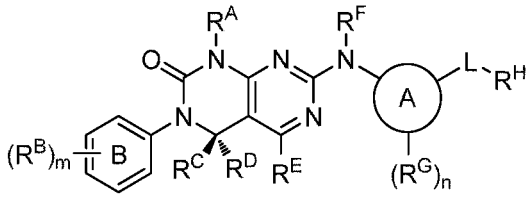
(YKL-06-061), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or

wherein the compound is of the formula:



(YKL-06-062), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

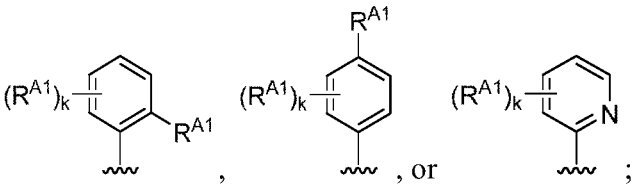
13. A compound of Formula (**I**):



(I),

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

wherein:

R^A is  ;

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, $–C(=NR^b)R^a$, $–C(=NR^b)OR^a$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^a$, $–NR^bC(=O)OR^a$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^b)_2$;

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;

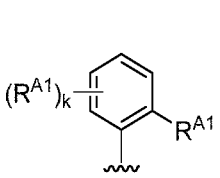
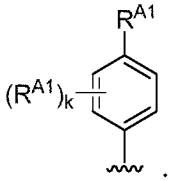
Ring A is phenyl, pyrazole, or pyridinyl;

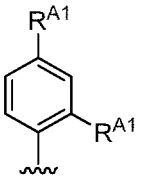
each instance of R^G is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted 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 $–OC(=O)N(R^b)_2$;

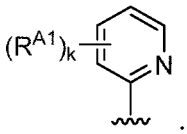
n is 0, 1, 2, 3, or 4, as valency permits;

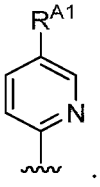
L is $–CH_2$; and

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.

14. The compound of claim 13, wherein R^A is  or  .

15. The compound of claim 13, wherein R^A is  .

16. The compound of claim 13, wherein R^A is  .

17. The compound of claim 13, wherein R^A is  .

18. The compound of any one of claims 13-17, wherein R^B is halogen or methyl, and/or

a) Ring A is phenyl, or

b) Ring A is pyrazole or pyridinyl,

and/or

i) R^H is methyl or ethyl, or

ii) R^H is substituted or unsubstituted heterocyclyl, preferably wherein R^H is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, or

iii) R^H is substituted or unsubstituted C_{1-6} alkyl, or

iv) R^H is –OH, or

v) R^H is $-N(R^c)_2$, preferably wherein each instance of R^c is substituted or unsubstituted C_{1-6} alkyl, even more preferably wherein each instance of R^c is methyl.

19. The compound of any one of claims 13-18, wherein R^C is hydrogen, and/or

R^D is hydrogen, and/or

R^E is hydrogen, and/or

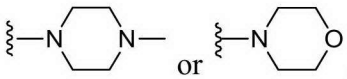
R^F is hydrogen.

20. The compound of any one of claims 13-19, wherein at least one instance of R^G is substituted or unsubstituted C_{1-3} alkyl, preferably wherein at least one instance of R^G is methyl, ethyl, or $–CF_3$, and/or

wherein at least one instance of R^G is halogen, preferably wherein at least one instance of R^G is Br, Cl, or F, and/or

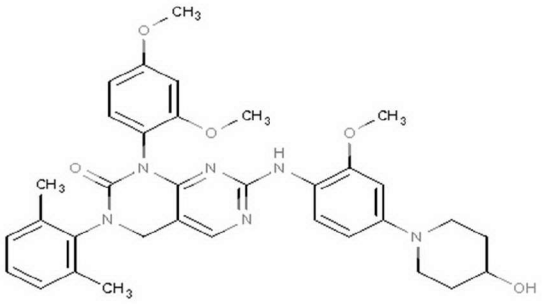
wherein at least one instance of R^G is $–OR^a$, wherein R^a is substituted or unsubstituted C_{1-6} alkyl, preferably wherein at least one instance of R^G is –OMe, –OEt, or –O(iPr), and/or

wherein at least one instance of R^G is substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, preferably wherein at least one instance of R^G is of the formula:

 or , and/or

n is 0, 1, or 2.

21. A compound which is of the formula:



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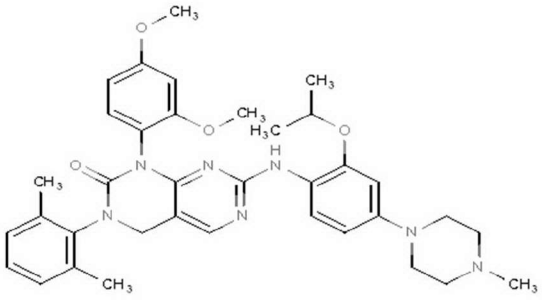
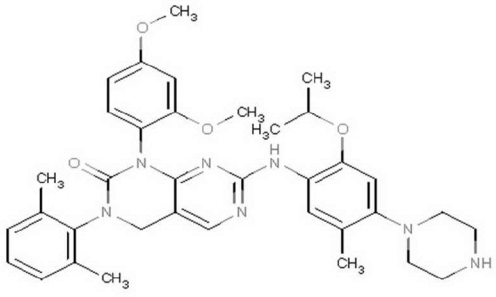
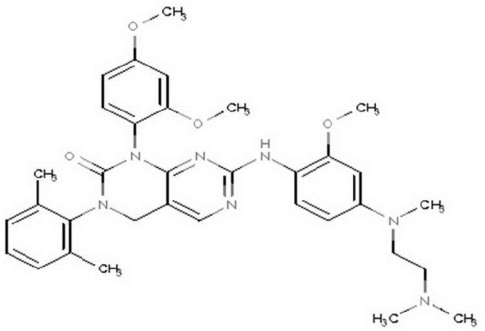


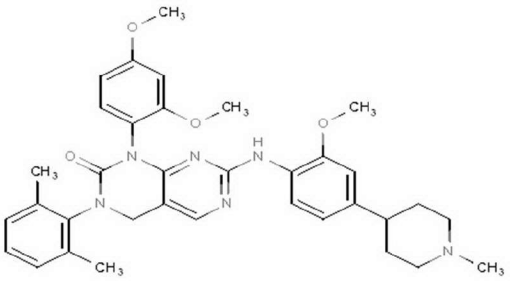
(YKL-05-58)



(YKL-05-59)



(YKL-05-60)



