PYRIDINONE COMPOUNDS, METHODS AND USES THEREOF

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 63/632,946, filed April 11, 2024, 63/675,151, filed July 24, 2024, 63/683,078, filed August 14, 2024 and 63/736,199, filed December 19, 2024, each of which is incorporated by reference in their entireties.

BACKGROUND

Field

[0002] The present application relates generally to therapeutic compounds for use in oncology, more specifically compounds that target DNA damage response mechanisms for the treatment of a broad range of cancers.

Description

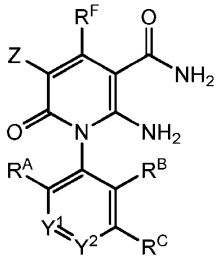
[0003] DNA is constantly damaged from the environment. Light, chemicals, stress, and cellular replication lead to single- or double-stranded breakage along DNA's backbone. Typically, organisms defend against DNA damage by repair proteins that either re-connect or re-synthesize damaged DNA. The correct functioning of these proteins are essential for life. The incorrect replacement of nucleotides into DNA can cause mutations (and other genetic alterations including, but not limited to, insertions, deletions, and frameshifts), genetic disease, and/or loss of protein function. The altogether loss of DNA repair can cause cell death, tumor progression, and/or cancer.

[0004] Cell cycle checkpoints are important for proper DNA repair, ensuring that cells do not progress with cellular replication until their genomic integrity is restored. CDC2 (also referred to as CDK1) promotes multiple biological processes that are critical for cell survival, including G2/M transition, checkpoint activation, DNA repair, and DNA replication. The membrane-associated tyrosine- and threonine-specific CDC2-inhibitory kinase is a

regulator of CDK1 phosphorylation and is a compelling therapeutic target for the treatment of certain types of DNA damage response cancers due to its established synthetic lethal relationship with *CCNE1* amplification. To date, no selective inhibitors have been reported for this kinase that would allow for investigation of the pharmacological role of the kinase.

SUMMARY

[0005] Various embodiments provide a compound represented by the following Formula (I'):



Formula (I')

or a pharmaceutically acceptable salt thereof, wherein ═══ and the variables $\mathbf{Y^1}$, $\mathbf{Y^2}$, **Z**, $\mathbf{R^A}$, $\mathbf{R^B}$, $\mathbf{R^C}$, $\mathbf{R^D}$, $\mathbf{R^E}$, $\mathbf{R^F}$, $\mathbf{R^G}$, $\mathbf{R^1}$ through $\mathbf{R^{36}}$, **m, n, p, q**, and **r** are as defined herein.

[0006] Another embodiment provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or the compound has a structure selected from those of Compound Nos. 1-A to 61-C as described herein (including pharmaceutically acceptable salts of any of the foregoing).

[0007] Another embodiment provides a pharmaceutical composition comprising an effective amount of a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C as described herein, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0008] Another embodiment provides a method of ameliorating or treating a cancer in a subject comprising administering to the subject an effective amount of a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C

as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition thereof.

[0009] Another embodiment provides a method of inhibiting replication of a malignant growth or a tumor in a subject comprising administering to the subject an effective amount of a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition thereof, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described herein.

[0010] Another embodiment provides a method of ameliorating or treating a malignant growth or a tumor in a subject comprising administering to the subject an effective amount of a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition thereof, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described herein.

DETAILED DESCRIPTION

[0011] The membrane-associated tyrosine- and threonine-specific CDC2-inhibitory kinase (PKMYT1) is a member of the WEE1 family and was first reported as a kinase capable of phosphorylated CDC2 efficiently on both threonine-14 and tyrosine-15 in *Xenopus*. PKMYT1 has been reported to inhibit cell cycle progression by inhibiting the activities of cell cycle-associated proteins, such as Cyclin A, CDK1, and CDK2. However, in recent reports, PKMYT1 was also found to drive the progression of a variety of tumors.

Definitions

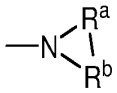
[0012] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0013] Whenever a group is described as being "a substituted or an unsubstituted" or "a substituted or an unsubstituted," that group may be unsubstituted or substituted with one

or more of the specified substituents. If no substituents are specified, it is meant that the group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), cycloalkyl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, -O-thiocarbamyl, -N-thiocarbamyl-, -C-amido, -N-amido, -S-sulfonamido, -N-sulfonamido-, -C-carboxy, -O-carboxy, nitro, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group and an amine(C_1-C_6 alkyl).

[0014] As used herein, "C_a to C_b" and "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in a group. The indicated group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" and "C_1-C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated, the broadest range described in these definitions is to be assumed.

[0015] If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0016] As used herein, the term "alkyl" refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched ($-CH(CH_3)_2$) or straight chain. Examples of branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as "1 to 30" refers to each integer in the given range; *e.g.*, "1 to 30 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon

atoms. An alkyl group may be substituted or unsubstituted. As a non-limiting example, a substituted alkyl group includes haloalkyls.

[0017] The term "heteroalkyl" used herein refers to an alkyl as defined herein, whereby one or more CH_2 groups each can be replaced with a heteroatom, such as, but not limited to, O, S, $P(=O)_2$ and NH. A heteroalkyl group may be substituted or unsubstituted. As a non-limiting example, a substituted heteroalkyl group includes haloheteroalkyls.

[0018] The term "alkenyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond(s) including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like. An alkenyl group may be unsubstituted or substituted. As a non-limiting example, a substituted alkenyl group includes haloalkenyls.

[0019] The term "alkynyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-butynyl, 2-butynyl and the like. An alkynyl group may be unsubstituted or substituted. As a non-limiting example, a substituted alkynyl group includes haloalkynyls.

[0020] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged cycloalkyl" refers to compounds wherein the cycloalkyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Cycloalkyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. As a non-limiting example, a substituted cycloalkyl group includes halocycloalkyls. Examples of mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl; examples of bridged cycloalkyl

groups are bicyclo[1.1.1]pentyl, adamantanyl and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

[0021] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). When composed of two or more rings, the rings may be connected in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted. As a non-limiting example, a substituted cycloalkenyl group includes halocycloalkenyls.

[0022] As used herein, "carbocyclyl" refers to a non-aromatic a mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion, as described herein. Carbocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A carbocyclyl group may be unsubstituted or substituted. As a non-limiting example, a substituted carbocyclyl group includes halocarbocyclyls. Examples of carbocyclyl groups include, but are in no way limited to, cycloalkyl groups and cycloalkenyl groups, as defined herein, and the non-aromatic portions of 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5H-cyclopenta[b]pyridine.

[0023] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group such as phenyl may be substituted or unsubstituted. As a non-limiting example, a substituted aryl group includes haloaryls.

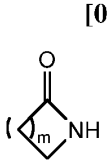
[0024] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1, 2 or 3 heteroatoms), that is, an element other than carbon,

including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s), such as nine carbon atoms and one heteroatom; eight carbon atoms and two heteroatoms; seven carbon atoms and three heteroatoms; eight carbon atoms and one heteroatom; seven carbon atoms and two heteroatoms; six carbon atoms and three heteroatoms; five carbon atoms and four heteroatoms; five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; or two carbon atoms and three heteroatoms. Furthermore, the term "heteroaryl" includes fused ring systems where two or more rings, such as at least one aryl ring and at least one heteroaryl ring or at least two heteroaryl rings in a bicyclic system, share at least one chemical bond. The term "heteroaryl" also includes spiro ring systems where two or more rings, such as at least one aryl ring and at least one heteroaryl ring or at least two heteroaryl rings in a bicyclic system, share at least one atom. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted. As a non-limiting example, a substituted heteroaryl group includes haloheteroaryls.

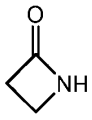
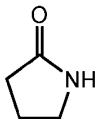
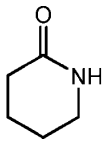
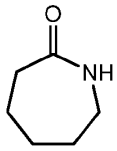
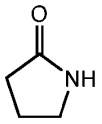
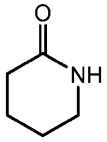
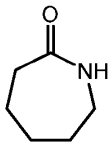
[0025] As used herein, "heterocyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed

of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged heterocyclyl" refers to compounds wherein the heterocyclyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Heterocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). For example, five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; two carbon atoms and three heteroatoms; one carbon atom and four heteroatoms; three carbon atoms and one heteroatom; or two carbon atoms and one heteroatom. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. As a non-limiting example, a substituted heterocyclyl group includes haloheterocyclyls. Examples of "heterocyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isooxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiomorpholine sulfone and their benzo-fused analogs (*e.g.*, tetrahydroquinoline and/or 3,4-methylenedioxyphenyl).

[0026] As used herein, a "lactam" is a cyclic amide having a general formula of



wherein m denotes the number of carbon atoms in an alkylene group as defined

below (*e.g.*, m can be 1, 2, 3, or 4). Non-limiting examples of lactam rings include  (4-membered lactam),  (5-membered lactam),  (6-membered lactam),  (7-membered lactam), etc. In one embodiment of a compound represented by Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^F}$ and the $-CONH_2$ shown in a Formula provided herein, together with the carbon atom that each of $\mathbf{R^F}$ and the $-CONH_2$ is respectively connected thereto, form a substituted or an unsubstituted . In one embodiment of a compound represented by Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^F}$ and the $-CONH_2$ shown in a Formula provided herein, together with the carbon atom that each of $\mathbf{R^F}$ and the $-CONH_2$ is respectively connected thereto, form a substituted or an unsubstituted . In one embodiment of a compound represented by Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^F}$ and the $-CONH_2$ shown in a Formula provided herein, together with the carbon atom that each of $\mathbf{R^F}$ and the $-CONH_2$ is respectively connected thereto, form a substituted or an unsubstituted .

[0027] As used herein, "alkylene groups" are straight-chained alkyl groups that are $-CH_2-$ tethering, forming bonds to connect molecular fragments via their terminal carbon atoms. Embodiments of alkylene groups may be represented herein by $-(CH_2)_c-$ where c is an integer in the range of 1 to 30. "Lower" alkylene groups are alkylene groups that contain

1 to 6 carbon atoms. Examples of lower alkylene groups include, but are not limited to, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-) and butylene (-$CH_2CH_2CH_2CH_2$-). An alkylene group can be substituted by replacing one or more hydrogens of the alkylene group and/or by substituting both hydrogens on the same carbon with a cycloalkyl group (*e.g.*, ).

[0028] As used herein, the term "hydroxy" refers to a –OH group.

[0029] As used herein, "alkoxy" refers to the Formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (iso-propoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted. As a non-limiting example, a substituted alkoxy group includes haloalkoxys.

[0030] As used herein, "acyl" refers to a hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) and heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0031] A "cyano" group refers to a "–CN" group.

[0032] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine. When the name of a group such as alkyl and alkoxy is preceded by "halo" (*e.g.*, haloalkyl, haloalkoxy, etc.), it means that one or more hydrogen atoms of the group is substituted with a halogen (*e.g.*, CF_3, CHF_2, etc.)

[0033] A "thiocarbonyl" group refers to a "–C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0034] An "O-carbamyl" group refers to a "–OC(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0035] An "N-carbamyl" group refers to an "ROC(=O)N(R_A)–" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0036] An "O-thiocarbamyl" group refers to a "–OC(=S)-N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0037] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R_A)–" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0038] A "C-amido" group refers to a "–C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0039] An "N-amido" group refers to a "RC(=O)N(R_A)–" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0040] An "S-sulfonamido" group refers to a "–SO_2N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0041] An "N-sulfonamido" group refers to a "RSO_2N(R_A)–" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0042] An "O-carboxy" group refers to a "RC(=O)O–" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl,

heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0043] The terms "ester" and "C-carboxy" refer to a "–C(=O)OR" group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0044] A "nitro" group refers to an "–NO_2" group.

[0045] A "sulfenyl" group refers to an "–SR" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0046] A "sulfinyl" group refers to an "–S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0047] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0048] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (*e.g.*, mono-haloalkyl, di-haloalkyl, tri-haloalkyl and polyhaloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl, 2-fluoroisobutyl and pentafluoroethyl.

[0049] As used herein, "haloalkoxy" refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (*e.g.*, mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy.

[0050] The term "amino" as used herein refers to a –NH_2 group.

[0051] A "mono-substituted amine" group refers to a "–NHR_A" group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, –NH(methyl), –NH(phenyl) and the like.

[0052] A "di-substituted amine" group refers to a "$-NR_AR_B$" group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. Examples of di-substituted amino groups include, but are not limited to, $-N(methyl)_2$, –N(phenyl)(methyl), –N(ethyl)(methyl) and the like.

[0053] As used herein, "amine(alkyl)" group refers to an –(alkylene)–NR'R" radical where R' and R" are independently hydrogen or alkyl as defined herein. An amine(alkyl) may be substituted or unsubstituted. Examples of amine(alkyl) groups include, but are not limited to, $-CH_2NH(methyl)$, $-CH_2NH(phenyl)$, $-CH_2CH_2NH(methyl)$, $-CH_2CH_2NH(phenyl)$, $-CH_2N(methyl)_2$, –CH_2N(phenyl)(methyl), –NCH_2(ethyl)(methyl), $-CH_2CH_2N(methyl)_2$, –CH_2CH_2N(phenyl)(methyl), –NCH_2CH_2(ethyl)(methyl) and the like.

[0054] Where the number of substituents is not specified (*e.g.*, haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0055] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term "radical" can be used interchangeably with the term "group."

[0056] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutically acceptable salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (*e.g.*, hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutically acceptable salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, trifluoroacetic,

benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutically acceptable salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. For compounds of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C as described herein, or a pharmaceutically acceptable salt of any of the foregoing, those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH_2), the nitrogen-based group can be associated with a positive charge (for example, NH_2 can become NH_3^+) and the positive charge can be balanced by a negatively charged counterion (such as Cl^-).

[0057] The terms "PKMYT1 inhibition", "PKMYT1 inhibitor" and similar terms as used herein refer to inhibiting the activity or function of a PKMYT1 tyrosine- and threonine-specific kinase, e.g., by reducing the activity of PKMYT1 tyrosine- and threonine-specific kinase with regard to mediating phosphorylation of CDK1.

[0058] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0059] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium), hydrogen-2 (deuterium), and hydrogen-3 (tritium). Compounds, conjugates, and immunoconjugates described herein can also include all isotopes of atoms occurring in the intermediates or final products. Isotopes include those atoms having the same

atomic number but different mass numbers. For example, isotopes of hydrogen include tritium, deuterium, and tritium.

[0060] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including, but not limited to, hydrogen-1 (protium), hydrogen-2 (deuterium), and hydrogen-3 (tritium). Thus, reference herein to a compound, conjugate, or immunoconjugate encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0061] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol or the like. Hydrates are formed when the solvent is water or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0062] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

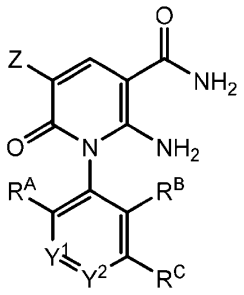
[0063] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should

be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' and the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components but may also include additional features or components.

[0064] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

Compounds

[0065] In a first embodiment, this disclosure relates to a compound represented by the following Formula (I'):

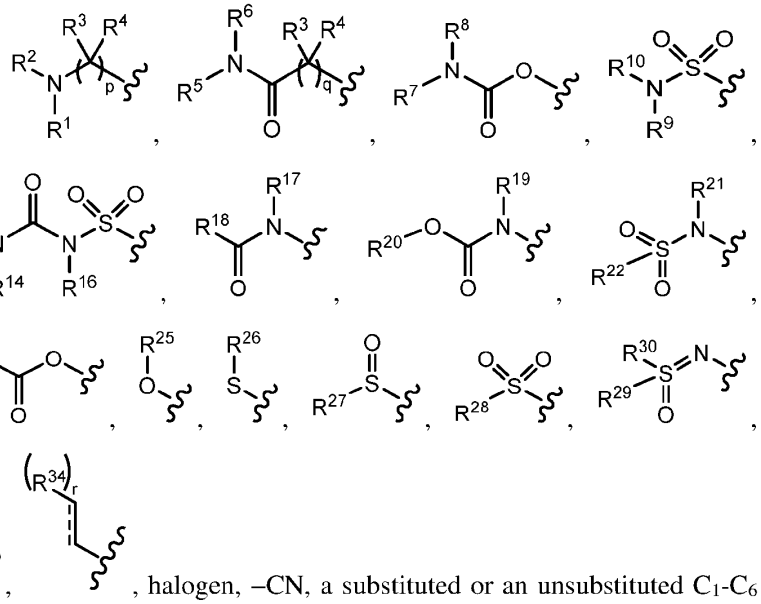


Formula (I')

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

≡ is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each

independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^A}$, $\mathbf{R^D}$, and $\mathbf{R^E}$ are each independently hydrogen, halogen, –CN, –OH, $-\mathbf{OR^{35}}$, $-\mathbf{SR^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and

$\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, $-\mathbf{OR^{35}}$, $-\mathbf{SR^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

$\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

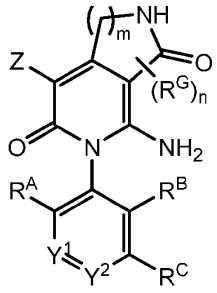
$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl; or alternatively

$\mathbf{Z}$ and $\mathbf{R^F}$, together with the carbon atom that each of $\mathbf{Z}$ and $\mathbf{R^F}$ is respectively connected thereto, form a substituted or an unsubstituted C_7 cycloalkyl, a substituted or an unsubstituted 7-membered heterocyclyl or a substituted or an unsubstituted 7-membered heteroaryl; or

$\mathbf{R^F}$ and the $-CONH_2$ shown in Formula (I'), together with the carbon atom that each of $\mathbf{R^F}$ and $-CONH_2$ is respectively connected thereto, form a substituted or an unsubstituted 5- to 7-membered lactam ring.

[0066] In some embodiments of the first embodiment, in a compound represented by Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^F}$ is hydrogen, F, Cl, Br, –CN, $-\mathbf{OR^{37}}$, $-\mathbf{SR^{38}}$, $-\mathbf{NR^{39}R^{40}}$, a substituted or an unsubstituted C_1-C_6 alkyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; wherein $\mathbf{R^{37}}$ is a substituted or an unsubstituted C_1-C_6 alkyl; or $\mathbf{R^F}$ is $-\mathbf{SR^{38}}$, wherein $\mathbf{R^{38}}$ is a substituted or an unsubstituted C_1-C_6 alkyl; or $\mathbf{R^F}$ is $-\mathbf{NR^{39}R^{40}}$, wherein $\mathbf{R^{39}}$ and $\mathbf{R^{40}}$ are independently hydrogen or a substituted or an unsubstituted C_1-C_6 alkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In some embodiments of the first embodiment, in a compound represented by Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^F}$ is hydrogen, F, Cl, methyl or methoxy; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0067] In a second embodiment, this disclosure relates to a compound represented by the following Formula (I'a):



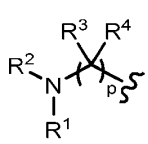
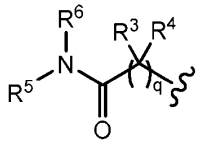
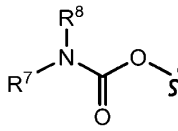
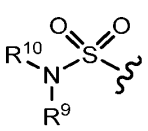
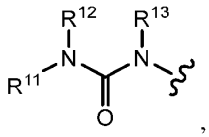
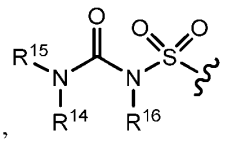
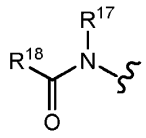
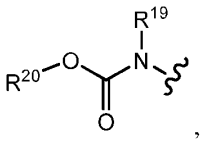
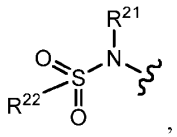
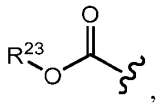
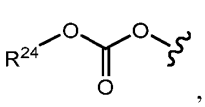
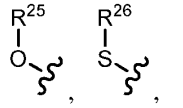
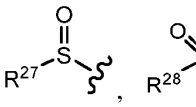
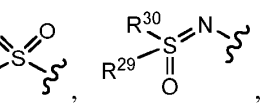
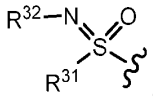
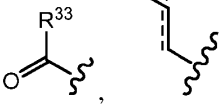
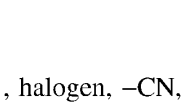
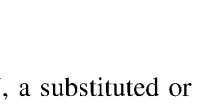
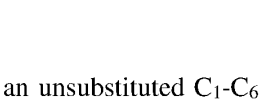
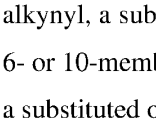
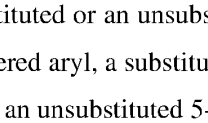
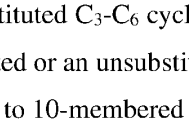
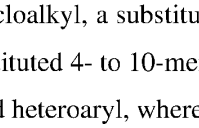
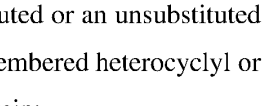
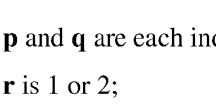
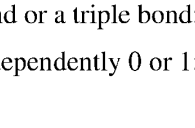
Formula (I'a)

or a pharmaceutically acceptable salt thereof, wherein:

m is 1, 2 or 3;

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , , , , , , , , , , , , , , , , , , , , , , , , , , , halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

≡ is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each

independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

R^{32} is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

R^{33} and R^{34} are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

R^A, R^D, and R^E are each independently hydrogen, halogen, –CN, –OH, $-OR^{35}$, $-SR^{36}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

R^B and R^C are each independently hydrogen, halogen, –CN, –OH, $-OR^{35}$, $-SR^{36}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

R^B and R^C, together with the carbon atom that each of R^B and R^C is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

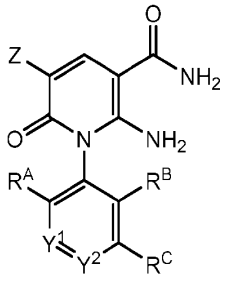
R^{35} and R^{36}, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

R^G, for each instance, is independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 alkoxy; and

n is 0, 1 or 2.