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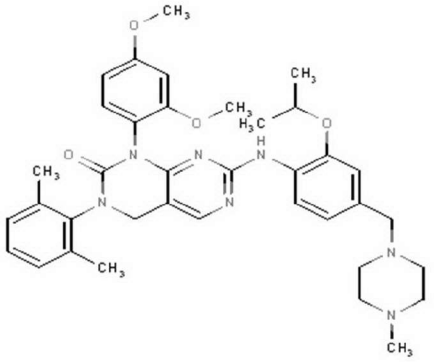
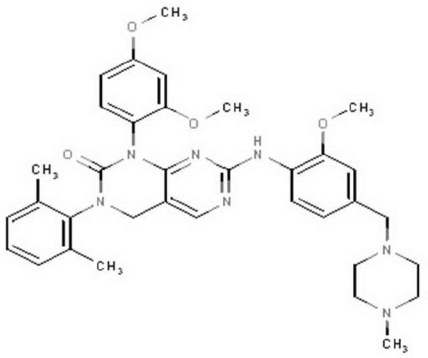
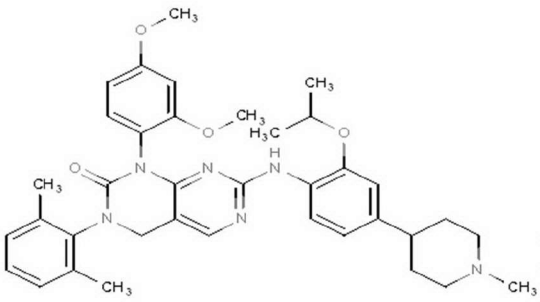


(YKL-05-69)



(YKL-05-70)



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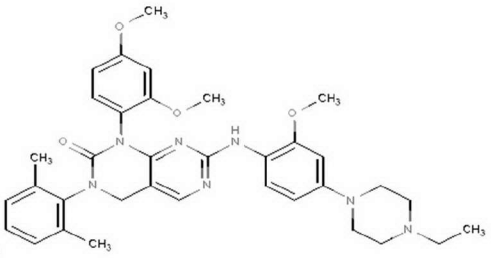

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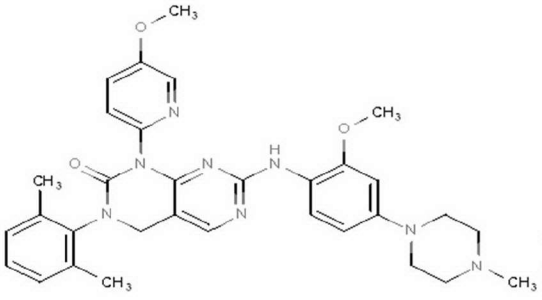

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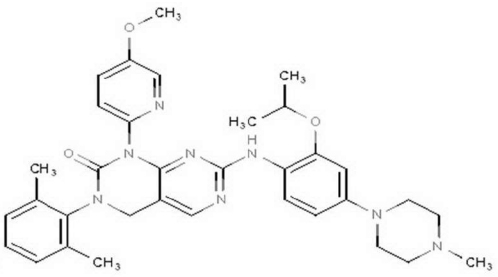

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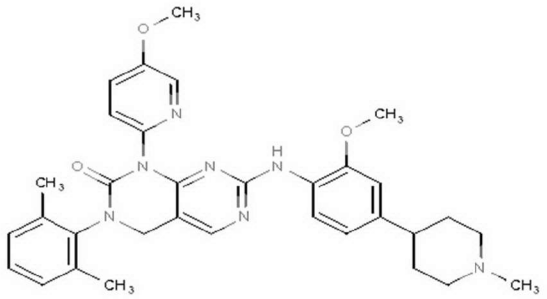

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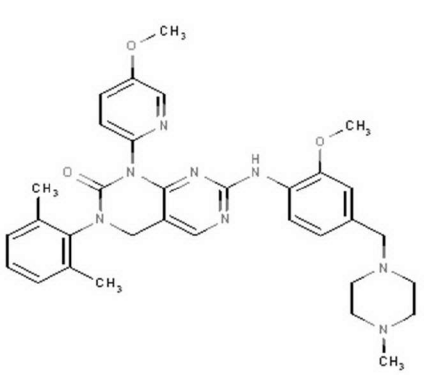

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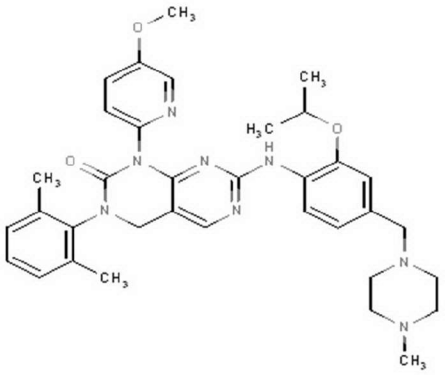

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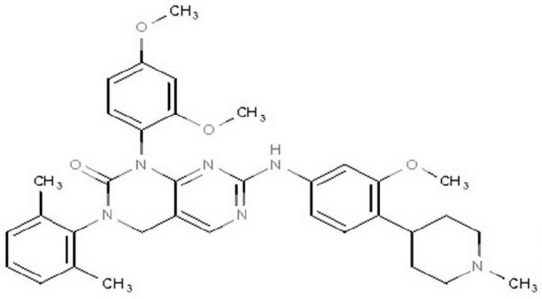

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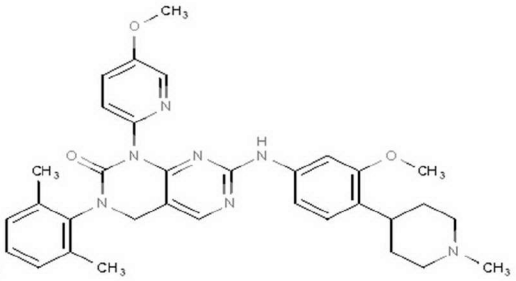

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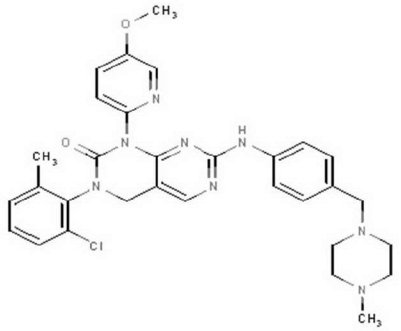

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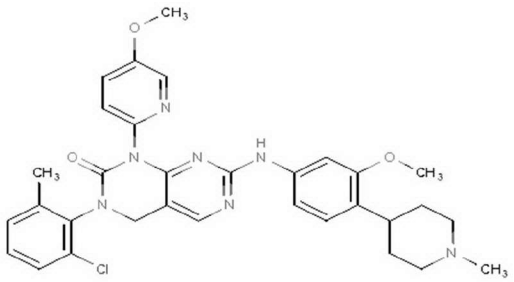