[0068] In some embodiments of the second embodiment, a compound represented by Formula (I') is a compound of Formula (I'a), or a pharmaceutically acceptable salt thereof. In some embodiments of the second embodiment, in a compound represented by Formula (I'a), or a pharmaceutically acceptable salt thereof, $\mathbf{R^G}$, for each instance, is independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In some embodiments of the second embodiment, in a compound represented by Formula (I'a), or a pharmaceutically acceptable salt thereof, **n** is 0; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In some embodiments of the second embodiment, in a compound represented by Formula (I'a), or a pharmaceutically acceptable salt thereof, **n** is 1; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0069] In a third embodiment, this disclosure relates to a compound represented by the following Formula (I):

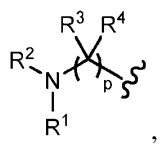
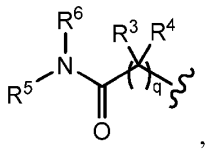
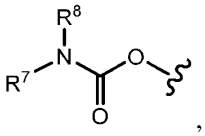
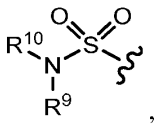
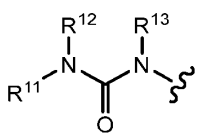
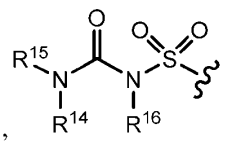
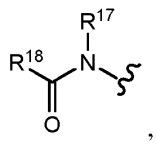
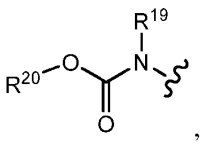
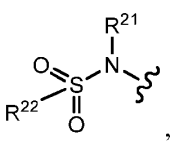


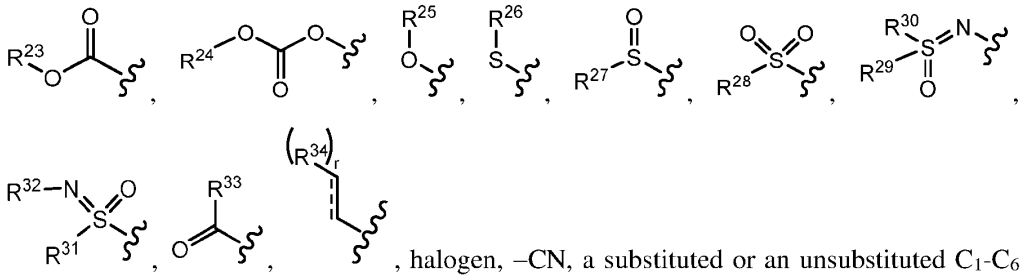
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , , , , , , , , ,



, halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

≡ is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted

4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a

substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^A}$, $\mathbf{R^D}$, and $\mathbf{R^E}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and

$\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

$\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl.

[0070] In a fourth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are each independently –CH, –CF or N (nitrogen); and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a fifth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are each independently –CH and –CF; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a sixth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{Y^1}$ is –CF and $\mathbf{Y^2}$ is **Y** is –CH; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a seventh embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are each –CH; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

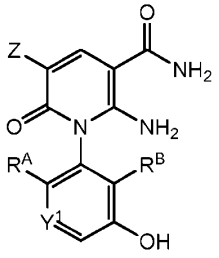
[0071] In an eighth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a ninth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, a substituted or an unsubstituted C_1-C_6 alkyl or a substituted or an unsubstituted C_1-C_6 alkoxy; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0072] In a tenth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, *e.g.* a substituted or an unsubstituted pyrazolyl, a substituted or an unsubstituted imidazolyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

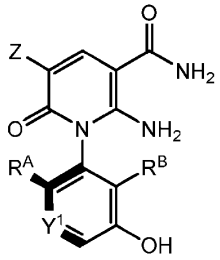
[0073] In an eleventh embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, F, Cl, Br, –CN, –OH or a substituted or an unsubstituted C_1-C_6 alkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a twelfth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, F, –CN, –OH, an unsubstituted C_1-C_4 alkyl or C_1-C_4 haloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a thirteenth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, F, –CN, –OH, an unsubstituted C_1-C_2 alkyl or C_1-C_2 haloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a fourteenth embodiment, in a compound represented by Formula (I'), (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are not all hydrogen (for example, one of $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ is not hydrogen, two of $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are not hydrogen or

all of $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are not hydrogen); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0074] In a fifteenth embodiment, a compound of this disclosure is represented by the following Formula (II) or (IIa):



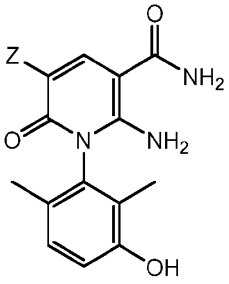
Formula (II)



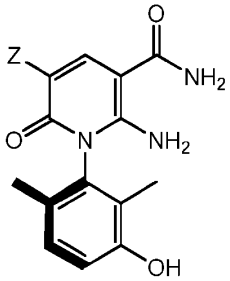
Formula (IIa)

or a pharmaceutically acceptable salt thereof; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0075] In a sixteenth embodiment, a compound of this disclosure is represented by the following Formula (III) or (IIIa):



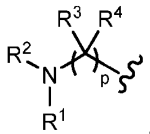
Formula (III)



Formula (IIIa)

or a pharmaceutically acceptable salt thereof; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

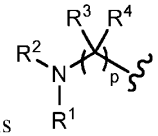
[0076] In a seventeenth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is , a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted phenyl, a substituted or

an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In an eighteenth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_6 alkyl (including branched alkyls such as, but not limited to, $-CH(CH_3)_2$ and including haloalkyls such as, but not limited to, $-CHF_2$ and $-CF_3$), a substituted or an unsubstituted C_2-C_6 alkenyl (including branched alkenyls such as, but not limited to, $-CH=CHCH_3$ and $-CH=C(CH_3)_2$), a substituted or an unsubstituted C_2-C_6 alkynyl (including, but not limited to, $-C\equiv CCH_3$), a substituted or an unsubstituted C_3-C_6 cycloalkyl (*e.g.*, monocyclic C_3-C_6 cycloalkyl, including substituted cyclopropyl, unsubstituted cyclopropyl, substituted cyclobutyl and unsubstituted cyclobutyl), a substituted or an unsubstituted phenyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl (*e.g.*, monocyclic 4- to 10-membered heterocyclyl, fully saturated heterocyclyls (such as, but not limited to, substituted tetrahydrofuranyl, unsubstituted tetrahydrofuranyl, substituted piperidinyl, unsubstituted piperidinyl, substituted pyrrolidinyl and unsubstituted pyrrolidinyl) and heterocyclyls having a double bond (such as, but not limited to, substituted 3,6-dihydro-2*H*-pyranyl, unsubstituted 3,6-dihydro-2*H*-pyranyl, substituted 2,5-dihydrofuranyl and unsubstituted 2,5-dihydrofuranyl)) or a substituted or an unsubstituted 5- to 10-membered heteroaryl (*e.g.*, monocyclic 5- to 10-membered heteroaryl, including substituted pyridinyl, unsubstituted pyridinyl, substituted pyrazolyl, unsubstituted pyrazolyl, substituted isothiazolyl, unsubstituted isothiazolyl, substituted imidazolyl, unsubstituted imidazolyl, substituted thiazolyl and unsubstituted thiazolyl); and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a nineteenth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_4 alkyl (including branched alkyls such as, but not limited to, $-CH(CH_3)_2$ and including haloalkyls such as, but not limited to, $-CHF_2$ and $-CF_3$, a substituted or an unsubstituted C_2-C_6 alkenyl (including branched alkenyls such as, but not limited to, $-CH=CHCH_3$ and $-CH=C(CH_3)_2$), a substituted or an unsubstituted C_2-C_6 alkynyl (including, but not limited to, $-C\equiv CCH_3$), a substituted or an unsubstituted C_3-C_5 cycloalkyl (*e.g.*, monocyclic C_3-C_5 cycloalkyl, including substituted cyclopropyl, unsubstituted cyclopropyl, substituted

cyclobutyl and unsubstituted cyclobutyl), a substituted or an unsubstituted phenyl, a substituted or an unsubstituted 4- to 8-membered heterocyclyl (*e.g.*, monocyclic 4- to 8-membered heterocyclyl, fully saturated heterocyclyls (such as, but not limited to, substituted tetrahydrofuranyl, unsubstituted tetrahydrofuranyl, substituted piperidinyl, unsubstituted piperidinyl and substituted pyrrolidinyl and unsubstituted pyrrolidinyl) and heterocyclyls having a double bond (such as, but not limited to, substituted 3,6-dihydro-2*H*-pyranyl, unsubstituted 3,6-dihydro-2*H*-pyranyl, substituted 2,5-dihydrofuranyl and unsubstituted 2,5-dihydrofuranyl)) or a substituted or an unsubstituted 5- to 8-membered heteroaryl (*e.g.*, monocyclic 5- to 8-membered heteroaryl, including substituted pyridinyl, unsubstituted pyridinyl, substituted pyrazolyl, unsubstituted pyrazolyl, substituted isothiazolyl, unsubstituted isothiazolyl, substituted imidazolyl, unsubstituted imidazolyl, substituted thiazolyl and unsubstituted thiazolyl); and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a twentieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_2 alkyl (including branched alkyls such as, but not limited to, $-CH(CH_3)_2$ and including haloalkyls such as, but not limited to, $-CHF_2$ and $-CF_3$), a substituted or an unsubstituted C_2-C_6 alkenyl (including branched alkenyls such as, but not limited to, $-CH=CHCH_3$ and $-CH=C(CH_3)_2$), a substituted or an unsubstituted C_2-C_6 alkynyl (including, but not limited to, $-C\equiv CCH_3$), a substituted or an unsubstituted C_3-C_5 cycloalkyl (*e.g.*, monocyclic C_3-C_5 cycloalkyl, including substituted cyclopropyl, unsubstituted cyclopropyl, substituted cyclobutyl and unsubstituted cyclobutyl), a substituted or an unsubstituted phenyl, a substituted or an unsubstituted 4- to 6-membered heterocyclyl (*e.g.*, monocyclic 4- to 6-membered heterocyclyl, fully saturated heterocyclyls (such as, but not limited to, substituted tetrahydrofuranyl, unsubstituted tetrahydrofuranyl, substituted piperidinyl, unsubstituted piperidinyl, substituted pyrrolidinyl and unsubstituted pyrrolidinyl) and heterocyclyls having a double bond (such as, but not limited to, substituted 3,6-dihydro-2*H*-pyranyl, unsubstituted 3,6-dihydro-2*H*-pyranyl, substituted 2,5-dihydrofuranyl and unsubstituted 2,5-dihydrofuranyl)) or a substituted or an unsubstituted 5- or 6-membered heteroaryl (*e.g.*, monocyclic 5- to 6-membered heteroaryl, including substituted pyridinyl, unsubstituted pyridinyl, substituted pyrazolyl, unsubstituted pyrazolyl, substituted isothiazolyl, unsubstituted isothiazolyl, substituted imidazolyl, unsubstituted

imidazolyl, substituted thiazolyl and unsubstituted thiazolyl); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0077] In a twenty-first embodiment, in a compound represented Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  and, for example, **p** is 0 and $\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently an unsubstituted C_1-C_6 alkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0078] In a twenty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a twenty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments. In a twenty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen or a substituted or an unsubstituted C_1-C_4 alkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0079] In a twenty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl (a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_1-C_3 alkyl, a

substituted or an unsubstituted C_1-C_2 alkyl, etc.), a substituted or an unsubstituted C_1-C_6 heteroalkyl (a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_1-C_4 heteroalkyl, a substituted or an unsubstituted C_1-C_3 heteroalkyl, a substituted or an unsubstituted C_1-C_2 heteroalkyl, etc.), a substituted or an unsubstituted C_1-C_6 alkoxy, (a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_1-C_4 alkoxy, a substituted or an unsubstituted C_1-C_3 alkoxy, a substituted or an unsubstituted C_1-C_2 alkoxy, etc.) a substituted or an unsubstituted C_3-C_6 cycloalkyl (a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted C_3 or C_4 cycloalkyl, etc.), a substituted or an unsubstituted 4- to 10-membered heterocyclyl (a substituted or an unsubstituted 4- to 10-membered heterocyclyl, a substituted or an unsubstituted 4- to 8-membered heterocyclyl, a substituted or an unsubstituted 5- to 8-membered heterocyclyl, a substituted or an unsubstituted 4- to 6-membered heterocyclyl, etc.) or a substituted or an unsubstituted 5- to 10-membered heteroaryl (a substituted or an unsubstituted 5- to 10-membered heteroaryl, a substituted or an unsubstituted 5- to 8-membered heteroaryl, a substituted or an unsubstituted 5- or 6-membered heteroaryl, a substituted or an unsubstituted 5-membered heteroaryl, a substituted or an unsubstituted 6-membered heteroaryl, etc.), wherein:

when a C_1-C_6 alkyl or a C_1-C_6 heteroalkyl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the group is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy and C_3-C_6 cycloalkyl;

when a C_3-C_6 cycloalkyl, a 4- to 10-membered heterocyclyl or a 5- to 10-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ is substituted, the group is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 alkoxy; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each independently form a substituted or an unsubstituted 4- to 10-membered

heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

when a 4- to 10-membered heterocyclyl or a 5- to 10-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ is substituted, the group is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 alkoxy.

[0080] In a twenty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl (a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_1-C_3 alkyl, a substituted or an unsubstituted C_1-C_2 alkyl, etc.), a substituted or an unsubstituted C_1-C_6 heteroalkyl (a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_1-C_4 heteroalkyl, a substituted or an unsubstituted C_1-C_3 heteroalkyl, a substituted or an unsubstituted C_1-C_2 heteroalkyl, etc.), a substituted or an unsubstituted C_3-C_6 cycloalkyl (a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted C_3 or C_4 cycloalkyl, etc.), a substituted or an unsubstituted 4- to 10-membered heterocyclyl (a substituted or an unsubstituted 4- to 10-membered heterocyclyl, a substituted or an unsubstituted 4- to 8-membered heterocyclyl, a substituted or an unsubstituted 5- to 8-membered heterocyclyl, a substituted or an unsubstituted 4- to 6-membered heterocyclyl, etc.) or a substituted or an unsubstituted 5- to 10-membered heteroaryl (a substituted or an unsubstituted 5- to 10-membered heteroaryl, a substituted or an unsubstituted 5- to 8-membered heteroaryl, a substituted or an unsubstituted 5- or 6-membered heteroaryl, a substituted or an unsubstituted 5-membered heteroaryl, a substituted or an unsubstituted 6-membered heteroaryl, etc.), wherein:

when a C_1-C_6 alkyl or a C_1-C_6 heteroalkyl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_1-C_6 alkyl or the C_1-C_6 heteroalkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy and C_3-C_6 cycloalkyl;

when a C_3-C_6 cycloalkyl, a 4- to 10-membered heterocyclyl or a 5- to 10-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_3-C_6 cycloalkyl, the 4- to 10-membered heterocyclyl or the 5- to 10-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 4- to 8-membered heterocyclyl (a substituted or an unsubstituted 4- to 8-membered heterocyclyl, a substituted or an unsubstituted 5- to 8-membered heterocyclyl, a substituted or an unsubstituted 4- to 6-membered heterocyclyl, etc.) or a substituted or an unsubstituted 5- to 8-membered heteroaryl (a substituted or an unsubstituted 5- to 8-membered heteroaryl, a substituted or an unsubstituted 5- or 6-membered heteroaryl, a substituted or an unsubstituted 5-membered heteroaryl, or a substituted or an unsubstituted 6-membered heteroaryl, etc.), wherein:

when a 4- to 8-membered heterocyclyl or a 5- to 8-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the 4- to 8-membered heterocyclyl or the 5- to 8-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0081] In a twenty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted 4- to 8-membered heterocyclyl or a substituted or an unsubstituted 5- to 8-membered heteroaryl, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected

from F, Cl, –CN, –OH, C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy and C_3 or C_4 cycloalkyl;

when a C_3-C_5 cycloalkyl, a 4- to 8-membered heterocyclyl or a 5- to 8-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_3-C_5 cycloalkyl, the 4- to 8-membered heterocyclyl or the 5- to 8-membered heteroaryl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkyl, C_1-C_2 alkyl substituted with C_1-C_2 alkoxy, C_1-C_2 haloalkyl and C_1-C_2 alkoxy; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 4- to 8-membered heterocyclyl or a substituted or an unsubstituted 5- or 6-membered heteroaryl, wherein:

when a 4- to 8-membered heterocyclyl or a 5- or 6-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the 4- to 8-membered heterocyclyl or the 5- or 6-membered heteroaryl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkyl substituted with C_1-C_2 alkoxy, C_1-C_2 haloalkyl and C_1-C_2 alkoxy;

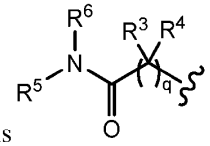
and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0082] In a twenty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^1}$ and $\mathbf{R^2}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 5- to 6-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 5-membered heterocyclyl containing at least one nitrogen atom or a substituted or an unsubstituted 6-membered heterocyclyl containing at least one nitrogen atom and/or at least one oxygen atom and optionally at least one double bond in the heterocyclyl) or a substituted or an unsubstituted 5- or 6-membered heteroaryl, wherein:

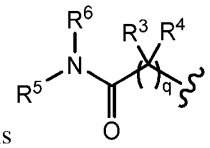
when a 5- to 6-membered heterocyclyl or a 5- or 6-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the 5- to 6-membered heterocyclyl or the 5- or 6-membered heteroaryl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkyl substituted with C_1-C_2 alkoxy, C_1-C_2 haloalkyl and C_1-C_2 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

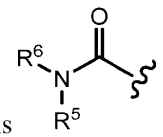
[0083] In a twenty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is , wherein q is 0; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0084] In a thirtieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is , wherein q is 1; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0085] In a thirty-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0086] In a thirty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^5}$ and $\mathbf{R^6}$ are each independently hydrogen or a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

when a C_1-C_6 alkyl represented by $\mathbf{R^5}$ or $\mathbf{R^6}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy; or alternatively

$\mathbf{R^5}$ and $\mathbf{R^6}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 4- to 8-membered heterocyclyl, wherein:

when a 4- to 8-membered heterocyclyl represented by $\mathbf{R^5}$ and $\mathbf{R^6}$ is substituted, the 4- to 8-membered heterocyclyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

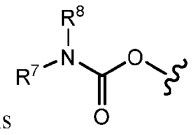
[0087] In a thirty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^5}$ and $\mathbf{R^6}$ are each independently hydrogen or a substituted or an unsubstituted C_1-C_4 alkyl, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^5}$ or $\mathbf{R^6}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy; or alternatively

$\mathbf{R^5}$ and $\mathbf{R^6}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 4- to 6-membered heterocyclyl, wherein:

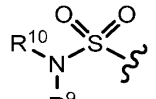
when a 4- to 6-membered heterocyclyl represented by $\mathbf{R^5}$ and $\mathbf{R^6}$ is substituted, the 4- to 6-membered heterocyclyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkyl substituted with C_1-C_2 alkoxy, C_1-C_2 haloalkyl and C_1-C_2 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

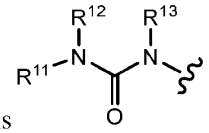
[0088] In a thirty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is 

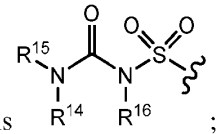
; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0089] In a thirty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0090] In a thirty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl (a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_1-C_3 alkyl, a substituted or an unsubstituted C_1-C_2 alkyl, etc.), a substituted or an unsubstituted C_1-C_6 alkoxy (a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_1-C_4 alkoxy, a substituted or an unsubstituted C_1-C_3 alkoxy, a substituted or an unsubstituted C_1-C_2 alkoxy, etc.) or a substituted or an unsubstituted C_3-C_6 cycloalkyl (a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted C_3 or C_4 cycloalkyl, etc.); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

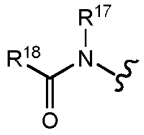
[0091] In a thirty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0092] In a thirty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0093] In a thirty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an

unsubstituted C_1-C_6 alkyl (a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_1-C_3 alkyl, a substituted or an unsubstituted C_1-C_2 alkyl, etc.) or a substituted or an unsubstituted C_3-C_6 cycloalkyl (a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted C_3 or C_4 cycloalkyl, etc.); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0094] In a fortieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is



; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0095] In a forty-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{17}}$ is hydrogen or a substituted or an unsubstituted C_1-C_6 alkyl; and $\mathbf{R^{18}}$ is a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

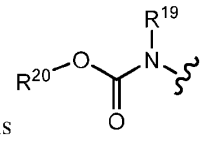
when a C_1-C_6 alkyl represented by $\mathbf{R^{17}}$ or $\mathbf{R^{18}}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

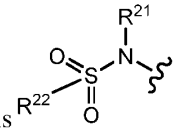
[0096] In a forty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{17}}$ is hydrogen or a substituted or an unsubstituted C_1-C_4 alkyl; and $\mathbf{R^{18}}$ is a substituted or an unsubstituted C_1-C_4 alkyl, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^{17}}$ or $\mathbf{R^{18}}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0097] In a forty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0098] In a forty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl (a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_4 alkyl, a substituted or an unsubstituted C_1-C_3 alkyl, a substituted or an unsubstituted C_1-C_2 alkyl, etc.), a substituted or an unsubstituted C_1-C_6 alkoxy (a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_1-C_4 alkoxy, a substituted or an unsubstituted C_1-C_3 alkoxy, a substituted or an unsubstituted C_1-C_2 alkoxy, etc.) or a substituted or an unsubstituted C_3-C_6 cycloalkyl (a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted C_3-C_5 cycloalkyl, a substituted or an unsubstituted C_3 or C_4 cycloalkyl, etc.); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0099] In a forty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0100] In a forty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{21}}$ is hydrogen or a substituted or an unsubstituted C_1-C_6 alkyl; and $\mathbf{R^{22}}$ is a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

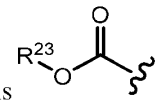
when a C_1-C_6 alkyl represented by $\mathbf{R^{21}}$ or $\mathbf{R^{22}}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy;

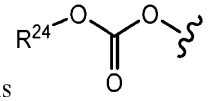
and all other variables are as defined in any one of the first through ninety-fifth embodiments.

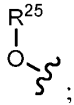
[0101] In a forty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{21}}$ is hydrogen or a substituted or an unsubstituted C_1-C_4 alkyl; and $\mathbf{R^{22}}$ is a substituted or an unsubstituted C_1-C_4 alkyl, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^{21}}$ or $\mathbf{R^{22}}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0102] In a forty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0103] In a forty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0104] In a fiftieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0105] In a fifty-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{25}}$ is a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

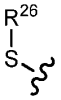
when a C_1-C_6 alkyl represented by $\mathbf{R^{25}}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy;

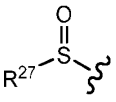
and all other variables are as defined in any one of the first through ninety-fifth embodiments.

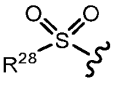
[0106] In a fifty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{25}}$ is a substituted or an unsubstituted C_1-C_4 alkyl, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^{25}}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy;

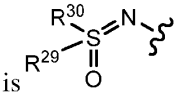
and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0107] In a fifty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0108] In a fifty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0109] In a fifty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0110] In a fifty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0111] In a fifty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{29}}$ and $\mathbf{R^{30}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

when a C_1-C_6 alkyl represented by $\mathbf{R^{29}}$ or $\mathbf{R^{30}}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0112] In a fifty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{29}}$ and $\mathbf{R^{30}}$ are each independently a substituted or an unsubstituted C_1-C_4 alkyl, wherein:

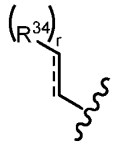
when a C_1-C_4 alkyl represented by $\mathbf{R^{29}}$ or $\mathbf{R^{30}}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

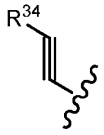
[0113] In a fifty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0114] In a sixtieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

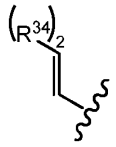
[0115] In a sixty-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0116] In a sixty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0117] In a sixty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

Z is  ; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0118] In a sixty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, $\mathbf{R^{34}}$, for each instance, is hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl (*e.g.*, $-CH_3$) or C_1-C_6 alkoxy, wherein:

when a C_1-C_6 alkyl represented by $\mathbf{R^{34}}$ is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0119] In a sixty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III) (IIIa), or a pharmaceutically acceptable salt of any of the foregoing,

$\mathbf{R^{34}}$, for each instance, is hydrogen, a substituted or an unsubstituted C_1-C_4 alkyl (*e.g.*, $-CH_3$) or C_1-C_4 alkoxy, wherein:

when a C_1-C_4 alkyl represented by $\mathbf{R^{34}}$ is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH and C_1-C_2 alkoxy; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0120] In a sixty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is halogen, and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0121] In a sixty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is F, and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0122] In a sixty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is Cl, and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0123] In a sixty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is –CN, and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0124] In a seventieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_6 alkyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0125] In a seventy-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_6 alkyl (including branched alkyls such as, but not limited to, $-CH(CH_3)_2$ and including haloalkyls such as, but not limited to, $-CHF_2$ and $-CF_3$), wherein:

when a C_1-C_6 alkyl represented by **Z** is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkoxy, a C_3-C_6 cycloalkyl and a 4- to 8-membered heterocyclyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0126] In a seventy-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_4 alkyl (including branched alkyls such as, but not limited to, $–CH(CH_3)_2$ and including haloalkyls such as, but not limited to, $–CHF_2$ and $–CF_3$), wherein:

when a C_1-C_4 alkyl represented by **Z** is substituted, the C_1-C_4 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkoxy, a C_3-C_5 cycloalkyl and a 5- or 6-membered heterocyclyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0127] In a seventy-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_1-C_2 alkyl (including haloalkyls such as, but not limited to, $–CHF_2$ and $–CF_3$), wherein:

when a C_1-C_2 alkyl represented by **Z** is substituted, the C_1-C_2 alkyl is substituted with one or more groups each independently selected from F, Cl, –CN, –OH, C_1-C_2 alkoxy, a C_3-C_5 cycloalkyl and a 5- or 6-membered heterocyclyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0128] In a seventy-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_2-C_6 alkenyl (*e.g.*, a C_2-C_6 alkenyl optionally substituted with one or more groups selected from halogen, –CN, –OH and C_1-C_2 alkoxy, etc.; and including branched alkenyls such as, but not limited to, $–CH=CHCH_3$ and $–CH=C(CH_3)_2$); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0129] In a seventy-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_2-C_6 alkenyl (*e.g.*, C_2-C_6 alkenyl, C_2-C_4 alkenyl.; and including branched alkenyls such as, but not limited to, $-CH=CHCH_3$ and $-CH=C(CH_3)_2$), wherein:

when a C_2-C_6 alkenyl (*e.g.*, C_2-C_6 alkenyl, C_2-C_4 alkenyl) represented by **Z** is substituted, the C_2-C_6 alkenyl (*e.g.*, C_2-C_6 alkenyl, C_2-C_4 alkenyl) is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkoxy, a C_3-C_6 cycloalkyl and a 4- to 8-membered heterocyclyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0130] In a seventy-sixth embodiment, in a compound represented Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_2-C_6 alkynyl (*e.g.*, a C_2-C_6 alkynyl optionally substituted with one or more groups selected from halogen, –CN, –OH and C_1-C_2 alkoxy, etc.; and including, but not limited to, $-C\equiv CCH_3$)); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0131] In a seventy-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_3-C_6 cycloalkyl (*e.g.*, substituted cyclopropyl, unsubstituted cyclopropyl, substituted cyclobutyl, unsubstituted cyclobutyl); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0132] In a seventy-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_3-C_6 cycloalkyl (*e.g.*, substituted cyclopropyl, unsubstituted cyclopropyl, substituted cyclobutyl, unsubstituted cyclobutyl), wherein:

when a C_3-C_6 cycloalkyl represented by **Z** is substituted, the C_3-C_6 cycloalkyl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_6 alkyl (*e.g.*, $-CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_6 alkyl

substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl (*e.g.*, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$), C_1-C_6 alkoxy and phenyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0133] In a seventy-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted C_3-C_5 cycloalkyl (*e.g.*, substituted cyclopropyl, unsubstituted cyclopropyl, substituted cyclobutyl, unsubstituted cyclobutyl), wherein:

when a C_3-C_5 cycloalkyl represented by **Z** is substituted, the C_3-C_5 cycloalkyl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $-CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$), C_1-C_4 alkoxy and phenyl;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0134] In an eightieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted phenyl; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0135] In an eighty-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted phenyl, wherein:

when a phenyl represented by **Z** is substituted, the phenyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl (*e.g.*, $-CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl (*e.g.*, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$) and C_1-C_6 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0136] In an eighty-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted phenyl, wherein:

when a phenyl represented by **Z** is substituted, the phenyl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$) and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0137] In an eighty-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl (*e.g.*, a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted 2,5-dihydrofuranyl, a substituted or an unsubstituted 6-membered heterocyclyl containing a double bond and/or at least one oxygen atom (such as, a substituted or an unsubstituted 3,6-dihydro-2*H*-pyranyl and a substituted or an unsubstituted tetrahydro-2*H*-pyranyl), a substituted or an unsubstituted piperidinyl, and a substituted and an unsubstituted pyrrolidinyl); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0138] In an eighty-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl (*e.g.*, a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted 2,5-dihydrofuranyl, a substituted or an unsubstituted 6-membered heterocyclyl containing a double bond and/or at least one oxygen atom (such as, a substituted or an unsubstituted 3,6-dihydro-2*H*-pyranyl and a substituted or an unsubstituted tetrahydro-2*H*-pyranyl), a substituted or an unsubstituted piperidinyl), and a substituted and an unsubstituted pyrrolidinyl, wherein:

when a 4- to 10-membered heterocyclyl represented by **Z** is substituted, the 4- to 10-membered heterocyclyl is substituted with one or more groups each independently selected

from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_6 alkyl (*e.g.*, $–CH_3$), C_1-C_6 alkyl substituted with –OH, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$) and C_1-C_6 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0139] In an eighty-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl, or a substituted or an unsubstituted 4- to 8-membered heterocyclyl, or a substituted or an unsubstituted 5- to 6-membered heterocyclyl, or a substituted or an unsubstituted 5-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 5-membered heterocyclyl containing a ring nitrogen (such as a substituted and an unsubstituted pyrrolidinyl), a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted 2,5-dihydrofuranyl) or a substituted or an unsubstituted 6-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 6-membered heterocyclyl containing a double bond and/or at least one oxygen atom (such as, a substituted or an unsubstituted 3,6-dihydro-2*H*-pyranyl and a substituted or an unsubstituted tetrahydro-2*H*-pyranyl), a substituted or an unsubstituted piperidinyl), wherein:

when a 4- to 10-membered heterocyclyl, or a substituted or an unsubstituted 4- to 8-membered heterocyclyl, or a substituted or an unsubstituted 5- to 6-membered heterocyclyl, or a substituted or an unsubstituted 5-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 5-membered heterocyclyl containing a ring nitrogen (such as a substituted and an unsubstituted pyrrolidinyl), a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted 2,5-dihydrofuranyl) or a substituted or an unsubstituted 6-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 6-membered heterocyclyl containing a double bond and/or at least one oxygen atom (such as, a substituted or an unsubstituted 3,6-dihydro-2*H*-pyranyl and a substituted or an unsubstituted tetrahydro-2*H*-pyranyl), a substituted or an unsubstituted piperidinyl) represented by **Z** is substituted, the 4- to 10-membered heterocyclyl, or the 4- to 8-membered heterocyclyl, or the 5- to 6-membered heterocyclyl, or the 5-membered heterocyclyl (*e.g.*, a substituted or an unsubstituted 5-membered heterocyclyl containing a ring nitrogen (such as pyrrolidinyl, a tetrahydrofuranyl, a 2,5-dihydrofuranyl) or the 6-membered heterocyclyl (*e.g.*, a 6-membered heterocyclyl

containing a double bond and/or at least one oxygen atom (such as, 3,6-dihydro-2*H*-pyranyl and tetrahydro-2*H*-pyranyl) and piperidinyl) is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$) and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0140] In an eighty-sixth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl (*e.g.*, a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted 2,5-dihydrofuranyl, a substituted or an unsubstituted 6-membered heterocyclyl containing a double bond and/or at least one oxygen atom (such as, a substituted or an unsubstituted 3,6-dihydro-2*H*-pyranyl and a substituted or an unsubstituted tetrahydro-2*H*-pyranyl), a substituted or an unsubstituted piperidinyl, and a substituted and an unsubstituted pyrrolidinyl), wherein:

when a 4- to 10-membered heterocyclyl represented by **Z** is substituted, the 4- to 10-membered heterocyclyl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$) and C_1-C_4 alkoxy;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0141] In an eighty-seventh embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 5- to 10-membered heteroaryl (*e.g.*, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted imidazolyl, etc.); and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0142] In an eighty-eighth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 5- to 10-membered heteroaryl (*e.g.*, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted imidazolyl, etc.), wherein:

when a 5- to 10-membered heteroaryl represented by **Z** is substituted, the 5- to 10-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$), C_1-C_6 alkoxy and a 4- to 6-membered heterocyclyl (*e.g.*, oxetane);

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0143] In an eighty-ninth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 5- to 10-membered heteroaryl (*e.g.*, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted imidazolyl, etc.), wherein:

when a 5- to 10-membered heteroaryl represented by **Z** is substituted, the 5- to 10-membered heteroaryl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$), C_1-C_4 alkoxy and a 4- to 6-membered heterocyclyl (*e.g.*, oxetane);

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0144] In a ninetieth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is a substituted or an unsubstituted 5- to 10-membered heteroaryl, a substituted or an unsubstituted 5- to 8-membered heteroaryl, a substituted or an unsubstituted 5- or 6-

membered heteroaryl, a substituted or an unsubstituted 5-membered heteroaryl (*e.g.*, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted imidazolyl, etc.) or a substituted or an unsubstituted 6-membered heteroaryl (*e.g.*, substituted or unsubstituted pyridinyl), wherein:

when a 5- to 10-membered heteroaryl, a substituted or an unsubstituted 5- to 8-membered heteroaryl, a substituted or an unsubstituted 5- or 6-membered heteroaryl, a substituted or an unsubstituted 5-membered heteroaryl a substituted or an unsubstituted 6-membered heteroaryl represented by **Z** is substituted, the 5- to 10- membered heteroaryl, or the 5- to 8- membered heteroaryl, or the 5- or 6- membered heteroaryl, or the 5- membered heteroaryl or the 6-membered heteroaryl is substituted with one or more groups each independently selected from halogen (*e.g.*, F, Cl), –CN, –OH, C_1-C_4 alkyl (*e.g.*, $–CH_3$), C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl (*e.g.*, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CF_3$), C_1-C_4 alkoxy and a 4- to 6-membered heterocyclyl (*e.g.*, oxetane);

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0145] In a ninety-first embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, **Z** is hydrogen; and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0146] In a ninety-second embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, and unless specifically defined differently:

any C_1-C_6 alkyl includes C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.;

any C_1-C_4 alkyl includes C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.;

any C_1-C_3 alkyl includes C_1-C_3 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.;

any C_1-C_2 alkyl includes C_1-C_2 alkyl, methyl, ethyl, etc.;

any C_2-C_6 alkenyl includes C_2-C_6 alkenyl, C_2-C_4 alkenyl, C_2-C_3 alkenyl, etc.;

any C_2-C_4 alkenyl includes C_2-C_4 alkenyl, C_2-C_3 alkenyl, etc.;

any C_2-C_6 alkynyl includes C_2-C_6 alkynyl, C_2-C_4 alkynyl, C_2-C_3 alkynyl, etc.;

any C_2-C_4 alkynyl includes C_2-C_4 alkynyl, C_2-C_3 alkynyl, etc.;

any C_1-C_6 alkoxy includes C_1-C_6 alkoxy, C_1-C_4 alkoxy, C_1-C_3 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.;

any C_1-C_4 alkoxy includes C_1-C_4 alkoxy, C_1-C_3 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.;

any C_1-C_3 alkoxy includes C_1-C_3 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.;

any C_1-C_2 alkoxy includes C_1-C_2 alkoxy, methoxy, ethoxy, etc.;

any C_1-C_6 heteroalkyl (*e.g.*, $-(CH_2)_aO(CH_2)_bCH_3$, $-(CH_2)_aNH(CH_2)_bCH_3$, $-(CH_2)_aS(CH_2)_bCH_3$, where a and b are each an integer but are not both 0) includes C_1-C_6 heteroalkyl, C_1-C_4 heteroalkyl, C_1-C_3 heteroalkyl, C_1-C_2 heteroalkyl, etc.;

any C_1-C_4 heteroalkyl includes C_1-C_4 heteroalkyl, C_1-C_3 heteroalkyl, C_1-C_2 heteroalkyl, etc.;

any C_1-C_3 heteroalkyl includes C_1-C_3 heteroalkyl, C_1-C_2 heteroalkyl, etc.;

any C_3-C_6 cycloalkyl includes C_3-C_6 cycloalkyl, C_4-C_6 cycloalkyl, C_3-C_5 cycloalkyl, C_3 or C_4 cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.;

any C_4-C_6 cycloalkyl includes C_4-C_6 cycloalkyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.;

any C_3-C_5 cycloalkyl includes C_3-C_5 cycloalkyl, C_3 or C_4 cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, etc.;

any C_3 or C_4 cycloalkyl includes cyclopropyl or cyclobutyl;

any 6- or 10-membered aryl includes 6- or 10-membered aryl, phenyl, etc.;

any 4- to 10-membered heterocyclyl includes 4- to 10-membered heterocyclyl, 4- to 9-membered heterocyclyl, 4- to 8-membered heterocyclyl, 5- to 10-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- or 6-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 4- to 9-membered heterocyclyl includes 4- to 9-membered heterocyclyl, 4- to 8-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5-

or 6-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 5- to 10-membered heterocyclyl includes 5- to 10-membered heterocyclyl, 4- to 9-membered heterocyclyl. 4- to 8-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- or 6-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 5- to 9-membered heterocyclyl includes 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- or 6-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 5- to 8-membered heterocyclyl includes 5- to 8-membered heterocyclyl, 5- or 6-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 7- to 9-membered heterocyclyl includes 7- to 9-membered heterocyclyl, 7- to 9-membered spiro heterocyclyl, 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, 9-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 7- or 8-membered heterocyclyl includes 7- or 8-membered heterocyclyl, 7- or 8-membered spiro heterocyclyl, 7-membered spiro heterocyclyl, 8-membered spiro heterocyclyl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 5- to 10-membered heteroaryl includes 5- to 10-membered heteroaryl, 5- to 8-membered heteroaryl, 5- or 6-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

any 5- to 8-membered heteroaryl includes 5- to 8-membered heteroaryl, 5- or 6-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, etc., each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms; and

any 5- or 6-membered heteroaryl includes 5- or 6-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, each of which containing, for example, 1, 2, 3 or 4 nitrogen atoms;

and all other variables are as defined in any one of the first through ninety-fifth embodiments.

[0147] In a ninety-third embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt thereof, and unless specifically defined differently, any group including any of the groups described in the ninety-second embodiment that is substituted can be substituted with one or more groups selected from:

halogen (including *e.g.*, F, Cl, Br, etc.);

–CN;

–OH;

C_1-C_6 alkyl (including *e.g.*, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.);

C_1-C_6 heteroalkyl (including *e.g.*, C_1-C_6 heteroalkyl, C_1-C_4 heteroalkyl, C_1-C_2 alkyl, etc.);

C_1-C_6 haloalkyl (including *e.g.*, C_1-C_6 haloalkyl, C_1-C_4 haloalkyl, C_1-C_2 haloalkyl, halomethyl, haloethyl, etc.);

C_1-C_6 alkyl (including *e.g.*, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.) substituted with C_1-C_6 alkoxy (including *e.g.*, C_1-C_6 alkoxy, C_1-C_4 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.);

C_1-C_6 alkoxy (including *e.g.*, C_1-C_6 alkoxy, C_1-C_4 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.);

C_1-C_6 haloalkoxy (including *e.g.*, C_1-C_6 haloalkoxy, C_1-C_4 haloalkoxy, C_1-C_2 haloalkoxy, halomethoxy, haloethoxy, etc.); and

C_3-C_6 cycloalkyl (including *e.g.*, C_3-C_6 cycloalkyl, C_4-C_6 cycloalkyl, C_3-C_5 cycloalkyl, C_3 or C_4 cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.).