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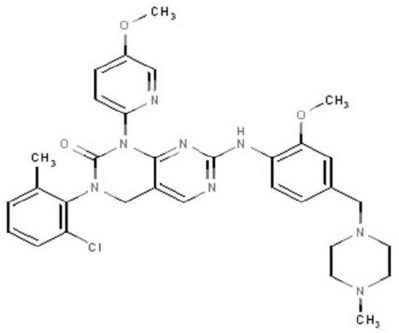

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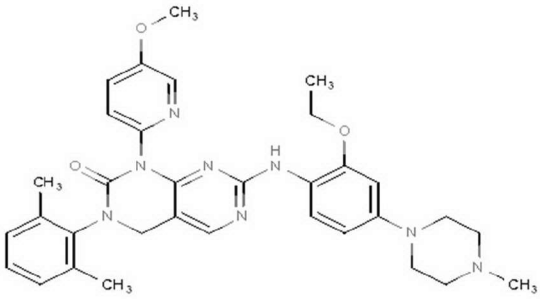

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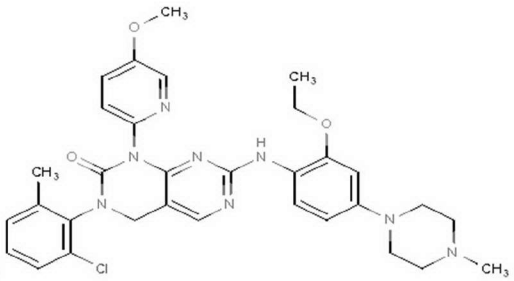

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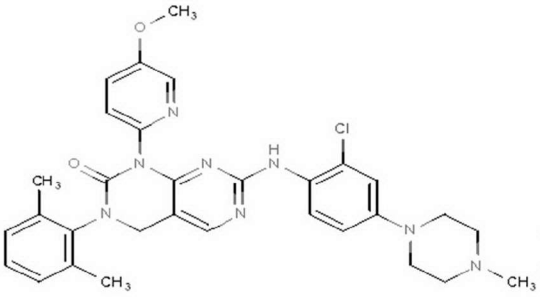
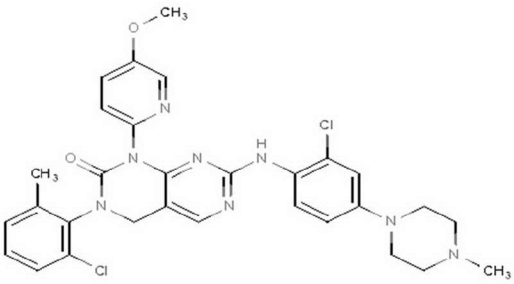


(YKL-05-153)



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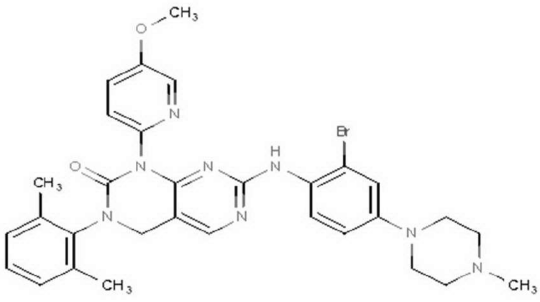

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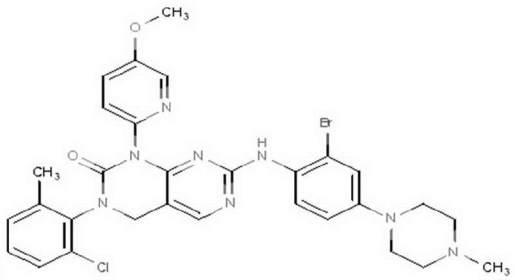

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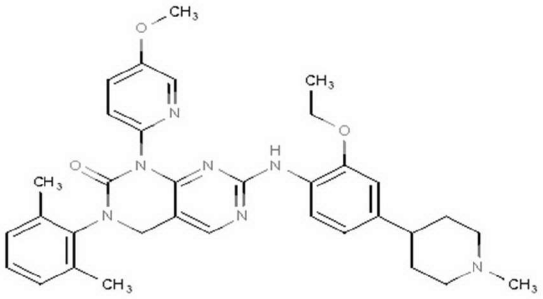

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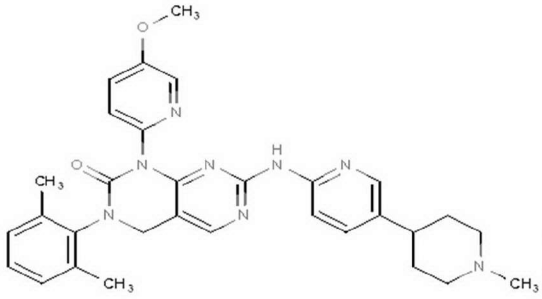

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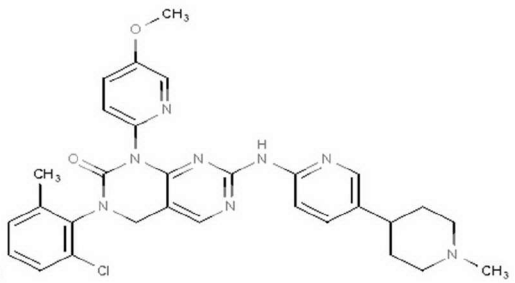

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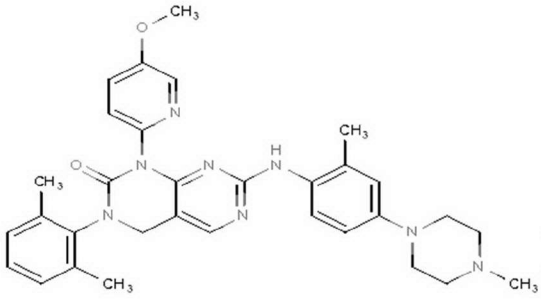

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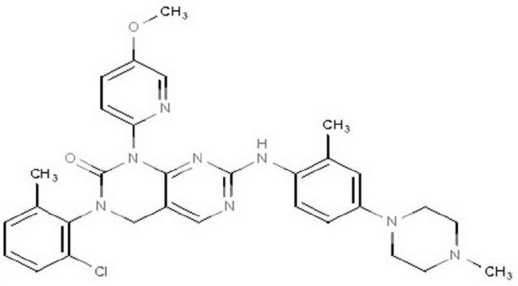

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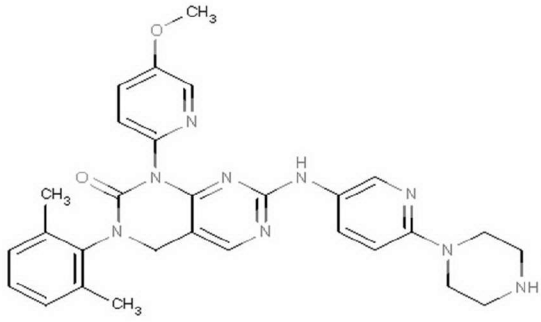

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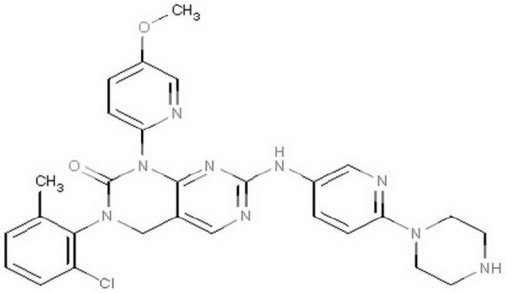

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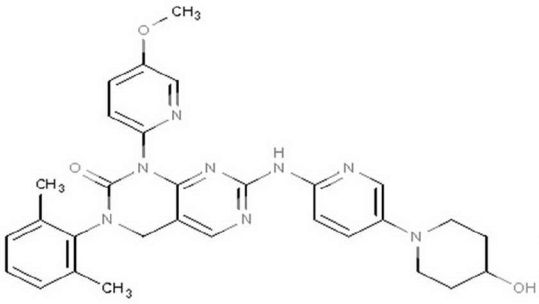

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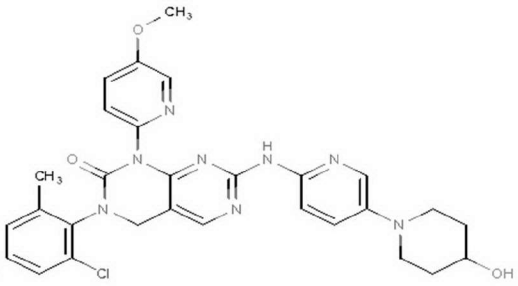

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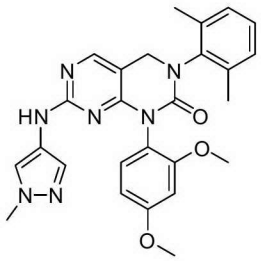
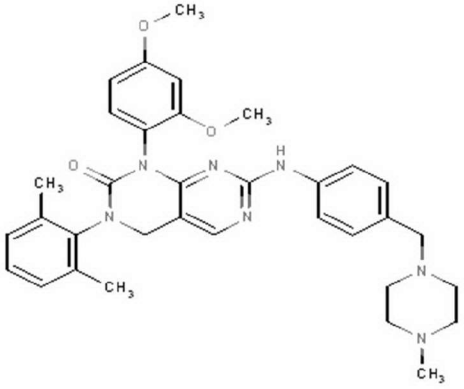
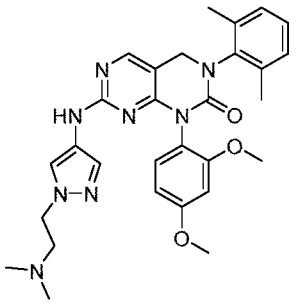


(Example 2)



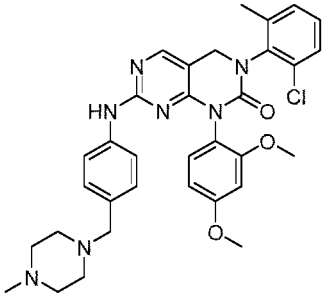
(YKL-04-136-1)

(SB1-D-01)



(SB1-D-02)

(YKL-04-136-2)



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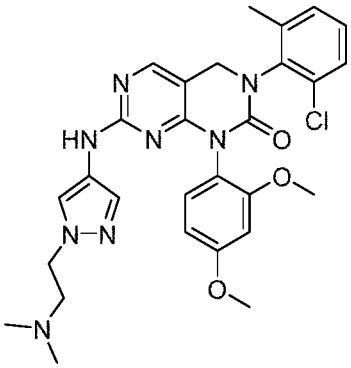
(YKL-04-136-9)



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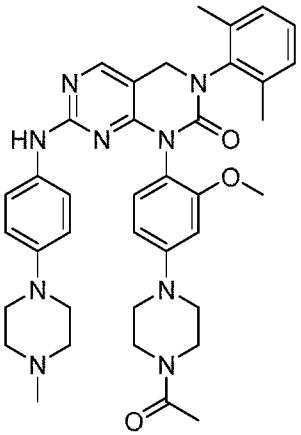

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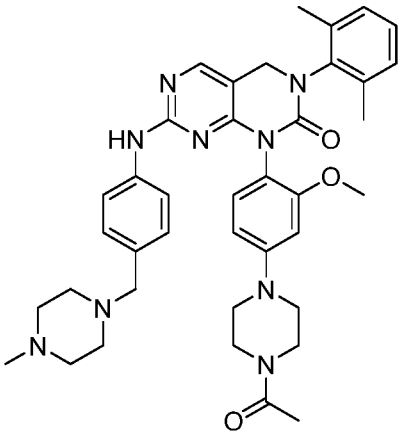

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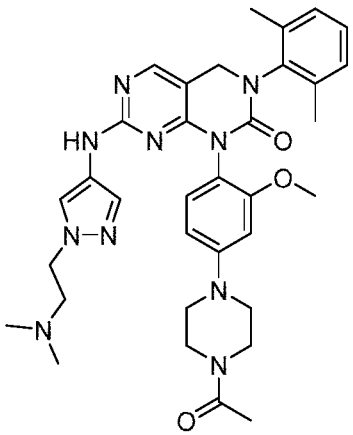
(YKL-04-136-11)



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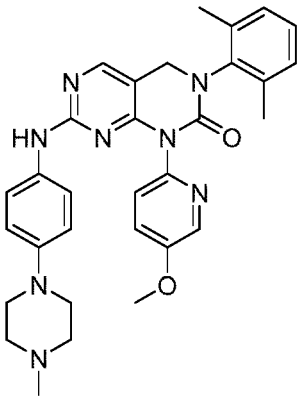

(SB1-D-09)

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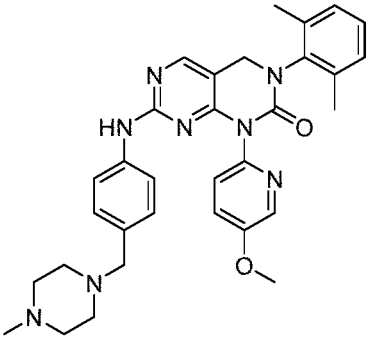

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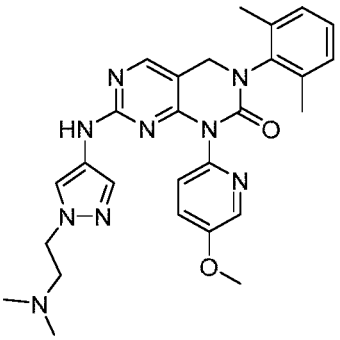