[0148] In a ninety-fourth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, and unless specifically defined differently, any group including any of the groups described in the ninety-second embodiment that is substituted can be substituted with one or more groups selected from:

halogen (including *e.g.*, F, Cl, Br, etc.);

–CN;

–OH;

C_1-C_6 alkyl (including *e.g.*, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.);

C_1-C_6 haloalkyl (including *e.g.*, C_1-C_6 haloalkyl, C_1-C_4 haloalkyl, C_1-C_2 haloalkyl, halomethyl, haloethyl, etc.);

C_1-C_6 alkyl (including *e.g.*, C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, methyl, ethyl, etc.) substituted with C_1-C_6 alkoxy (including *e.g.*, C_1-C_6 alkoxy, C_1-C_4 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.); and

C_1-C_6 alkoxy (including *e.g.*, C_1-C_6 alkoxy, C_1-C_4 alkoxy, C_1-C_2 alkoxy, methoxy, ethoxy, etc.).

[0149] In a ninety-fifth embodiment, in a compound represented by Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or a pharmaceutically acceptable salt of any of the foregoing, and unless specifically defined differently, any group including any of the groups described in the ninety-second embodiment that is substituted can be substituted with one or more groups selected from:

halogen (including *e.g.*, F, Cl, Br, etc.);

–CN;

–OH;

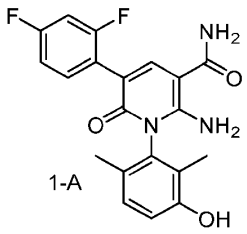
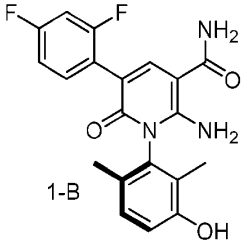
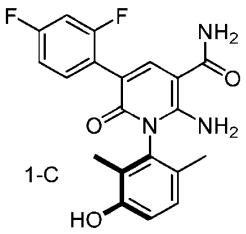
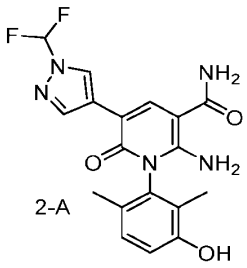
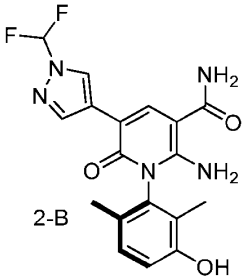
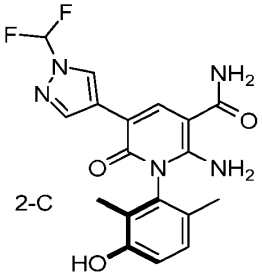
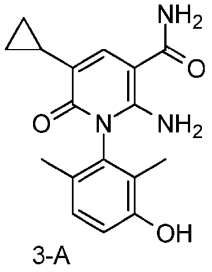
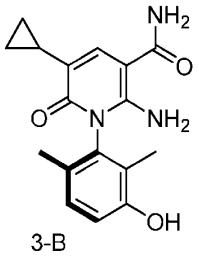
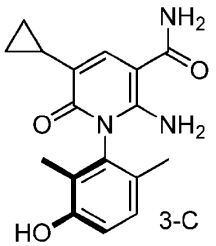
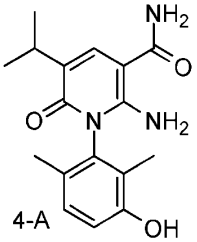
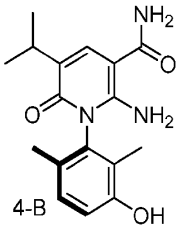
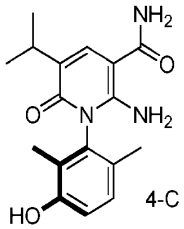
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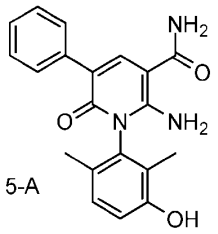
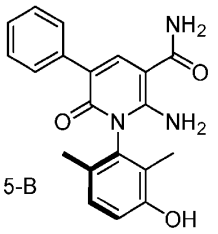
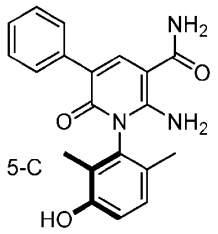
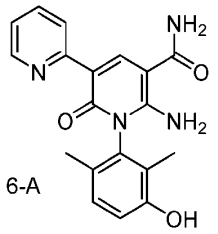
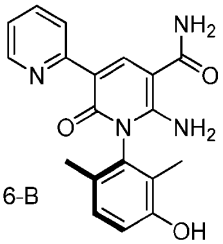
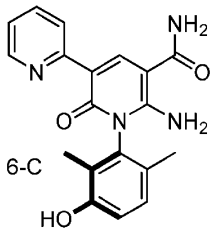
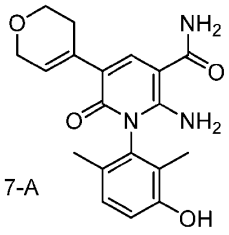
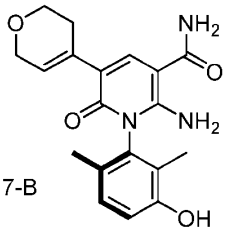
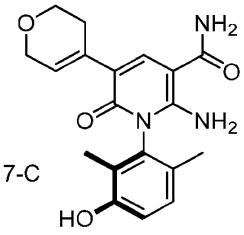
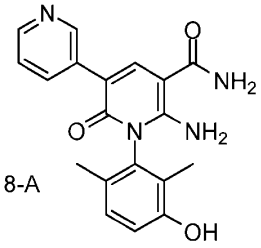
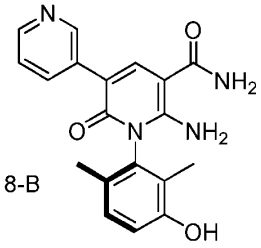
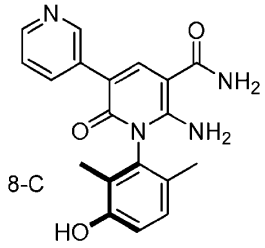
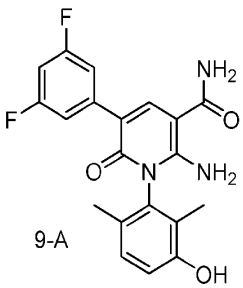
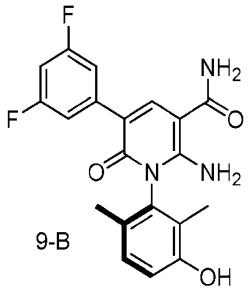
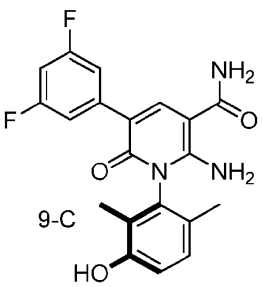
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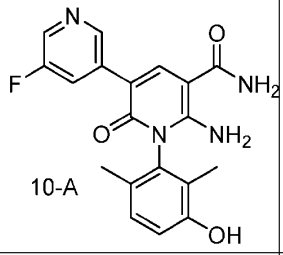
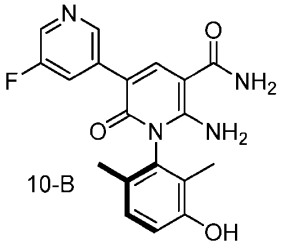
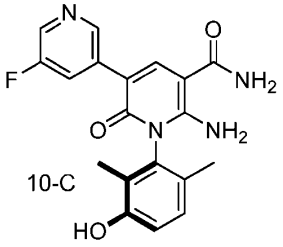
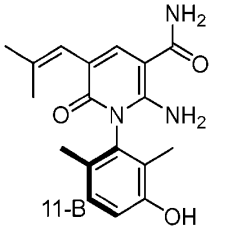
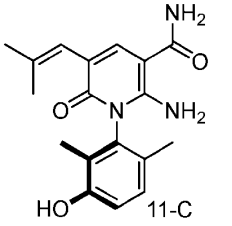
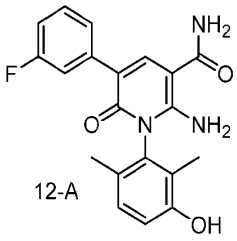
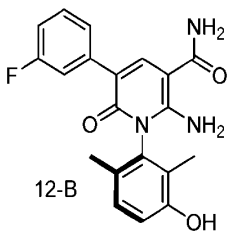
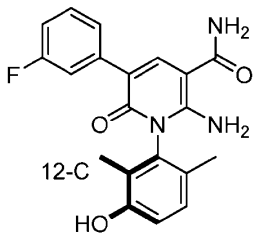
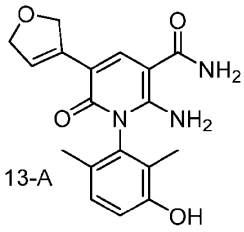
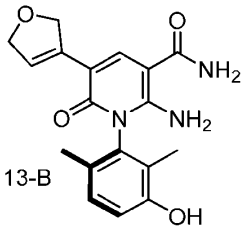
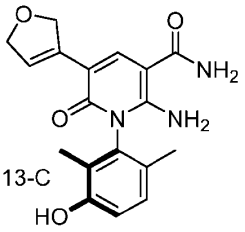
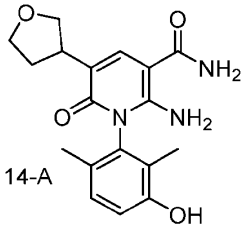
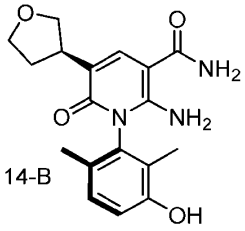
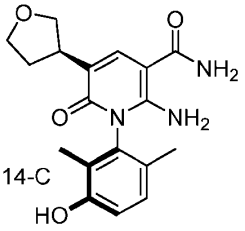
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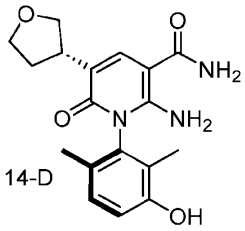
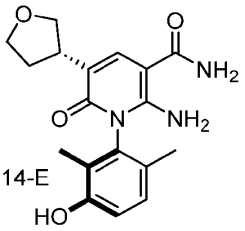
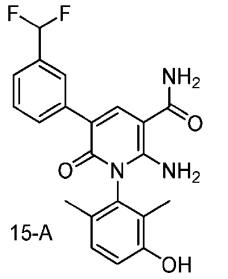
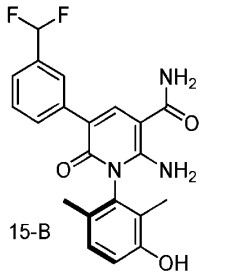
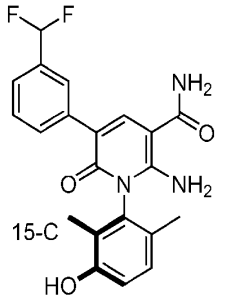
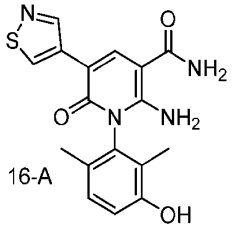
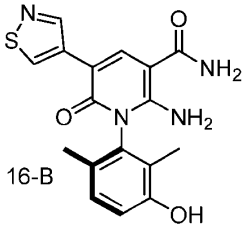
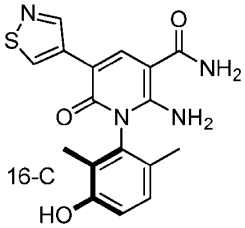
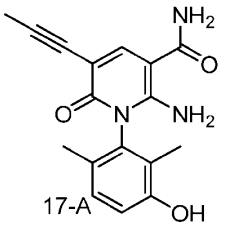
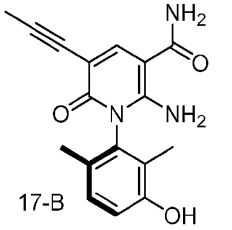
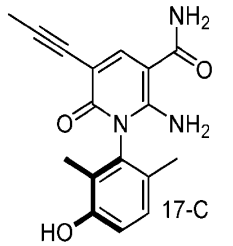
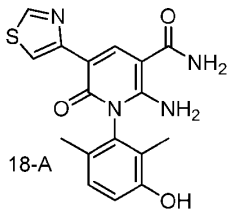
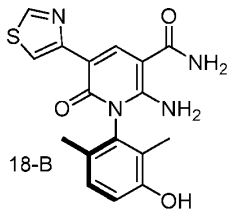
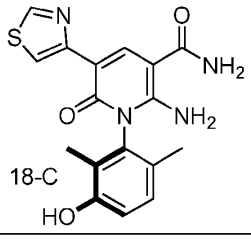
[0150] Various embodiments provide a compound (*e.g.*, a compound of Formula (I)), wherein the compound has a structure selected from those of Compound Nos. 1-A to 61-C, as listed in the following Table 1, or a pharmaceutically acceptable salt thereof:

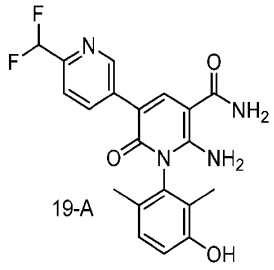
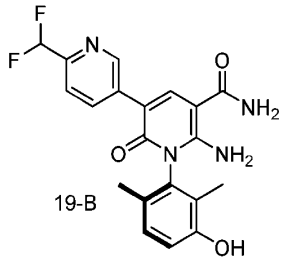
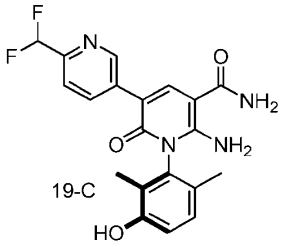
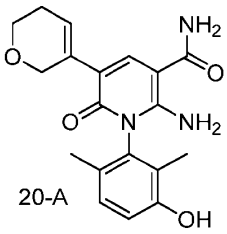
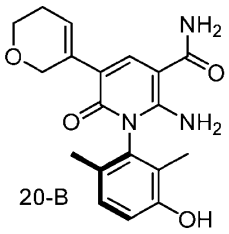
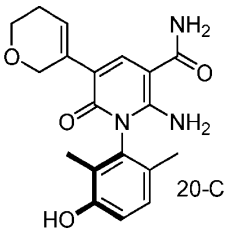
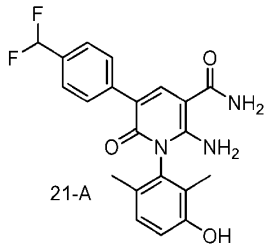
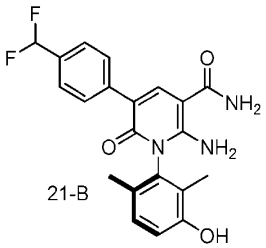
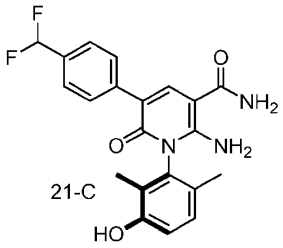
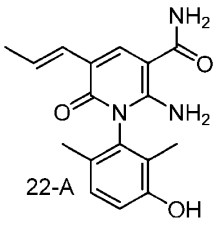
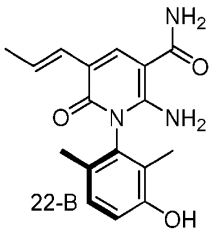
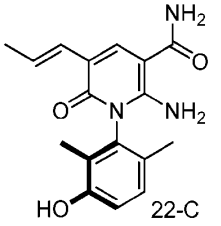
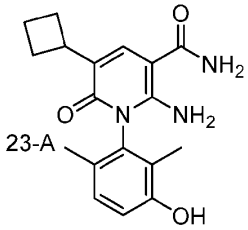
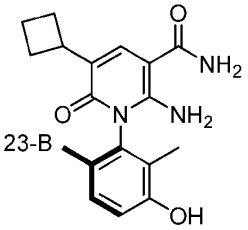
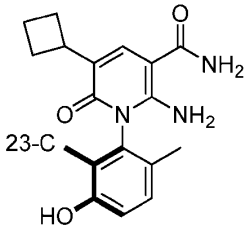
Table 1. Exemplary Compound Nos. 1-A to 61-C.

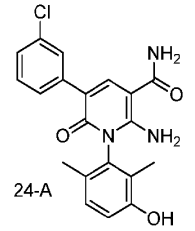
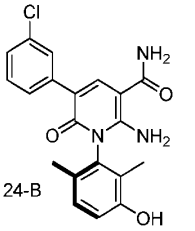
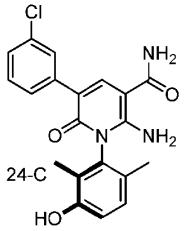
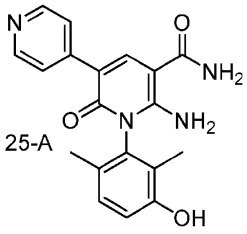
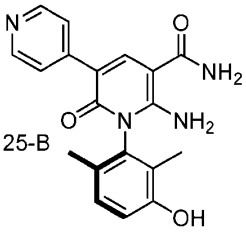
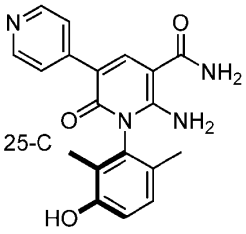
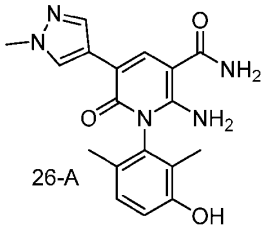
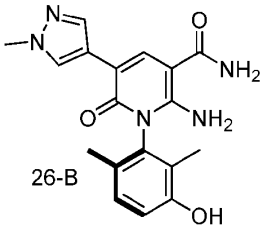
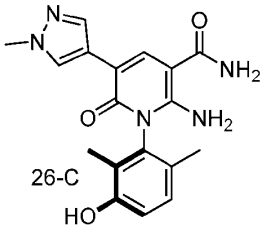
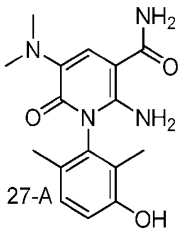
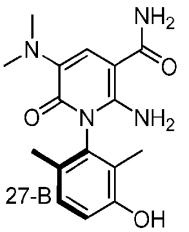
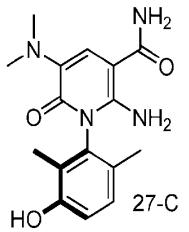
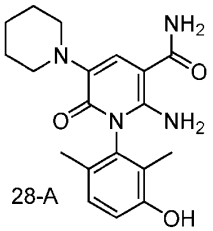
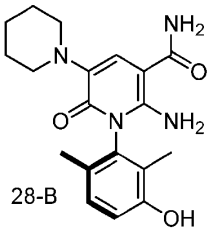
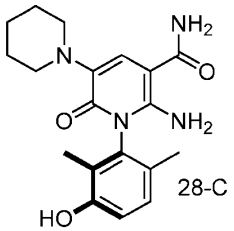
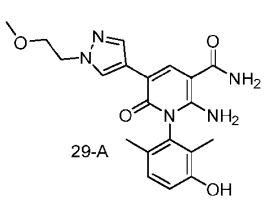
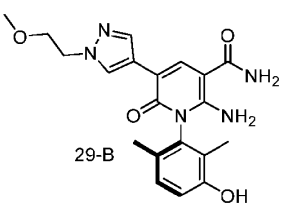
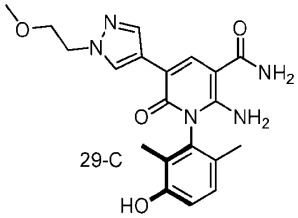
No.	Structure	Structure	Structure
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2-A 2-B 2-C			
3-A 3-B 3-C			
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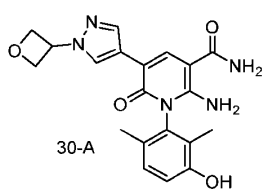
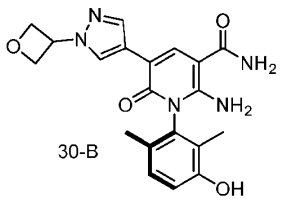
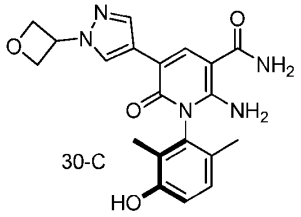
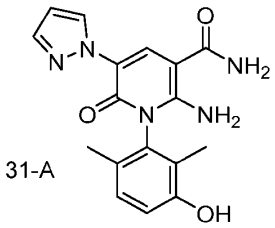
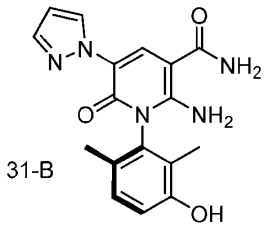
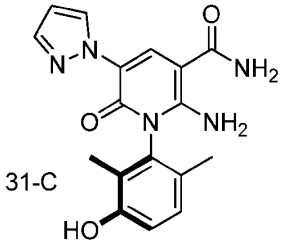
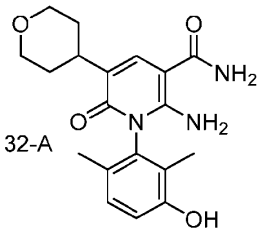
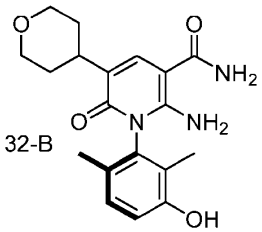
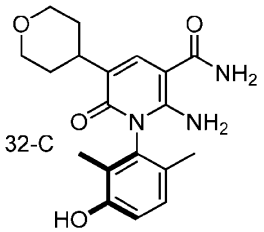
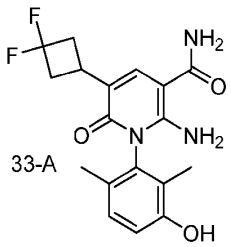
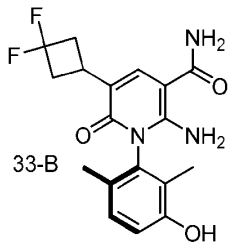
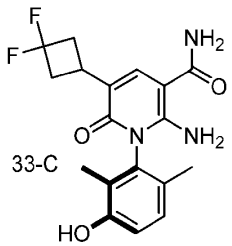
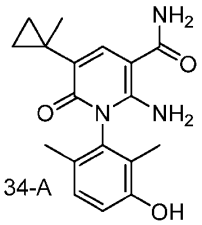
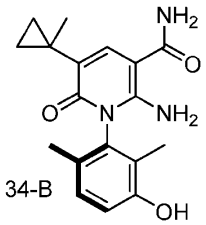
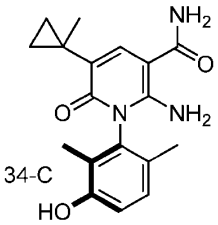
No.	Structure	Structure	Structure
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6-A 6-B 6-C			
7-A 7-B 7-C			
8-A 8-B 8-C			
9-A 9-B 9-C			