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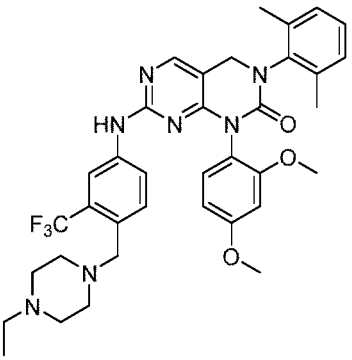

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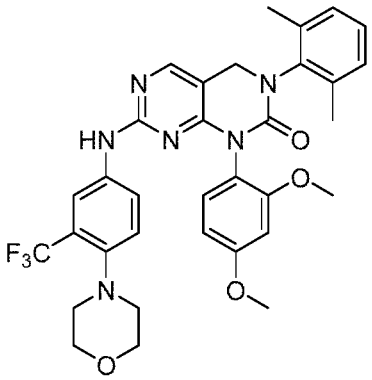
(YKL-04-136-10)

(YKL-04-136-8)



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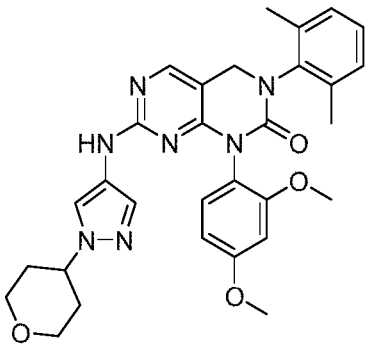
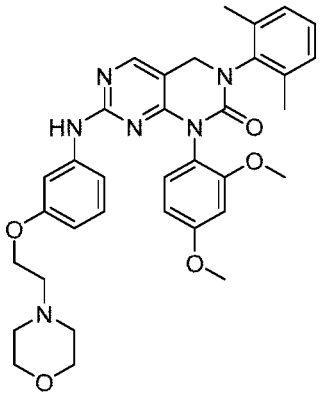


(YKL-04-105)



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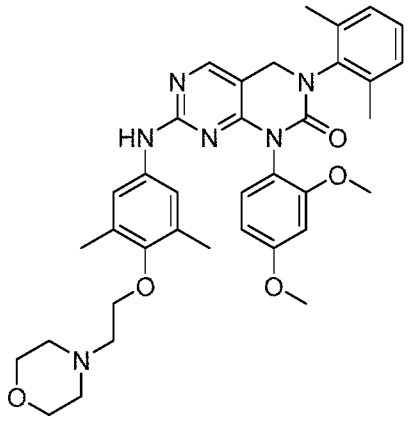
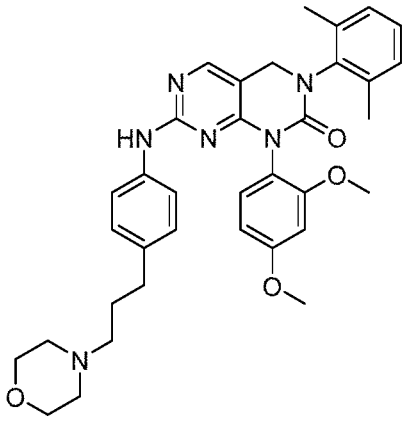
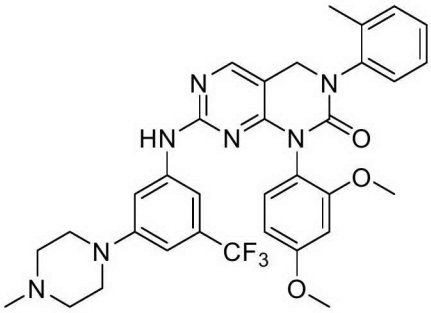


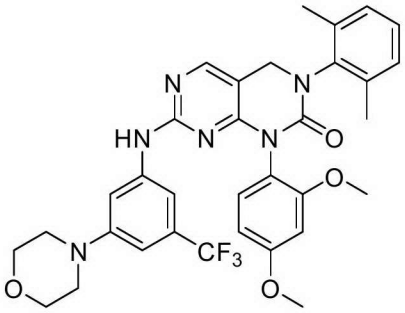
(YKL-04-107)



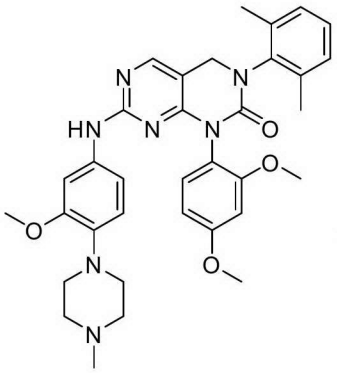
(YKL-04-108)



(YKL-04-112)



(YKL-04-113)



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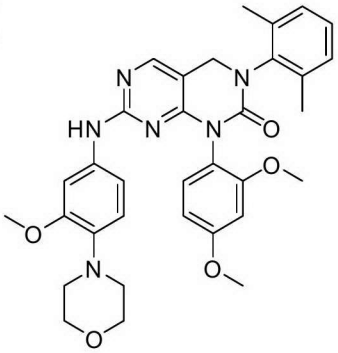

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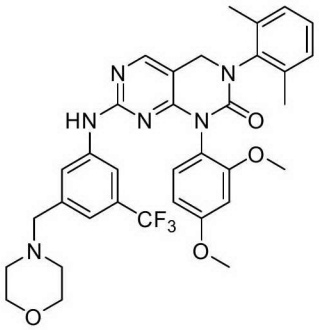

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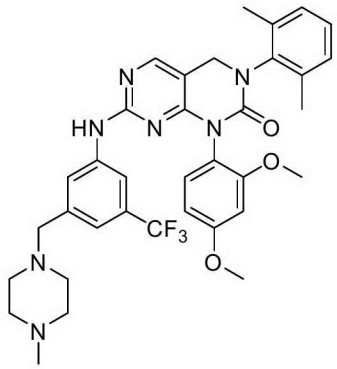

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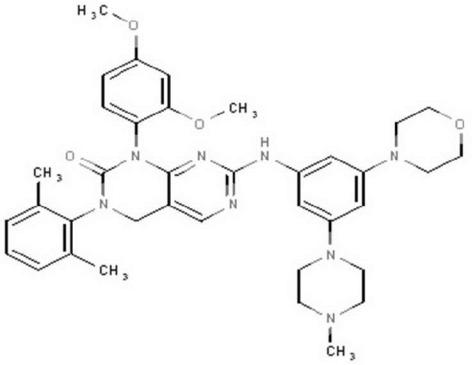
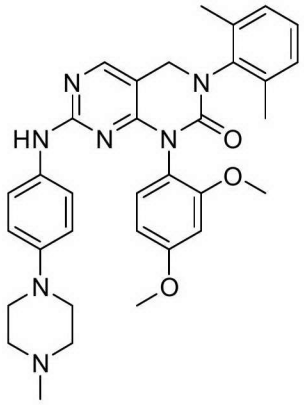
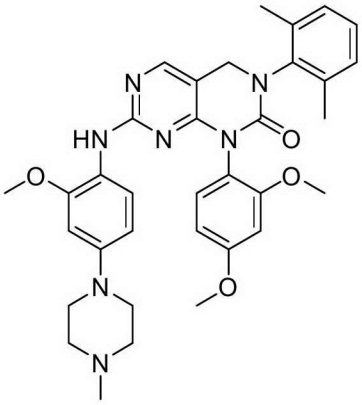


(HG-11-143-01)



(HG-11-136-01)



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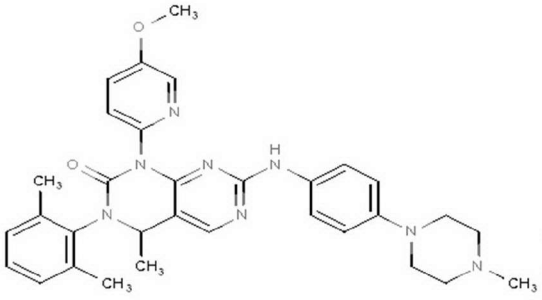
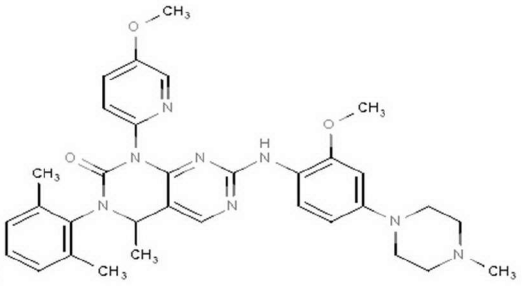


(YKL-06-038)

(SB1-D-40)



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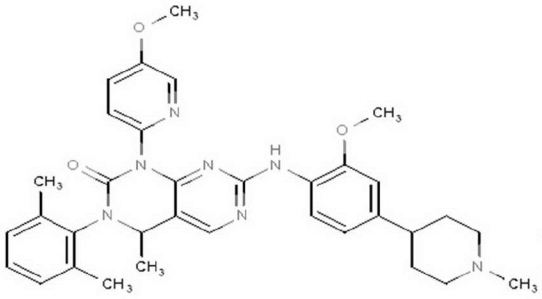

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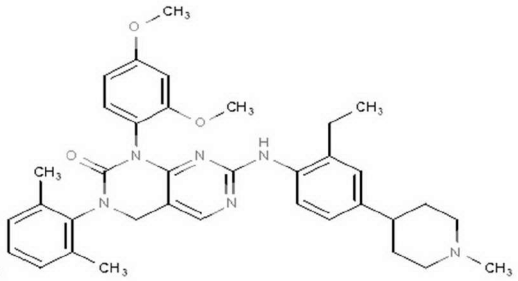

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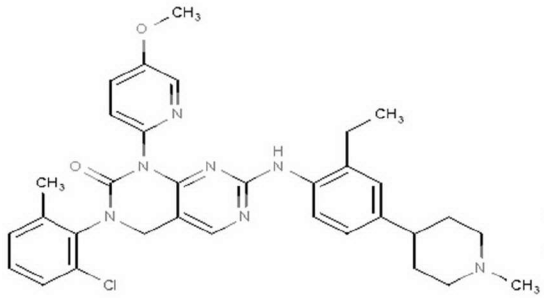

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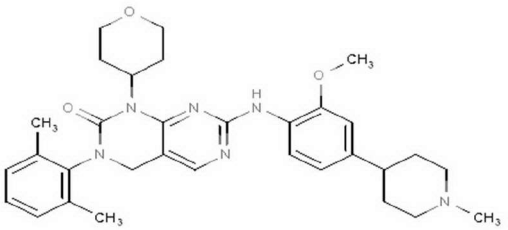

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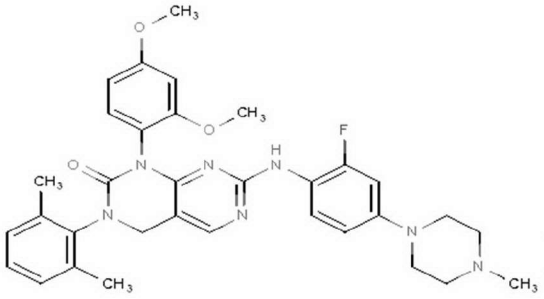

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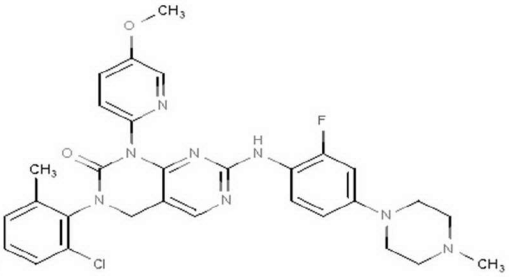

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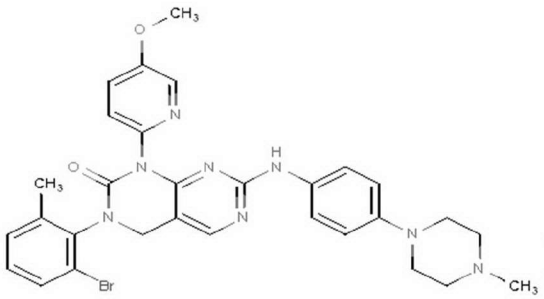

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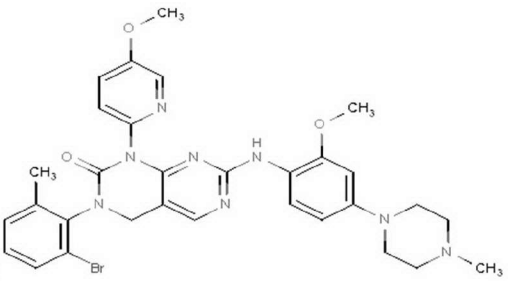

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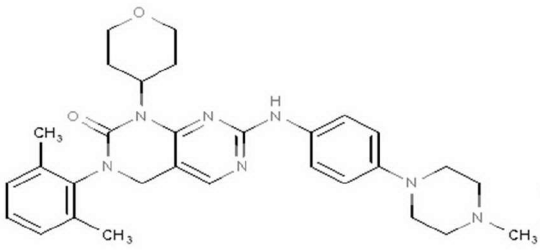
(SB1-D-43)



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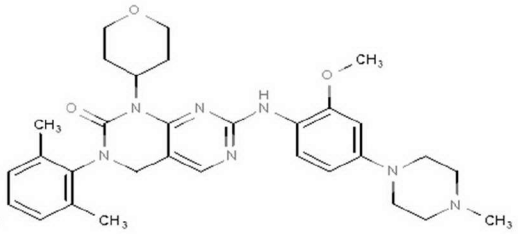
(SB1-D-57)