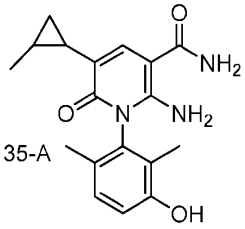
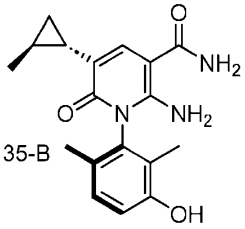
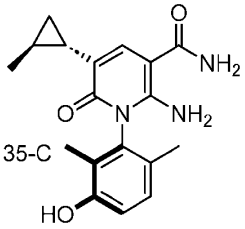
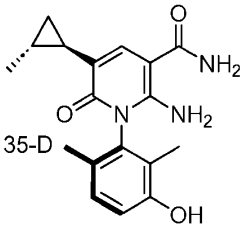
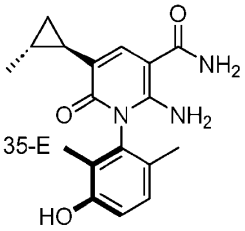
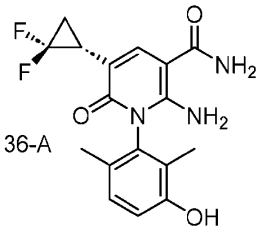
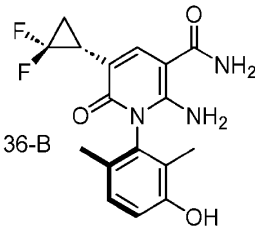
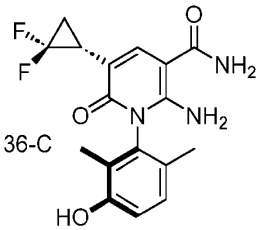
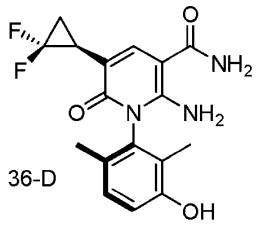
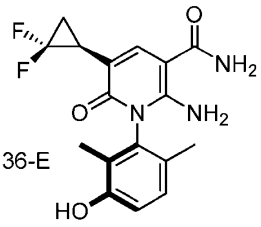
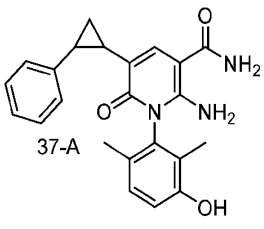
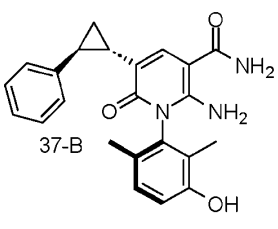
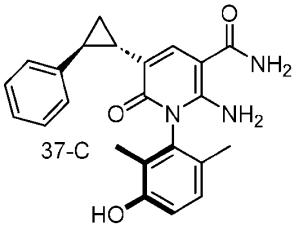
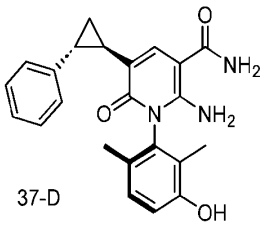
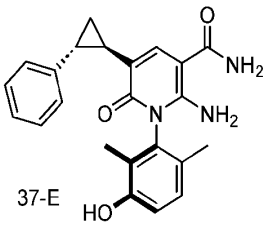
No.	Structure	Structure	Structure
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11-A 11-B 11-C			
12-A 12-B 12-C			
13-A 13-B 13-C			
14-A 14-B 14-C			

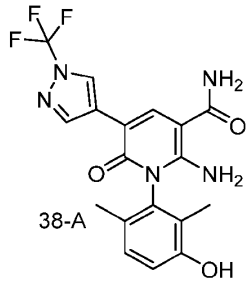
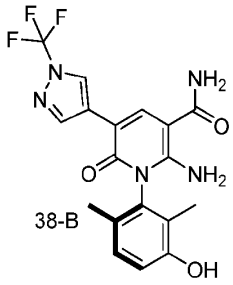
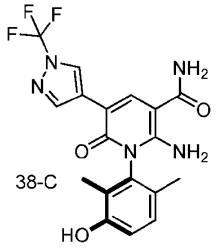
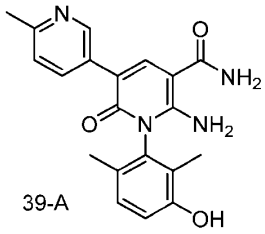
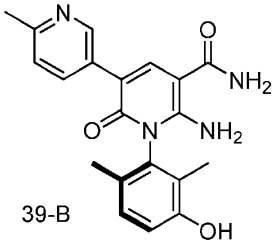
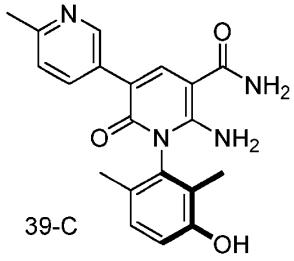
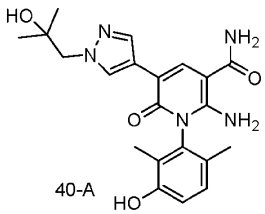
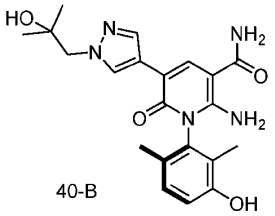
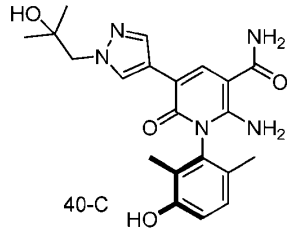
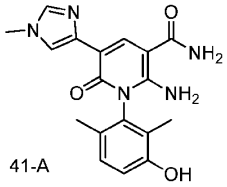
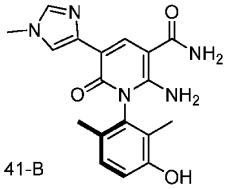
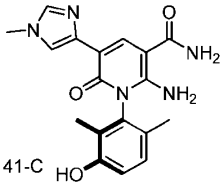
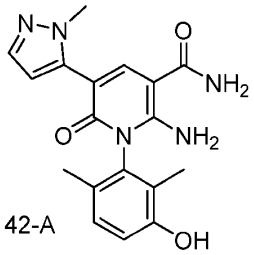
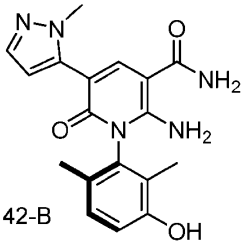
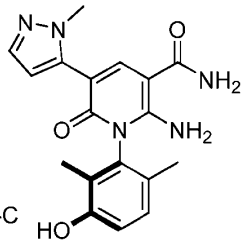
No.	Structure	Structure	Structure
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15-A 15-B 15-C			
16-A 16-B 16-C			
17-A 17-B 17-C			
18-A 18-B 18-C			

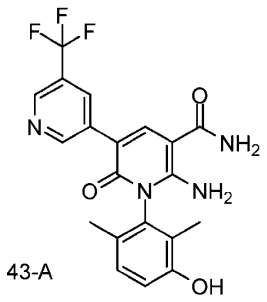
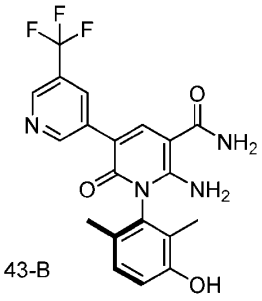
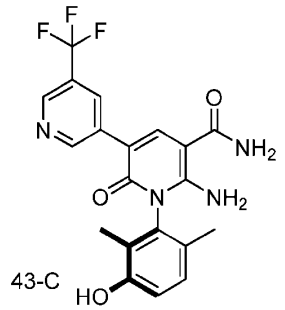
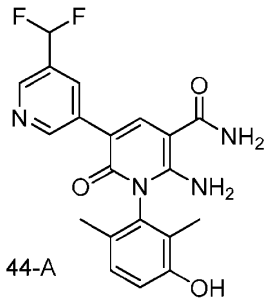
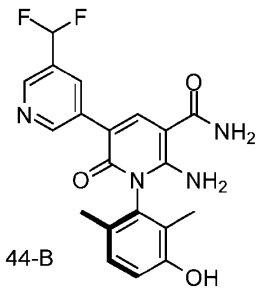
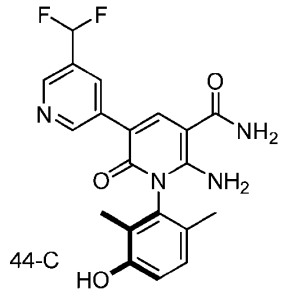
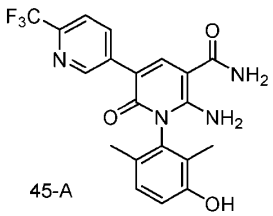
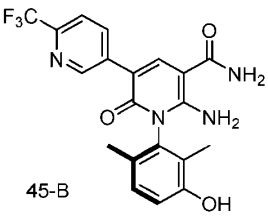
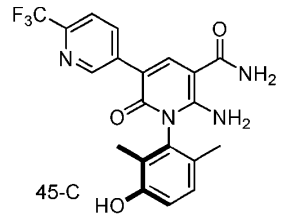
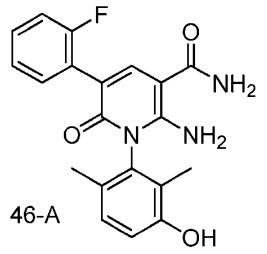
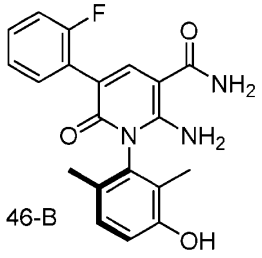
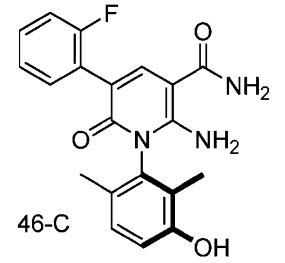
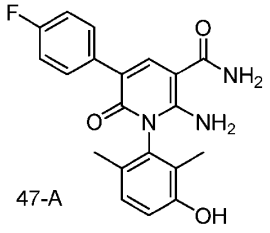
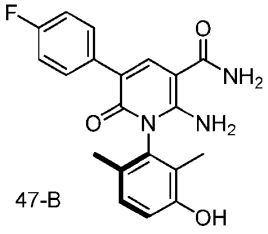
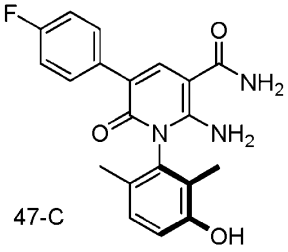
No.	Structure	Structure	Structure
19-A 19-B 19-C			
20-A 20-B 20-C			
21-A 21-B 21-C			
22-A 22-B 22-C			
23-A 23-B 23-C			

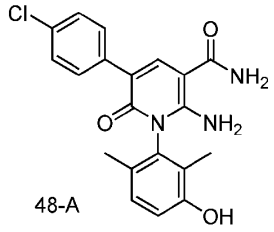
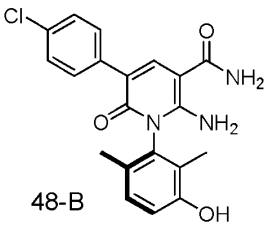
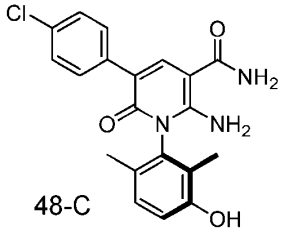
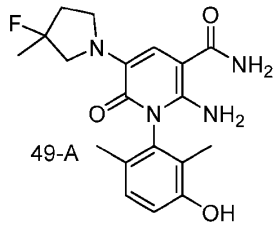
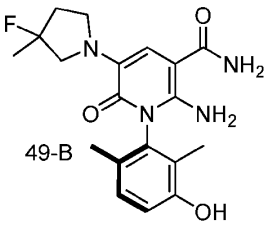
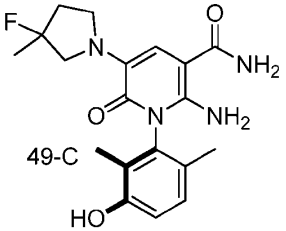
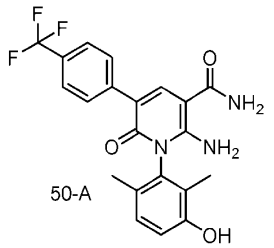
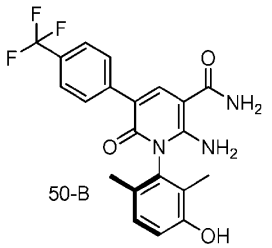
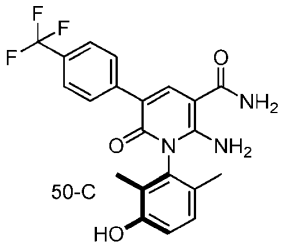
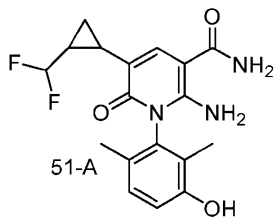
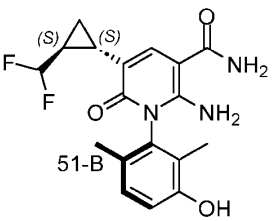
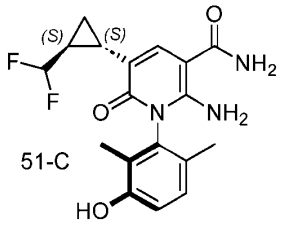
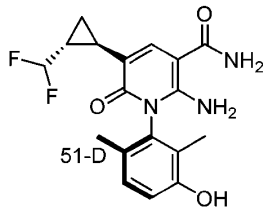
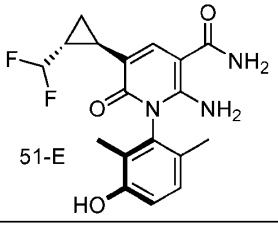
No.	Structure	Structure	Structure
24-A 24-B 24-C			
25-A 25-B 25-C			
26-A 26-B 26-C			
27-A 27-B 27-C			
28-A 28-B 28-C			
29-A 29-B 29-C			

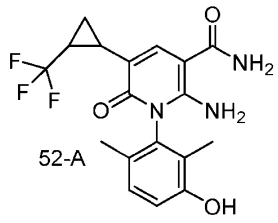
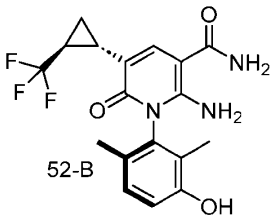
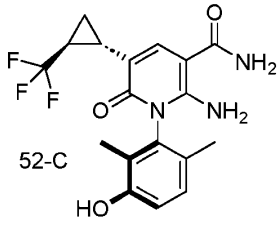
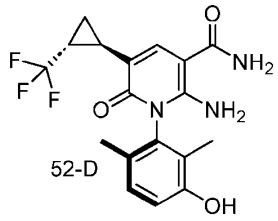
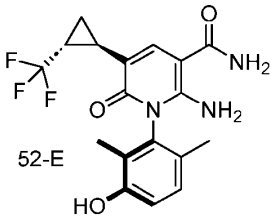
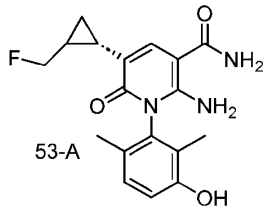
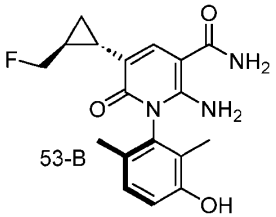
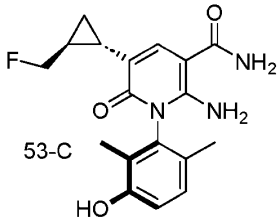
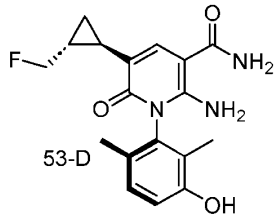
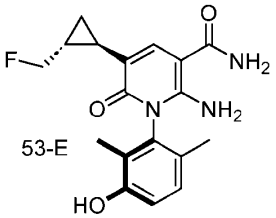
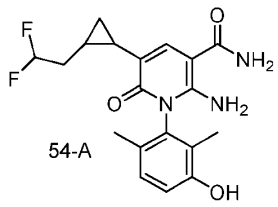
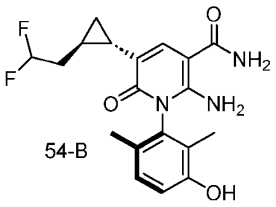
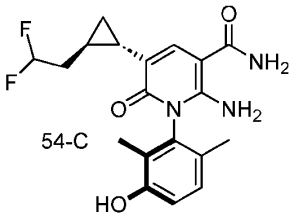
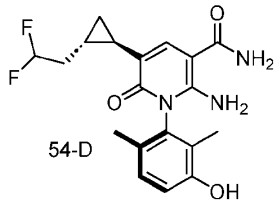
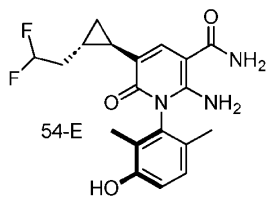
No.	Structure	Structure	Structure
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31-A 31-B 31-C			
32-A 32-B 32-C			
33-A 33-B 33-C			
34-A 34-B 34-C			