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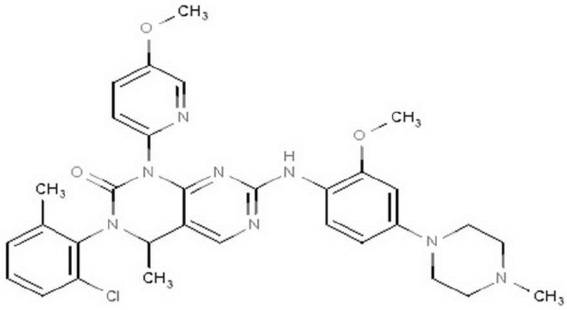
(SB1-D-58)



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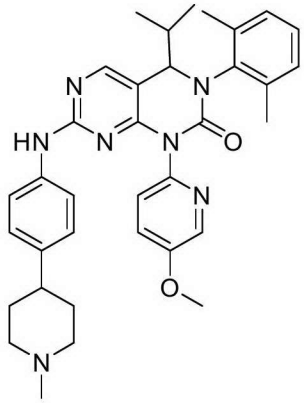
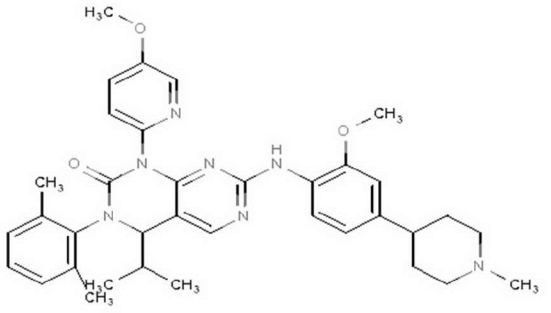
(SB1-D-60)



(YKL-06-081-1)

(SB1-D-61)



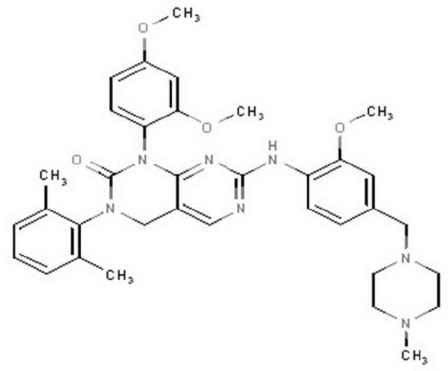
,

(YKL-06-082)

(SB1-D-62)

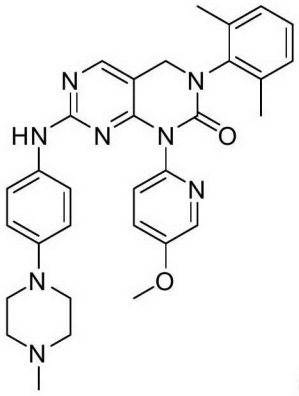
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

22. The compound of claim 21, wherein the compound is of the formula:



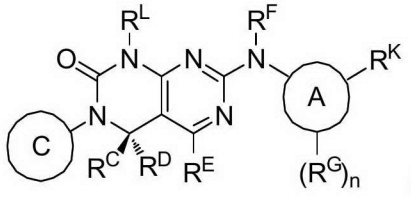
(YKL-05-70), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or

wherein the compound is of the formula:



(SB1-D-09; YKL-04-136-6), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

23. A compound of Formula (**III**):

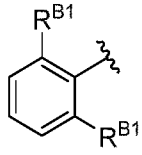


(**III**),

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

wherein:

R^L is substituted or unsubstituted alkyl;

Ring C is unsubstituted phenyl or of the formula:  ;

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, $–C(=NR^d)R^a$, $–C(=NR^d)OR^a$, $–C(=NR^d)N(R^d)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^d)_2$, $–NO_2$, $–NR^dC(=O)R^a$, $–NR^dC(=O)OR^a$, $–NR^dC(=O)N(R^a)_2$, $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^d)_2$;

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, $–C(=O)R^a$, 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;

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, $–C(=NR^b)R^a$, $–C(=NR^b)OR^a$, $–C(=NR^a)N(R^a)_2$, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^a)_2$, $–NO_2$, $–NR^bC(=O)R^a$, –

$NR^bC(=O)OR^a$, $-NR^bC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, 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 substituted or unsubstituted heterocyclyl; and

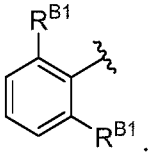
R^Y is substituted phenyl.

24. The compound of claim 23, wherein R^L is substituted or unsubstituted C_{1-6} alkyl.

25. The compound of claim 23, wherein R^L is Me, Et, iPr, or Pr.

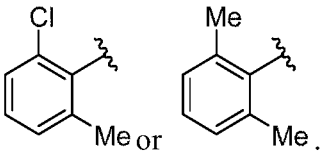
26. The compound of any one of claims 23-25, wherein Ring C is unsubstituted phenyl.

27. The compound of any one of claims 23-25, wherein Ring C is of the formula:



.

28. The compound of claim 27, wherein Ring C is of the formula:



.

29. The compound of claim 23, wherein R^K is substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl.

30. The compound of any one of claims 23-29, wherein at least one instance of R^G is $–OR^a$, wherein R^a is substituted or unsubstituted C_{1-6} alkyl, and/or

a) wherein each one of R^C and R^D is hydrogen, or

b) 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,

and/or

wherein R^E is hydrogen, and/or

wherein R^F is hydrogen, and/or

i) wherein n is 1, or

ii) wherein n is 0,

and/or

wherein at least one instance of R^G is halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted heterocyclyl, or $–OR^a$.

31. The compound of any one of claims 23-29, wherein n is 0.

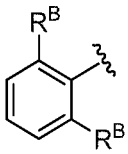
32. The compound of any one of claims 23-29, wherein R^C is hydrogen, and/or

R^D is hydrogen, and/or

R^E is hydrogen, and/or

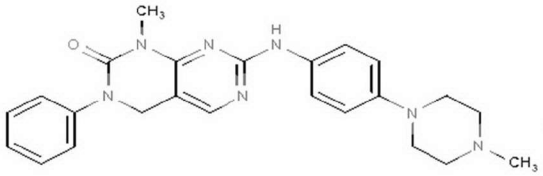
R^F is hydrogen.

33. The compound of claim 25, wherein 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, or

wherein Ring C is of the formula: 

, R^C, R^D, R^E, and R^F are each hydrogen, R^G is $–OR^a$, methyl, or ethyl, R^L is substituted or unsubstituted C_{1-6} alkyl, and R^K is substituted or unsubstituted piperidinyl, or substituted or unsubstituted piperazinyl.