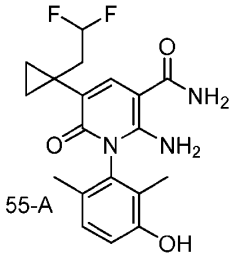
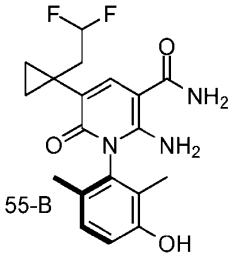
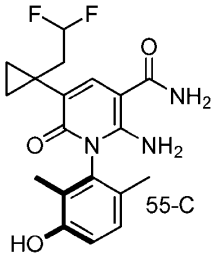
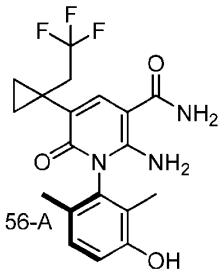
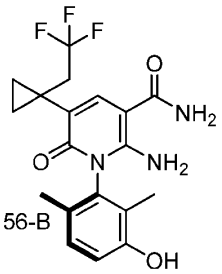
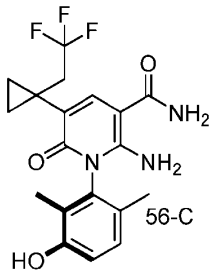
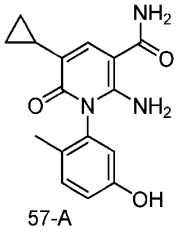
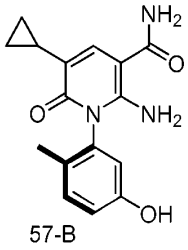
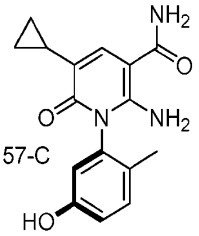
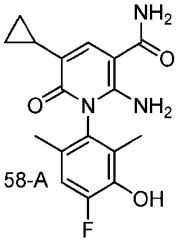
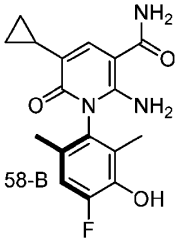
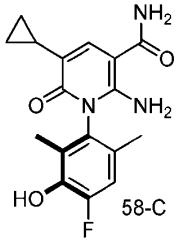
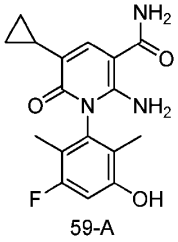
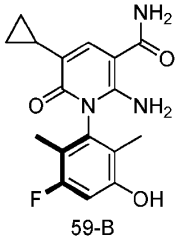
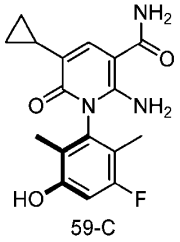
No.	Structure	Structure	Structure
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35-D 35-E			
36-A 36-B 36-C			
36-D 36-E			
37-A 37-B 37-C			
37-D 37-E			

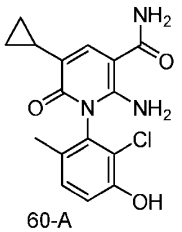
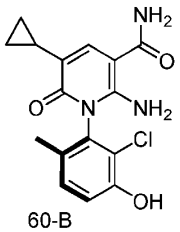
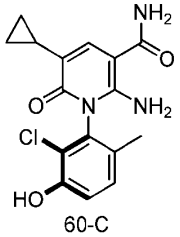
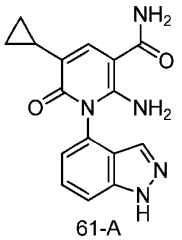
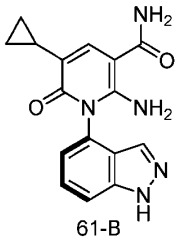
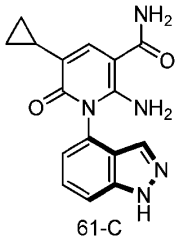
No.	Structure	Structure	Structure
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39-A 39-B 39-C			
40-A 40-B 40-C			
41-A 41-B 41-C			
42-A 42-B 42-C			

No.	Structure	Structure	Structure
43-A 43-B 43-C			
44-A 44-B 44-C			
45-A 45-B 45-C			
46-A 46-B 46-C			
47-A 47-B 47-C			

No.	Structure	Structure	Structure
48-A 48-B 48-C			
49-A 49-B 49-C			
50-A 50-B 50-C			
51-A 51-B 51-C			
51-D 51-E			

No.	Structure	Structure	Structure
52-A 52-B 52-C			
52-D 52-E			
53-A 53-B 53-C			
53-D 53-E			
54-A 54-B 54-C			
54-D 54-E			

No.	Structure	Structure	Structure
55-A 55-B 55-C			
56-A 56-B 56-C			
57-A 57-B 57-C			
58-A 58-B 58-C			
59-A 59-B 59-C			

No.	Structure	Structure	Structure
60-A 60-B 60-C	 60-A	 60-B	 60-C
61-A 61-B 61-C	 61-A	 61-B	 61-C

Synthesis

[0151] Compounds of the Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or pharmaceutically acceptable salts of any of the foregoing, can be made in various ways by those skilled using known techniques as guided by the detailed teachings provided herein, including the Examples provided below. For example, in an embodiment, compounds of the Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, (including pharmaceutically acceptable salts of any of the foregoing) are prepared in accordance with the procedures illustrated in General Scheme 1, and schemes provided in the intermediate and compound examples herein. Any preliminary reaction steps required to form starting compounds or other precursors can be carried out by those skilled in the art, for example by appropriate adjustment of the reagents and conditions described in the Examples. In General Scheme 1, the variables including $\mathbf{Y^1}$, $\mathbf{Y^2}$, **Z**, $\mathbf{R^A}$, $\mathbf{R^B}$, $\mathbf{R^C}$, $\mathbf{R^D}$, $\mathbf{R^E}$, $\mathbf{R^F}$, $\mathbf{R^G}$, $\mathbf{R^1}$ through $\mathbf{R^{36}}$, **m, n**, **p**, **q**, and **r** are as defined herein can be as described elsewhere herein, taking into consideration the synthetic conversions involved as understood by those of skill in the art.

Pharmaceutical Compositions

[0152] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0153] The term "pharmaceutical composition" refers to a mixture of one or more compounds and/or salts disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0154] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound nor cause appreciable damage or injury to an animal to which delivery of the composition is intended.

[0155] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0156] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0157] As used herein, an "excipient" refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency,

stability, binding ability, lubrication, disintegrating ability etc., to the composition. For example, stabilizers such as anti-oxidants and metal-chelating agents are excipients. In an embodiment, the pharmaceutical composition comprises an anti-oxidant and/or a metal-chelating agent. A "diluent" is a type of excipient.

[0158] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0159] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0160] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, can be administered orally.

[0161] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0162] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Uses and Methods of Treatment

[0163] Some embodiments described herein relate to a method for ameliorating and/or treating a cancer described herein that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) in the manufacture of a medicament for ameliorating and/or treating a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition

that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) for ameliorating and/or treating a cancer described herein.

[0164] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor that can include contacting the growth or the tumor with an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing), wherein the malignant growth or tumor is due to a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0165] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a malignant growth or a tumor with an effective amount of a compound described herein (for example, a compound of

Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) in the manufacture of a medicament for ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) for ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0166] Some embodiments described herein relate to a method for inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells) that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) to a cancer cell from a cancer

described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) for inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells). Some embodiments described herein relate to a method for inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells) that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) to a cancer cell from a cancer described herein. Other embodiments described herein relate to a method for inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells) that can include contacting a cancer cell from a cancer described herein with an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa),

or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing), and thereby inhibiting the activity of PKMYT1.

[0167] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells) using an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) in the manufacture of a medicament for ameliorating or treating a cancer described herein by inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) for ameliorating or treating a cancer described herein by inhibiting the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1

CCNE1-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells). Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a cancer cell with an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing), wherein the compound inhibits the activity of PKMYT1 (for example, inhibiting the activity in PKMYT1 *CCNE1*-overexpressing or *CCNE1*-amplified cells and/or decreasing the overexpression of PKMYT1 in cells).

[0168] Some embodiments disclosed herein relate to a method for inhibiting the activity of PKMYT1 that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) to a subject having a cancer described herein or a cancer cell from a cancer described herein. Other embodiments disclosed herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) in the manufacture of a medicament for inhibiting the activity of PKMYT1. Still other embodiments disclosed herein relate to a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound

of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt thereof) for inhibiting the activity of PKMYT1.

[0169] Examples of suitable cancers include, but are not limited to: brain cancers, cervicocerebral cancers, esophageal cancers, thyroid cancers, small cell cancers, non-small cell cancers, breast cancers, lung cancers (for example non-small cell lung cancer and small cell lung cancer), stomach cancers, gallbladder/bile duct cancers, liver cancers, pancreatic cancers, colon cancers, rectal cancers, ovarian cancers, choriocarcinomas, uterus body cancers, uterocervical cancers, renal pelvis/ureter cancers, bladder cancers, prostate cancers, penis cancers, testicular cancers, fetal cancers, Wilms' cancer, skin cancers, malignant melanoma, neuroblastomas, osteosarcomas, Ewing's tumors, soft part sarcomas, acute leukemia, chronic lymphatic leukemias, chronic myelocytic leukemias, polycythemia vera, malignant lymphomas, multiple myeloma, Hodgkin's lymphomas and non-Hodgkin's lymphomas.

[0170] As described herein, a cancer can become resistant to one or more anti-cancer agents. In some embodiments, a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing) can be used to treat and/or ameliorate a cancer that has become resistant to one or more anti-cancer agents (such as one or more PKMYT1 inhibitors). Examples of anti-cancer agents that a subject may have developed resistance to include, but are not limited to, PKMYT1 inhibitors (such as RP-6306 or lunresertib, including pharmaceutically acceptable salts of any of the foregoing). In some embodiments, the cancer that has become resistant to one or more anti-cancer agents can be a cancer described herein.

[0171] Several known PKMYT1 inhibitors can cause one or more undesirable side effects in the subject being treated. Examples of undesirable side effects include, but are not limited to, thrombocytopenia, neutropenia, anemia, diarrhea, vomiting, nausea, abdominal pain, and constipation. In some embodiments, a compound described herein (for example, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C,

or a pharmaceutically acceptable salt of any of the foregoing) can decrease the number and/or severity of one or more side effects associated with a known PKMYT1 inhibitor. In some embodiments, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, can result in a severity of a side effect (such as one of those described herein) that is 25% less than compared to the severity of the same side effect experienced by a subject receiving a known PKMYT1 inhibitor (such as RP-6306, 1*H*-Pyrrolo[2,3-*b*]pyridine-3-carboxamide, 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5,6-dimethyl-, (1*S*) or (1*S*)-2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5,6-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (including pharmaceutically acceptable salts of any of the foregoing)). In some embodiments, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, results in a number of side effects that is 25% less than compared to the number of side effects experienced by a subject receiving a known PKMYT1 inhibitor (for example, RP-6306). In some embodiments, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, results in a severity of a side effect (such as one of those described herein) that is less in the range of about 10% to about 30% compared to the severity of the same side effect experienced by a subject receiving a known PKMYT1 inhibitor (such as RP-6306). In some embodiments, a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, results in a number of side effects that is in the range of about 10% to about 30% less than compared to the number of side effects experienced by a subject receiving a known PKMYT1 inhibitor (for example, RP-6306, or a pharmaceutically acceptable salt thereof).

[0172] The one or more compounds of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, that can be used to treat, ameliorate and/or inhibit the growth of a cancer wherein inhibiting the activity of PKMYT1 is beneficial is provided in any of the embodiments described under the heading titled "Compounds" above.

[0173] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates

and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human. In some embodiments, the subject can be a child (*i.e.*, $\geq$ 1 year and < 18 years old) and/or an infant (*i.e.*, < 1 year old), for example, a child or infant with a fever. In other embodiments, the subject can be an adult (*i.e.*, $\geq$ 18 years old).

[0174] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of the disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject's overall feeling of well-being or appearance.

[0175] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, which elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound, salt or composition can be the amount needed to prevent, alleviate or ameliorate symptoms of the disease or condition, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease or condition being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0176] For example, an effective amount of a compound, or radiation, is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor. In the treatment of lung cancer (such as non-small cell lung cancer) a therapeutically effective amount is that

amount that alleviates or eliminates cough, shortness of breath and/or pain. As another example, an effective amount, or a therapeutically effective amount of an PKMYT1 inhibitor and/or degrader is the amount which results in the reduction in PKMYT1 activity and/or phosphorylation (such as phosphorylation of CDC2). The reduction in PKMYT1 activity is known to those skilled in the art and can be determined by the analysis of PKMYT1 intrinsic kinase activity and downstream substrate phosphorylation.

[0177] The amount of the compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or a pharmaceutically acceptable salt of any of the foregoing, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive diseases or conditions.

[0178] In general, however, a suitable dose will often be in the range of from about 0.05 mg/kg to about 10 mg/kg. For example, a suitable dose may be in the range from about 0.10 mg/kg to about 7.5 mg/kg of body weight per day, such as about 0.15 mg/kg to about 5.0 mg/kg of body weight of the recipient per day, about 0.2 mg/kg to 4.0 mg/kg of body weight of the recipient per day, or any amount in between. The compound may be administered in unit dosage form; for example, containing 1 to 500 mg, 10 to 100 mg, 5 to 50 mg or any amount in between, of active ingredient per unit dosage form.

[0179] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[0180] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, the mammalian species treated, the particular

compounds employed and the specific use for which these compounds are employed. The determination of effective dosage levels, which is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example, useful dosages of a compound of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C, or pharmaceutically acceptable salts of any of the foregoing, can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as cisplatin and/or gemcitabine)

[0181] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0182] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the disease or condition to be treated and to the route of administration. The severity of the disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency will also vary according to the age, body weight and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0183] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be

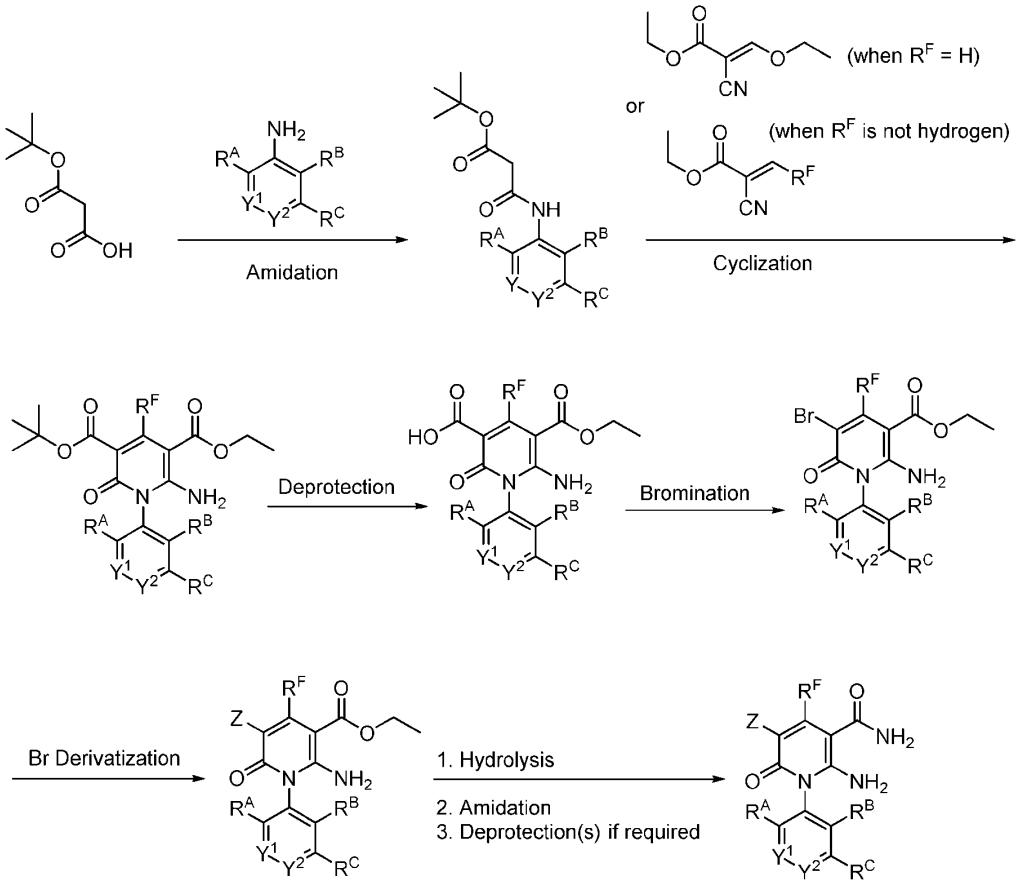
established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

EXAMPLES

[0184] The compounds of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C (including pharmaceutically acceptable salts of any of the foregoing) as described herein are prepared using General Scheme 1, wherein variables $\mathbf{Y^1}$, $\mathbf{Y^2}$, **Z**, $\mathbf{R^A}$, $\mathbf{R^B}$, $\mathbf{R^C}$, $\mathbf{R^D}$, $\mathbf{R^E}$, $\mathbf{R^F}$, $\mathbf{R^G}$, $\mathbf{R^1}$ through $\mathbf{R^{36}}$, **m**, **n**, **p**, **q**, and **r** are as defined herein. A person having ordinary skill in the art would readily appreciate that synthesis of the compounds of Formula (I'), (I'a), (I), (II), (IIa), (III), (IIIa), or Compound Nos. 1-A to 61-C (including pharmaceutically acceptable salts of any of the foregoing), each having a pyridinone core, would involve different intermediate synthesis, functionalization steps, and reagents from the synthesis of pyridine, pyrimidine, and phenol analogs, including, but not limited to, the compounds as described in International Patent Application Publication No. WO 2023/220831.

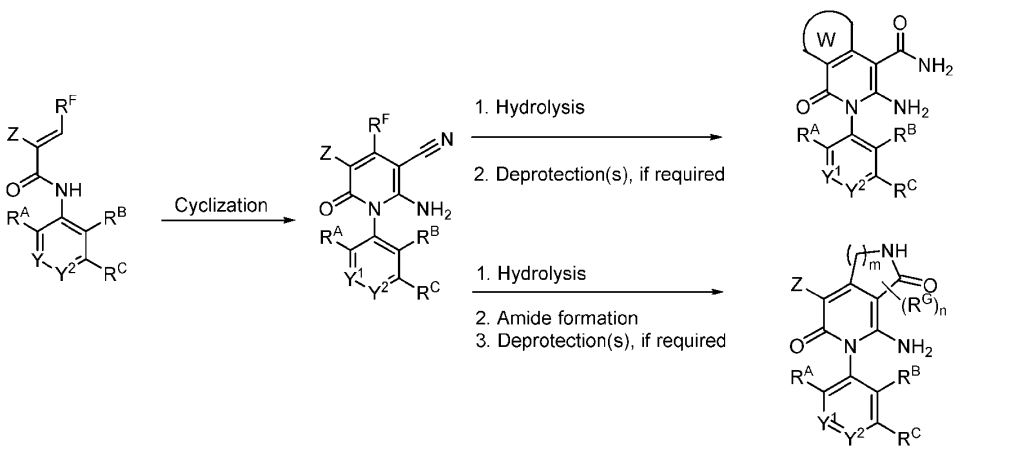
General Scheme 1

(Formula (I') when **Z** and $\mathbf{R^F}$ or **Z** and –$CONH_2$ do not cyclize)



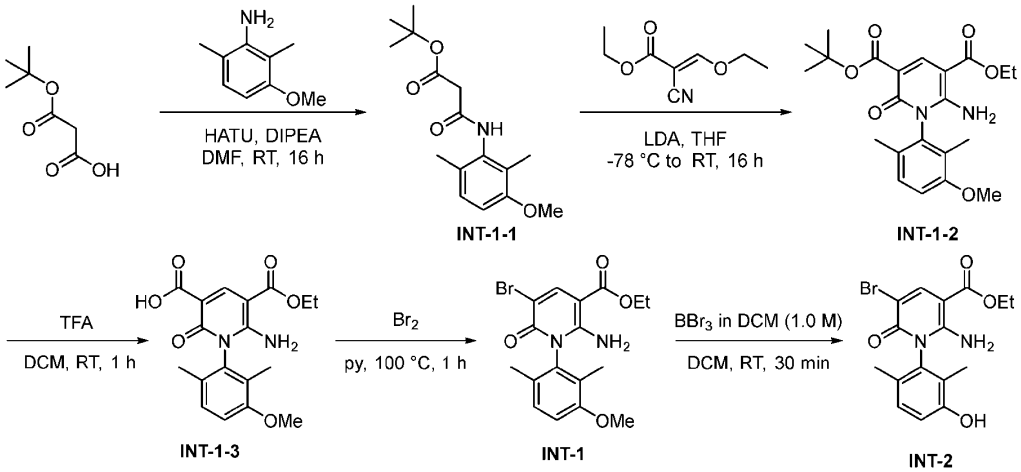
General Scheme 2

(Formula (I') when **Z** and $\mathbf{R^F}$ or **Z** and –$CONH_2$ cyclize as defined in Formula (I'); or Formula (I'a))



Intermediate 1 and Intermediate 2

Ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-1**) and ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**)



Preparation of *tert*-butyl 3-((3-methoxy-2,6-dimethylphenyl)amino)-3-oxopropanoate (**INT-1-1**)

[0185] To a stirred mixture of 3-(*tert*-butoxy)-3-oxopropanoic acid (20.0 g, 125 mmol) and 3-methoxy-2,6-dimethylaniline (18.9 g, 125 mmol) in DMF (200 mL), were added DIPEA (69.0 mL, 375 mmol) and HATU (57.0 g, 150 mmol) at room temperature (rt). After stirring at rt for 16 h, the mixture was diluted with ice water (100 mL) and extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to give *tert*-butyl 3-((3-methoxy-2,6-dimethylphenyl)amino)-3-oxopropanoate (**INT-2-1**) (22.0 g, 60%). MS (ESI) m/z: 238.16 $[M-56]^+$.

Preparation of 3-(*tert*-butyl) 5-ethyl 6-amino-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**INT-1-2**)

[0186] To a stirred mixture of *tert*-butyl 3-((3-methoxy-2,6-dimethylphenyl)amino)-3-oxopropanoate (**INT-2-1**) (22.0 g, 74.9 mmol) in THF (250 mL) at -78 °C, was added LDA (2M in THF, 37.5 mL, 75.0 mmol). The mixture was stirred at -78 °C for 1 h, and a solution of ethyl (*E*)-2-cyano-3-ethoxyacrylate (13.9 g, 82.5 mmol) in THF (80 mL) added at -78 °C. After gradually warming up to rt and stirring at rt for 16 h, the mixture was quenched with aq. NH_4Cl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford 3-(*tert*-butyl) 5-ethyl 6-amino-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**INT-2-2**) (28.0 g, 89%). MS (ESI) m/z: 417.4 $[M+H]^+$.

Preparation of 6-amino-5-(ethoxycarbonyl)-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**INT-1-3**)

[0187] To a stirred mixture of 3-(*tert*-butyl) 5-ethyl 6-amino-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate (**INT-1-2**) (28.0 g, 67.2 mmol) in DCM (280 mL) was added TFA (16.4 mL, 202 mmol) at rt. After stirring at rt for 2 h, it was quenched with saturated $NaHCO_3$ (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 6-amino-5-(ethoxycarbonyl)-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-

1,2-dihydropyridine-3-carboxylic acid (**INT-2-3**) (20.0 g, crude), which was used directly for the next step without further purification. MS (ESI) m/z: 361.3 $[M+H]^+$.

Preparation of ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-1**)

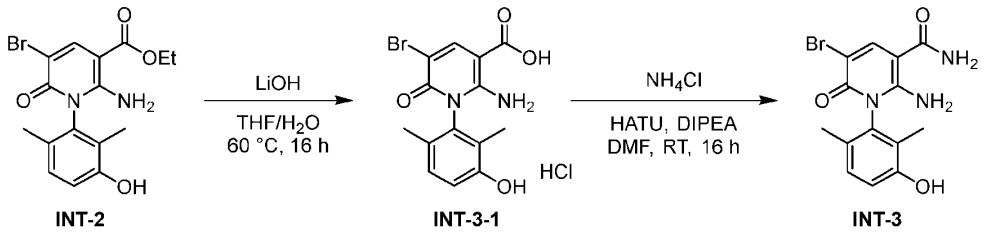
[0188] To a stirred mixture of 6-amino-5-(ethoxycarbonyl)-1-(3-methoxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**INT-1-3**) (20.0 g, 55.5 mmol) and pyridine (200 mL) at rt, was added bromine (4.29 mL, 83.2 mmol). The mixture was stirred at 100 °C for 1 h, then cooled and quenched with saturated $Na_2S_2O_3$ (300 mL). The mixture was extracted with EtOAc (3 × 500 mL). The combined organic layers washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to give ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-1**) (20.0 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.00–6.00 (bs, 2H), 8.20 (s, 1H), 7.26 (d, *J*=8.8 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 3.83 (s, 3H), 1.87 (s, 3H), 1.78 (s, 3H), 1.29 (t, *J*=7.2, 3H); MS (ESI) m/z: 395.25 $[M+H]^+$.

Preparation of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**)

[0189] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-1**) (0.800 g, 2.02 mmol) in DCM (8.0 mL) at 0 °C, was added BBr_3 (1M in DCM, 8.10 mL, 8.10 mmol). After stirring at rt for 30 min, the mixture was quenched with saturated $NaHCO_3$ (50 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.06 g, 78%), which was used directly for the next step without further purification. MS (ESI) m/z: 383.19 $[M+H]^+$.

Intermediate 3

2-Amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**)



Preparation of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid hydrochloride (**INT-3-1**)

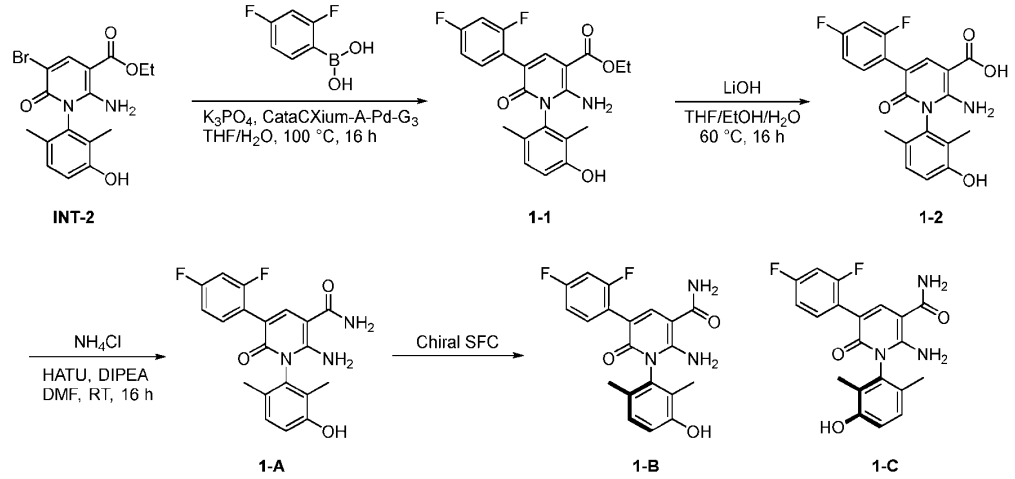
[0190] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (4.00 g, 10.5 mmol) in THF (52 mL) and H_2O (13 mL) was added $LiOH•H_2O$ (1.26 g, 52.5 mmol). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to rt, concentrated, diluted with water, and adjusted to pH 2~3 with 1 M HCl. The resulting solids were collected by filtration and dried to afford 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid hydrochloride (**INT-3-1**) (3.80 g). LCMS (MS, ESI): 352.90, 354.90 $[M+H]^+$.

Preparation of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**)

[0191] To a stirred mixture of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid hydrochloride (**INT-3-1**) (2.54 g, 6.51 mmol) and ammonium chloride (6.97 g, 130 mmol) in DMF (50 mL), were added HATU (12.4 g, 32.6 mmol) and DIEA (34.0 mL, 195 mmol). The mixture was stirred at rt for 16 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (10 × 100 mL). The combined organic layers washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue purified by column chromatography (SiO_2, 10% MeOH/DCM) to afford 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**) (1.60 g, 69%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 (s, 1H), 8.38 (s, 1H), 7.92-7.28 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.82 (s, 3H), 1.75 (s, 3H). LCMS (MS, ESI): 352.00, 354.00 $[M+H]^+$.

Example 1

(*S*)-2-Amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-B**) and (*R*)-2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-C**)



Preparation of ethyl 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**1-1**)

[0192] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.800 g, 2.10 mmol) and (2,4-difluorophenyl)boronic acid (0.66 g, 4.2 mmol) in THF (8.0 mL) and water (2.0 mL) was added K_3PO_4 (1.33 g, 6.3 mmol). The mixture was purged with nitrogen for 2 min, CataCXium-A-Pd-G_3 (153 mg, 0.210 mmol) added, and purged again with nitrogen for 1 min. After stirring at 100 °C for 16 h, it was diluted with water (25 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers dried over $MgSO_4$, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford ethyl 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**1-1**) (0.80 g, 91%). MS (ESI) m/z: 415.34 $[M+H]^+$.

Preparation of 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**1-2**)

[0193] To a stirred mixture of ethyl 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**1-1**) (0.800 g, 1.90 mmol) in THF (4.0 mL), EtOH (4.0 mL), and H_2O (4.0 mL) was added LiOH (0.320 g, 13.5

mmol) at rt. After stirring at 60 °C for 16 h, it was concentrated, residue triturated with toluene (3 × 15 mL), filtered, and dried to afford 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**1-2**) (1.2 g, crude), which was used directly for the next step without further purification. MS (ESI) 387.22 m/z: $[M+H]^+$.

Preparation of 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-A**)

[0194] To a stirred mixture of 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**1-2**) (1.10 g, 2.80 mmol) and NH_4Cl (3.05 g, 56.9 mmol) in DMF (11.0 mL), were added DIPEA (15.7 mL, 85.4 mmol) and HATU (5.40 g, 14.2 mmol) at rt. After stirring at rt for 16 h, it was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers dried over $MgSO_4$, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, MeOH/DCM) to afford 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-A**) (0.40g, 36%). MS (ESI) 386.30 m/z: $[M+H]^+$.

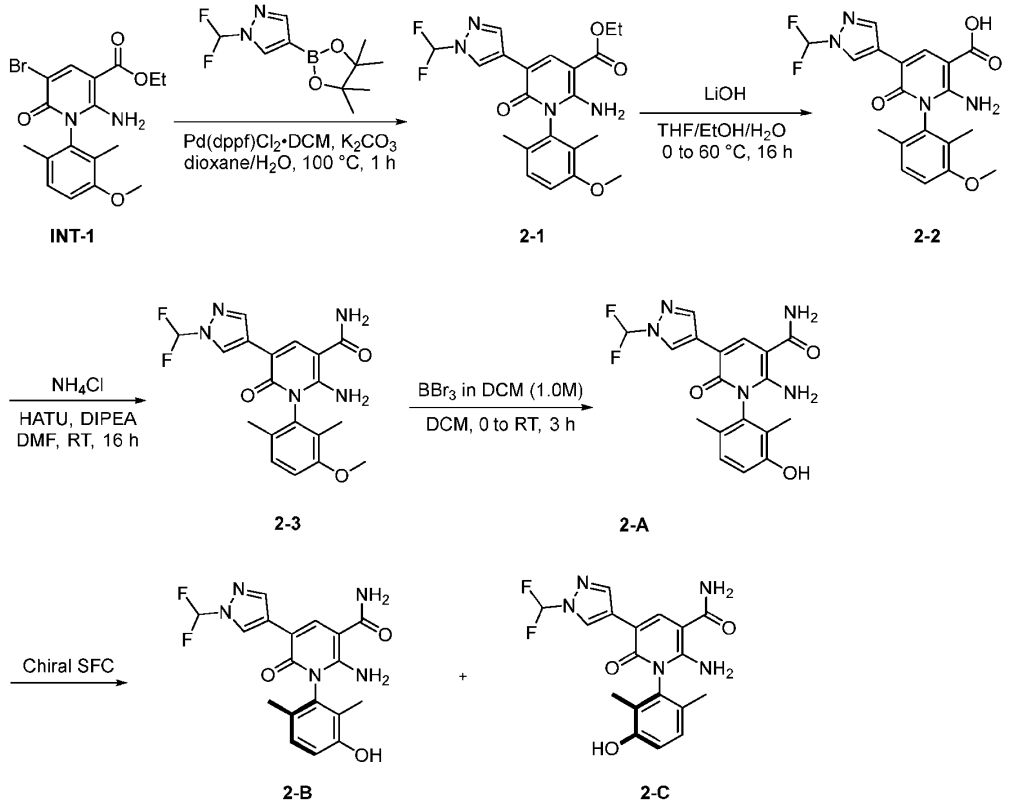
Separation of (*S*)-2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-B**), and (*R*)-2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-C**)

[0195] The racemic mixture of 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**1-A**) (200 mg) was subjected to chiral SFC purification [LUX CELLULOSE-4, 30 × 250 mm column, CO_2/30% IPA/ACN (1:1) with 0.1% isopropylamine], followed by prep-HPLC (C18, ACN/10mM NH_4HCO_3 in H_2O), to afford 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide carboxamide (**1-B**) (41 mg, 20%), and 2-amino-5-(2,4-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide carboxamide (**1-C**) (32 mg, 16%). **1-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.51 (s, 1H), 9.40-7.44 (m, 4H), 7.34-6.40 (m, 6H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) m/z: 386.23 $[M+H]^+$; Chiral purity 99.4%. **1-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.48 (s, 1H), 8.67-7.15 (m, 6H), 7.10-6.48 (m, 4H), 1.88 (s, 3H), 1.80 (s, 3H); MS

(ESI) m/z: 386.27 $[M+H]^+$; Chiral purity 99.6%. Compounds (**1-B**) and (**1-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 2

(*S*)-2-Amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-B**) and (*R*)-2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-C**)



INT-1 2-1 2-2 2-3 2-A 2-B 2-C

Preparation of ethyl 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2-1**)

[0196] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-1**) (1.00 g, 2.50 mmol) and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.920 g, 3.80 mmol) in 1,4-dioxane (16 mL) and water (4 mL), was added K_2CO_3 (1.05 g, 7.60 mmol) at rt. The mixture purged with N_2 for 10 min, and Pd(dppf)Cl_2•DCM (0.21 g, 0.25 mmol)

added. The mixture was stirred under N_2 at 100 °C for 1 h. The mixture was diluted with water (20 mL) and then extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford ethyl 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2-1**) (1.06 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.55 (s, 1H), 8.29 (s, 1H), 8.05 (s, 1H), 7.23 (d, *J* =8.4 Hz, 1H), 6.94 (d, *J*=7.2 Hz, 1H), 4.37 (q, *J*=7.2 Hz, 2H), 3.86 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); MS (ESI) m/z: 433.23 $[M+H]^+$.

Preparation of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**2-2**)

[0197] To a stirred mixture of ethyl 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2-1**) (1.00 g, 2.31 mmol) in THF (5 mL), EtOH (5 mL), and H_2O (5 mL) at 0 °C, was added $LiOH.H_2O$ (0.970 g, 23.1 mmol). The mixture was stirred at 60 °C for 16 h. The mixture was concentrated, acidified w) and HCl (~30 mL), and the formed solids collected by filtration. The solids were washed with water (2 × 20 mL), and dried to afford 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**2-2**) (0.66 g, 70%), which was used directly for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.60 (br s, 1H), 8.53 (s, 1H), 8.24 (s, 1H), 7.77 (t, *J*=59.2 Hz, 1H), 7.27 (d, *J*=8.4 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 1H), 3.84 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H); MS (ESI) m/z: 405.23 $[M+H]^+$.

Preparation of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-3**)

[0198] To a stirred mixture of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**2-2**) (0.630 g, 1.56 mmol) and NH_4Cl (0.830 g, 15.6 mmol) in DMF (6.3 mL), were added DIPEA (1.44 mL, 7.79 mmol) and HATU (0.890 g, 2.34 mmol) at rt. The mixture was stirred at rt for 16 h, then quenched with ice cold saturated NH_4Cl (30 mL). The formed solids were collected by filtration, washed with petroleum ether (2 × 25 mL), and dried to afford 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-

dihydropyridine-3-carboxamide (**2-3**) (0.61 g, 97%), which was used directly for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.50 (s, 1H), 8.43 (s, 1H), 8.33 (s, 1H), 7.79 (t, *J*=59.2 Hz, 1H), 7.78 (br s, 1H), 7.25 (d, *J*=8.4 Hz, 1H), 7.18 (br s, 1H), 7.03 (d, *J*=8.4 Hz, 1H), 3.84 (s, 3H), 1.88 (s, 3H), 1.79 (s, 3H); MS (ESI) m/z: 404.34 $[M+H]^+$.

Preparation of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-A**)

[0199] To a stirred mixture of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-3**) (0.600 g, 1.49 mmol) in DCM (12 mL) at 0 °C, was added BBr_3 (1M in DCM, 6 mL). The mixture was stirred at rt for 3 h, then quenched with ice cold $Na_2S_2O_3$ (15 mL). The mixture was extracted with 20% MeOH in DCM (2 × 15 mL). The combined organic layers washed with saturated $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue purified by reverse-phase Prep-HPLC (X-bridge, 19 × 250 mm column, ACN/10mM NH_4HCO_3 in H_2O) to afford 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-A**) (0.103 g, 18%). MS (ESI) m/z: 390.26 $[M+H]^+$.

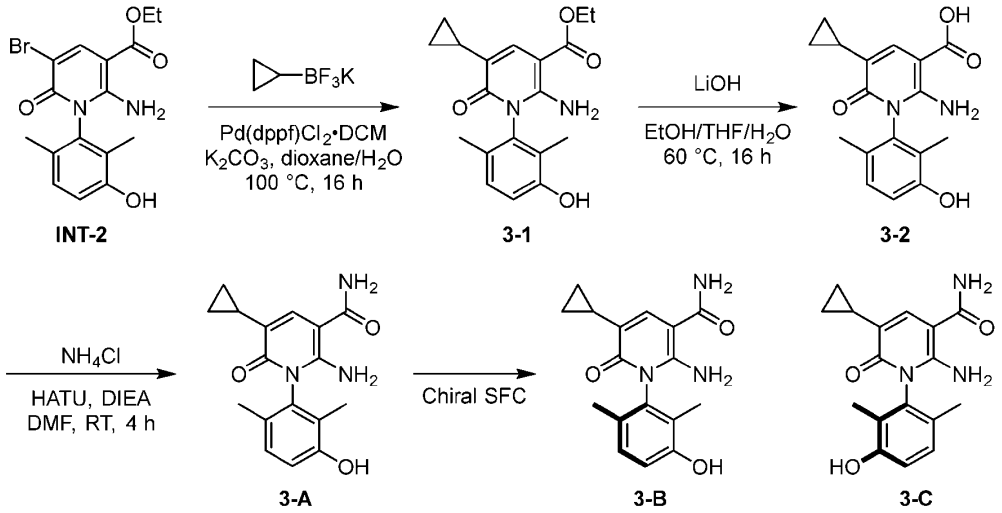
Separation of (*S*)-2-Amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-B**), and (*R*)-2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-C**)

[0200] The racemic mixture of 2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-A**) (103 mg) was subjected to chiral SFC purification (Chiralpak AD-H, 30 × 250 mm column, CO_2/30% IPA with 0.1% isopropylamine) to afford (*S*)-2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-B**) (39 mg, 7%), and (*R*)-2-amino-5-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**2-C**) (38 mg, 7%). **2-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.55 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 7.79 (t, *J*=59.2 Hz, 1H), 7.76 (br s, 2H), 7.15 (br s, 2H), 7.07 (d, *J*=8.4 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 3H); MS (ESI) m/z: 390.26 $[M+H]^+$; Chiral purity 99.86%. **2-C**:

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.54 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 7.79 (t, *J*=59.2 Hz, 1H,), 7.76 (br s, 2H), 7.15 (br s, 2H), 7.07 (d, *J*=8.4 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 3H); MS (ESI) m/z: 390.30 $[M+H]^+$; Chiral purity 99.41%. Compounds (**2-B**) and (**2-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 3

(*S*)-2-Amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-B**) and (R)-2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-C**)



Preparation of ethyl 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3-1**)

[0201] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.600 g, 1.574 mmol) in dioxane (4.8 mL) and water (1.2 mL), were added potassium cyclopropyltrifluoroborate (0.676 g, 7.87 mmol) and potassium carbonate (0.653 g, 4.72 mmol), followed by purging with nitrogen for 15 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.129 g, 0.157 mmol) was added, and the mixture was purged again with nitrogen for 10 min. After stirring at 100 °C for 16 h, the reaction was quenched with water (25 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers washed with brine, dried over sodium sulphate, filtered, and concentrated. The residue

purified by flash silica gel column chromatography using 20% ethyl acetate in petroleum ether to provide ethyl 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3-1**) (0.30 g, 56%). MS (ESI) 343.32 $[M+H]^+$.

Preparation of 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**3-2**)

[0202] To a stirred mixture of ethyl 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3-1**) (0.250 g, 0.730 mmol) in ethanol (1.25 mL), THF (1.25 mL) and water (0.50 mL), was added lithium hydroxide (0.0520 g, 2.19 mmol) at rt. After stirring at 60 °C for 16 h, the mixture was concentrated to remove all volatiles, diluted with water and acidified using 1N HCl solution to pH 3 at 0 °C. The solid formed was collected by filtration, washed with water (5 mL) and dried under vacuum to give 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**3-2**) (0.20 g, 87%). MS (ESI) 315.44 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.22 (s, 1H), 9.51 (s, 1H), 7.39 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 1.99 (s, 3H), 1.82 (s, 3H), 1.30-1.23 (m, 1H), 0.73 (d, J = 7.6 Hz, 2H), 0.48 (d, J = 3.6 Hz, 2H).