34. The compound of claim 23, wherein the compound is of the formula:



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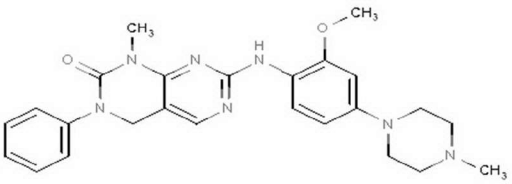
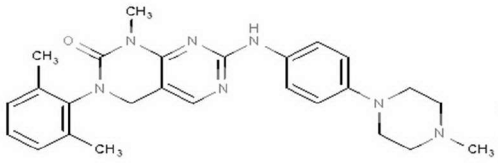


(HG-11-139-02)



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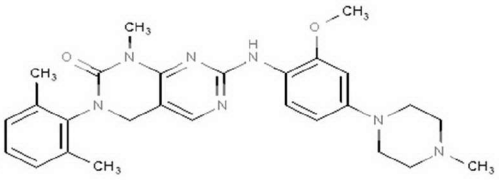

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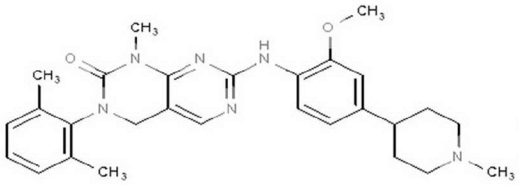

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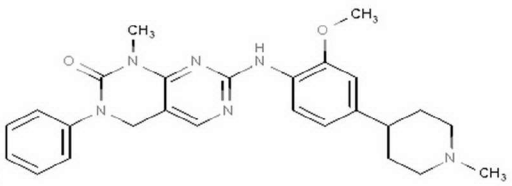
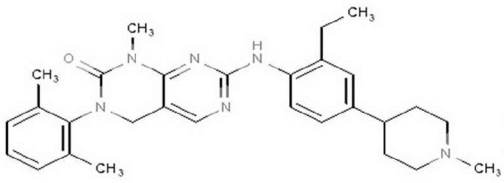


(YKL-06-033)



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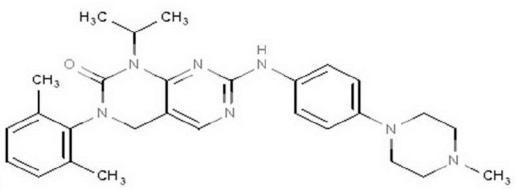

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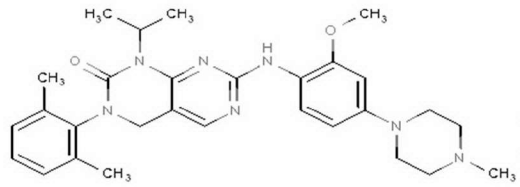

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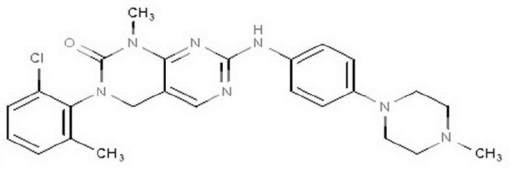

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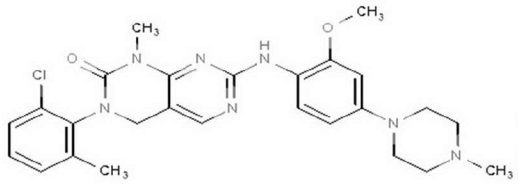

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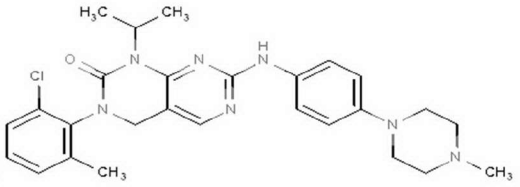
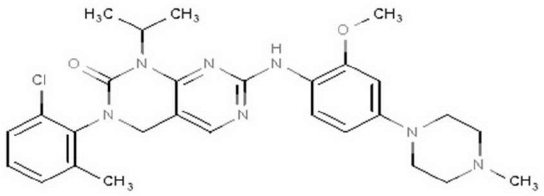


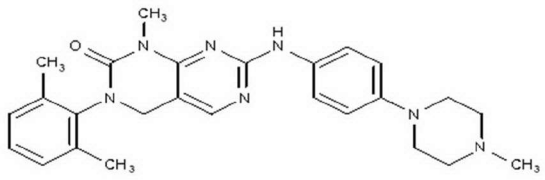
(YKL-06-086)



(YKL-06-087)

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

35. The compound of claim 34, wherein the compound is of the formula:



(YKL-06-029), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

36. A pharmaceutical composition comprising a compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof; and optionally a pharmaceutically acceptable excipient.

37. The pharmaceutical composition of claim 36, further comprising an additional pharmaceutical agent.

38. The pharmaceutical composition of claim 37, wherein the additional pharmaceutical agent is a kinase inhibitor, or
wherein the additional pharmaceutical agent is a salt-inducible kinase (SIK) inhibitor, or
wherein the additional pharmaceutical agent is a salt-inducible kinase 2 (SIK2) inhibitor.

39. A method of treating a disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition of any one of claims 36-38, wherein the disease is associated with aberrant activity of a protein kinase.

40. The method of claim 39, wherein the protein kinase is a salt-inducible kinase (SIK) or salt-inducible kinase 2 (SIK2).

41. The method of claim 39 or 40, wherein the disease is a genetic disease, or
wherein the disease is a proliferative disease, or
wherein the disease is cancer, or
wherein the disease is benign neoplasm, or
wherein the disease is pathological angiogenesis, or
wherein the disease is an inflammatory disease, or
wherein the disease is a musculoskeletal disease, or
wherein the disease is an autoimmune disease, or
wherein the disease is a hematological disease, or
wherein the disease is a neurological disease, or
wherein the disease is a painful condition, or
wherein the disease is a psychiatric disorder, or
wherein the disease is a metabolic disorder.

42. The method of any one of claims 39-41, wherein the subject is a human.

43. Use of a compound of any of claims 1-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition of any one of claims 36-38 for the manufacture of a medicament for treating a disease in a subject in need thereof, wherein the disease is associated with aberrant activity of a protein kinase.

44. A method of preventing a disease in a subject in need thereof, the method comprising administering to the subject a prophylactically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition of any one of claims 36-38, wherein the disease is associated with aberrant activity of a protein kinase.

45. A method of modulating the activity of a protein kinase in a subject or cell, the method comprising administering to the subject or contacting a cell with an effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition of any one of claims 36-38.

46. A method of screening a library of compounds, the method comprising:

obtaining at least two different compounds of any one of claims 1-35, or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, or prodrugs thereof; and

performing at least one assay using the different compounds, pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, or prodrugs to detect one or more characteristics associated with the treatment or prevention of a disease, wherein the disease is associated with aberrant activity of a protein kinase.