Preparation of 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-A**)

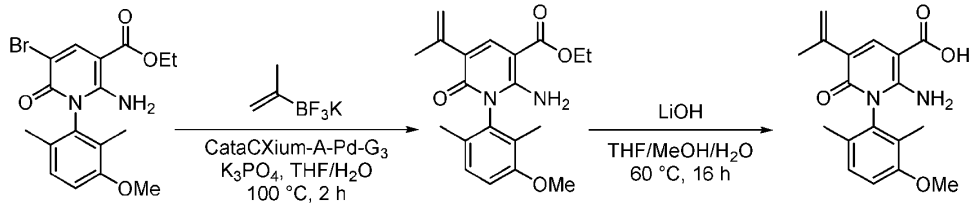
[0203] To a stirred mixture of 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-2**) (0.170 g, 0.543 mmol) in DMF (10 mL), were added HATU (0.309 g, 0.814 mmol), diisopropylethylamine (0.274 g, 2.71 mmol), and ammonium chloride (0.290 g, 5.42 mmol) at 0 °C. After stirring at rt for 4 h, the mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers washed with brine, dried over sodium sulphate, filtered, and concentrated. The residue purified by RP-HPLC (Column: X Bridge C18, 3.5u (4.6mmX150mm), Mobile Phase C: 10mM Ammonium Bicarbonate in water, B: 100% ACN; Gradient (T%B): 0/10, 0.5/10, 8.0/95, 11/95, 13/10, 15/10; Flow Rate: 1.0 mL/min., Sample Diluent: water + ACN) to give 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-A**) (0.075 g, 44%). HPLC purity: 97.11%.

Separation of (S)-2-Amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-B**) and (R)-2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-C**)

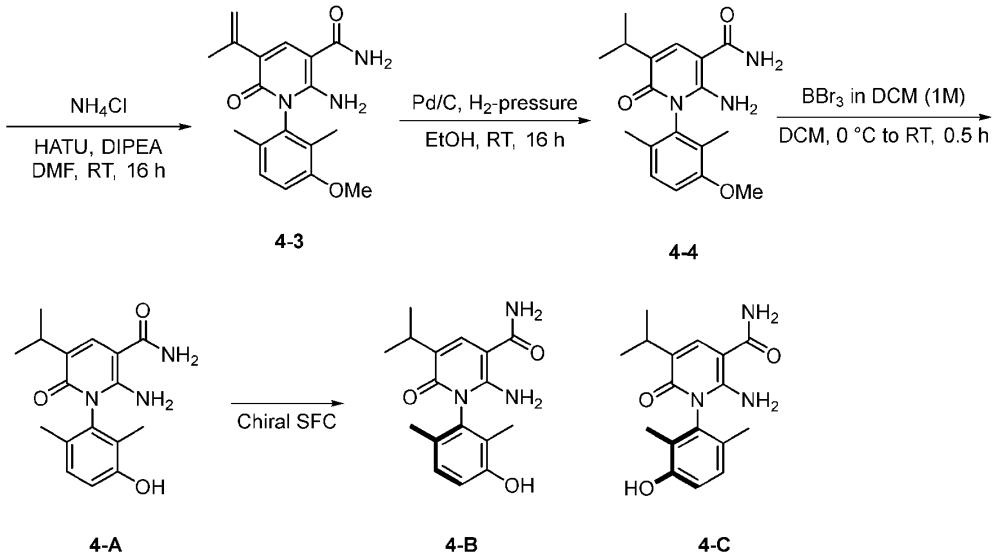
[0204] The racemic mixture of 2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-A**) (0.100 g) was subjected to chiral SFC (column: LUX CELLULOSE-4 (4.6 x 250) mm,5µ; % CO2: 65%; % Co solvent: 35% (0.1% 7N Methanolic ammonia in MeOH); Flow: 100 mL/min.; Back Pressure: 100 bar; Temperature: 30 °C; UV: 285 nm), to give *(S)*-2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-B**) (0.0155g, 15%), and *(R)*-2-amino-5-cyclopropyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**3-C**) (0.0200g, 20%). **3-B**: MS (ESI) 314.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 9.47 (s, 1H), 8.40-6.52 (m, 7H), 1.81 (s, 3H), 1.80-1.75 (m, 1H), 1.73 (s, 3H), 0.75-0.67 (m, 2H), 0.63-0.55 (m, 2H). HPLC purity: 99.91%; Chiral purity: 99.90%. **3-C**: MS (ESI) 314.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 9.47 (s, 1H), 8.10-6.47 (m, 7H), 1.81 (s, 3H), 1.80-1.75 (m, 1H), 1.73 (s, 3H), 0.75-0.67 (m, 2H), 0.63-0.55 (m, 2H). HPLC purity: 95.14%; Chiral purity 98.58%. Compounds (**3-B**) and (**3-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 4

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-C**)



INT-1 **4-1** **4-2**



Preparation of ethyl 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylate (**4-1**)

[0205] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (2.00 g, 5.06 mmol) and potassium trifluoro(prop-1-en-2-yl)borate (1.50 g, 10.1 mmol) in THF (40 mL) and water (8 mL), was added K_3PO_4 (3.22 g, 15.18 mmol). The mixture was degassed with argon for 3 min, then cataCXium-A-Pd-G3 (369 mg, 0.510 mmol) was added, and the mixture degassed again with argon for 2 min. The mixture was stirred at 100 °C for 2 h, then diluted with water (50 mL). The mixture was extracted with EtOAc (2 × 40 mL). The combined organic layers washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford ethyl 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylate (**4-1**) (1.20 g, 66%). MS (ESI) m/z: 357.34 $[M+H]^+$.

Preparation of 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylic acid (**4-2**)

[0206] To a stirred mixture of ethyl 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylate (**4-1**) (1.20 g, 3.37 mmol), THF (8.4 mL), MeOH (1.2 mL), and H_2O (2.4 mL), was added LiOH (0.564 g, 23.6 mmol) at rt. The mixture was stirred at 60 °C for 16 h. The mixture was concentrated, diluted with water

(20 mL) and acidified to pH~3 with 5N HCl. The formed solids were collected by filtration, washed with water (20 mL), and dried to give 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylic acid (**4-2**) (950 mg, crude), which was used directly for the next step without further purification. MS (ESI) m/z: 329.28 $[M+H]^+$.

Preparation of 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**4-3**)

[0207] To a stirred mixture of 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxylic acid (**4-2**) (0.950 g, 2.89 mmol) and NH_4Cl (1.08 g, 20.2 mmol) in DMF (9.5 mL), were added DIPEA (4.27 mL, 23.2 mmol) and HATU (1.32 g, 3.47 mmol) at rt. The mixture was stirred at rt for 16 h. The mixture was diluted with ice cold water (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**4-3**) (0.50 g, 52%). MS (ESI) m/z: 328.25 $[M+H]^+$.

Preparation of 2-amino-5-isopropyl-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-4**)

[0208] To a stirred mixture of ethyl 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**4-3**) (0.300 g, 0.920 mmol) in EtOH (3 mL) was added 10% Pd/C (50% wet, 0.29 g, 2.75 mmol) at rt. The mixture was stirred at rt for 16 h under 1 atmosphere of H_2. The mixture was filtered through a pad of celite, washed with methanol (200 mL), and concentrated to give 2-amino-5-isopropyl-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-4**) (0.25 g, crude), which was used directly for the next step without further purification. MS (ESI) m/z: 330.33 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-A**)

[0209] To a stirred mixture of 2-amino-5-isopropyl-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-4**) (0.250 g, 0.759 mmol) in DCM (12.5 mL) at 0 °C, was added BBr_3 (1M in DCM, 3.04 mL, 3.04 mmol) dropwise. The

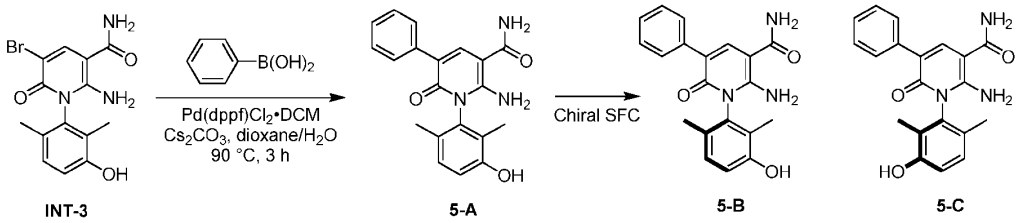
mixture was stirred at rt for 30 min, then quenched with saturated $NaHCO_3$ (~ 20 mL). The mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether) to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-A**) (0.095 g, 39%). MS (ESI) m/z: 316.32 $[M+H]^+$.

Separation of (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-C**)

[0210] The racemic mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-A**) (95 mg) was subjected to chiral SFC purification (CHIRALPAK AD-H, 30 × 250 mm column, CO_2/20% MeOH with 0.2% DEA) to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-B**) (0.020 g, 9%), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4-C**) (0.030 g, 11%). **4-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.47 (s, 1H), 8.40-6.20 (bs, 4H), 7.65 (s, 1H), 7.03 (d, *J*=8.00 Hz, 1H), 6.83 (d, *J*=8.00 Hz, 1H), 2.92-2.85 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.11 (dd, *J*=6.8, 2.0 Hz, 6H); MS (ESI) m/z: 316.31 $[M+H]^+$; Chiral purity 99.98%. **4-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.48 (s, 1H), 8.40-6.20 (bs, 4H), 7.65 (s, 1H), 7.03 (d, *J*=8.4 Hz, 1H), 6.83 (d, *J*=8.00 Hz, 1H), 2.93-2.83 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.11 (dd, *J*=6.8, 2.0 Hz, 6H); MS (ESI) 316.35 $[M+H]^+$; Chiral purity 99.60%. Compounds (**4-B**) and (**4-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 5

(*S*)-2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-C**)



INT-3 5-A 5-B 5-C

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-A**)

[0211] To a stirred mixture of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**) (1.00 g, 2.84 mmol), phenylboronic acid (0.420 g, 3.41 mmol) in 1,4-dioxane (24 mL) and H_2O (6 mL), were added $Pd(dppf)Cl_2$ (0.180 g, 0.284 mmol) and Cs_2CO_3 (2.78 g, 8.52 mmol). After purging with nitrogen five times and stirring at 90 °C for 3 h, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (5 × 50 mL). The combined organic layers washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, 50% EtOAc/DCM) to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-A**) (0.800 g, 80%). LCMS (MS, ESI): 349.90 $[M+H]^+$.

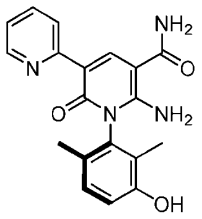
Separation of (S)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-B**) (R)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-C**)

[0212] The racemic mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-A**) (50 mg), was subjected to chiral SFC purification [LUX CELLULOSE-4, 30 x 250 mm column, CO_2/40% MeOH/ACN (1:1) with 0.1% methanolic NH_3] to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-B**) (14 mg, 28%), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxamide (**5-C**) (14 mg, 28%). **5-B**: ^1H NMR (400 MHz, DMSO-d_6): δ ppm 9.50 (s, 1H), 8.16 (s, 1H), 8.04-7.39 (brs, 2H), 7.71 (d, *J*=8.4 Hz, 2H), 7.32 (t, *J*=7.60 Hz, 2H), 7.19 (t, *J*=7.2 Hz, 1H), 7.15-9.93

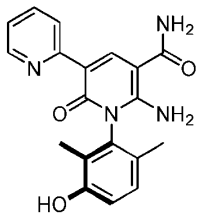
(brs, 1H), 7.06 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) m/z: 350.28 $[M+H]^+$; Chiral purity 99.88%. **5-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.49 (s, 1H), 8.16 (s, 1H), 8.10-7.40 (brs, 2H), 7.71 (d, *J*=8.4 Hz, 2H), 7.40-7.10 (brs, 1H), 7.32 (t, *J*=7.60 Hz, 2H), 7.19 (t, *J*=7.20 Hz, 1H), 7.10-6.70 (brs, 1H), 7.06 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) 350.28 $[M+H]^+$; Chiral purity 98.7%. Compounds (**5-B**) and (**5-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 6

(*S*)-6'-Amino-1'-(3-hydroxy-2,6-dimethylphenyl)-2'-oxo-1',2'-dihydro-[2,3'-bipyridine]-5'-carboxamide (**6-B**) and (*R*)-6'-amino-1'-(3-hydroxy-2,6-dimethylphenyl)-2'-oxo-1',2'-dihydro-[2,3'-bipyridine]-5'-carboxamide (**6-C**)



6-B



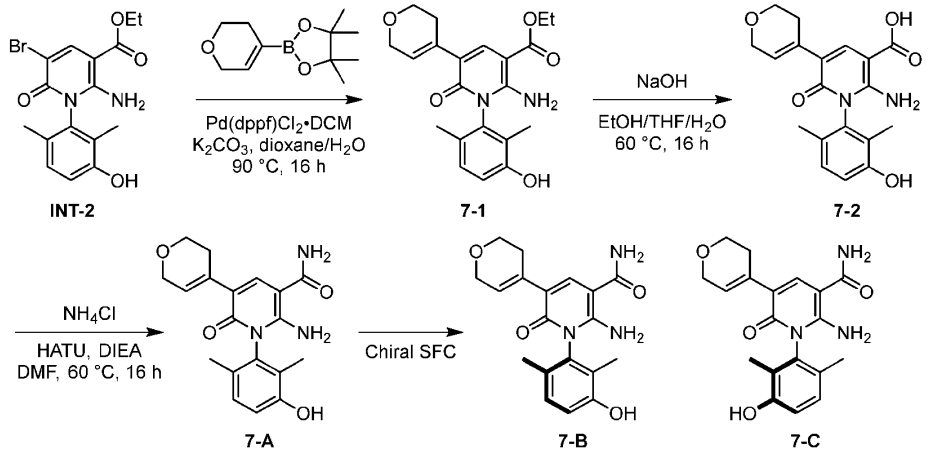
6-C

[0213] The racemic mixture of 6'-amino-1'-(3-hydroxy-2,6-dimethylphenyl)-2'-oxo-1',2'-dihydro-[2,3'-bipyridine]-5'-carboxamide (**6-A**) (50 mg) was prepared according to the procedure described in Example 2, and was subjected to chiral SFC purification (LUX CELLULOSE-4, 30 × 250 mm column, CO_2/35% IPA with 0.1% isopropylamine) to afford (*S*)-6'-amino-1'-(3-hydroxy-2,6-dimethylphenyl)-2'-oxo-1',2'-dihydro-[2,3'-bipyridine]-5'-carboxamide (**6-B**) (12 mg, 25%), and (*R*)-6'-amino-1'-(3-hydroxy-2,6-dimethylphenyl)-2'-oxo-1',2'-dihydro-[2,3'-bipyridine]-5'-carboxamide (**6-C**) (14 mg, 28%). **6-B:** ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (brs, 1H), 8.86 (s, 1H), 8.7-7.6 (brs, 2H), 8.58 (d, *J*=4.0 Hz, 1H), 8.26 (d, *J*=8.0 Hz, 1H), 7.70-7.66 (m, 1H), 7.55-6.65 (brs, 2H), 7.17-7.14 (m, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) m/z: 351.27 $[M+H]^+$; Chiral purity 99.51%. **6-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (brs, 1H), 8.86 (s, 1H), 8.59 (d, *J*=4.0 Hz, 1H), 8.32-7.50 (brs, 2H), 8.26 (d, *J*=8.4 Hz, 1H), 7.70-7.66 (m, 1H), 7.45-6.69 (brs, 2H), 7.17-7.14 (m, 1H), 7.08 (d, *J*=8.4 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) m/z: 351.27 $[M+H]^+$; Chiral purity 95.31%.

Compounds (**6-B**) and (**6-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 7

(S)-2-Amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-B**) and (*R*)-2-amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-C**)



Preparation of ethyl 2-amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**7-1**)

[0214] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.500 g, 1.31 mmol), and (3,6-dihydro-2*H*-pyran-4-yl)boronic acid (0.336 g, 2.62 mmol) in dioxane (6.5 mL) and water (1.0 mL), were added potassium carbonate (0.543 g, 3.93 mmol), and $PdCl_2$(dppf)DCM (0.107 g, 0.131 mmol). After purging with argon for 2 min and stirring at 90 °C for 16 h, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers dried over sodium sulphate, filtered, and concentrated. The residue purified by flash silica gel column chromatography eluting with 30% ethyl acetate in petroleum ether to give ethyl 2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**7-1**) (0.45 g, 89%). MS (ESI) 385.71 $[M+H]^+$.

Preparation of 2-amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**7-2**)

[0215] To a stirred mixture of ethyl 2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**7-1**) (0.400 g, 1.04 mmol) in ethanol (3.20 mL), THF (3.20 mL) and water (0.80 mL), was added sodium hydroxide (0.125 g, 3.12 mmol). After stirring at 60 °C for 16 h, the mixture was concentrated, diluted with water, acidified with aqueous 1N HCl solution (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulphate, concentrated and dried to give 2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**7-2**) (0.31 g, 84%), which was used directly for the next step without further purification. MS (ESI) 357.52 $[M+H]^+$.

Preparation of 2-Amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-A**)

[0216] To a stirred mixture of 2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**7-2**) (0.310 g, 0.870 mmol) and HATU (0.496 g, 1.30 mmol) in DMF (3.1 mL), were added *N,N*-diisopropylethylamine (0.337 g, 2.61 mmol) and ammonium chloride (0.140 g, 2.61 mmol). After stirring at 60 °C for 16 h, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over magnesium sulphate, filtered, and concentrated. The residue purified by RP-HPLC (Column/dimensions: X BRIDGE PHENYL (19*250*5um), Mobile phase A: 10mM Ammonium bicarbonate in water, Mobile phase B: Acetonitrile (org), Gradient (Time/%B): 0/10, 3/10, 10/45, 13/45, 13.1/100, 15/100, 15.1/10, 17/10; Flow rate: 15 mL/min, to afford 2-Amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-A**) (100 mg). MS (ESI) m/z: 356.29 $[M+H]^+$.

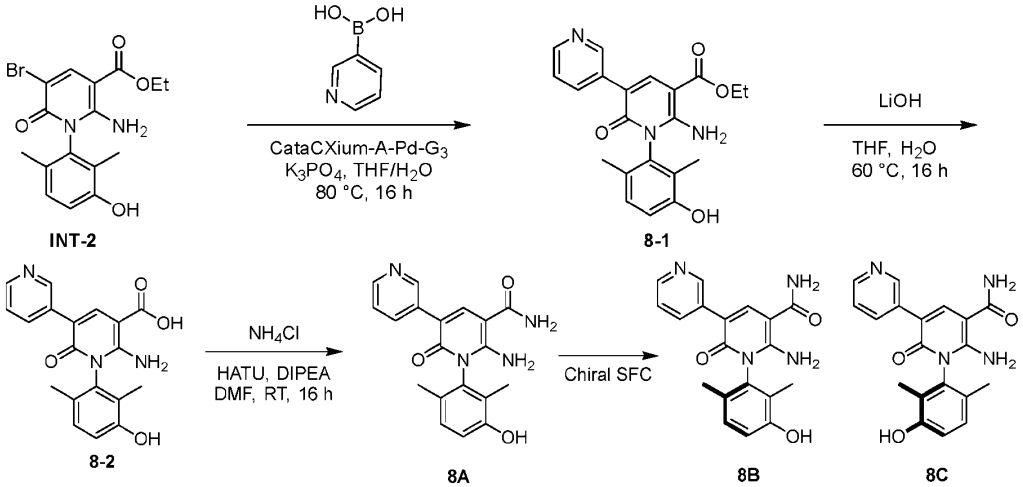
Separation of (S)-2-Amino-5-(3,6-dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-B**), and (R)-2-amino-5-(3,6-

dihydro-2H-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-C**)

[0217] The racemic mixture of 2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-A**) (80 mg), was subjected to chiral SFC purification [Chiralcel OJ-H, 30 x 250 mm column, CO_2/20% IPA/ACN (1:1) with 0.1% isopropylamine], to afford (*S*)-2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-B**) (33 mg, 41%), and (*R*)-2-amino-5-(3,6-dihydro-2*H*-pyran-4-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**7-C**) (32 mg, 40%). **7-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.49 (s, 1H), 8.40–6.72 (m, 7H), 6.60 (s, 1H), 4.15 (d, *J*=2.4 Hz, 2H), 3.76 (t, *J*=5.6 Hz, 2H), 2.41 (s, 2H), 1.81 (s, 3H), 1.73 (s, 3H); MS (ESI) m/z: 356.29 $[M+H]^+$; Chiral purity 99.72%. **7-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.50 (s, 1H), 8.40–6.72 (m, 7H), 6.60 (s, 1H), 4.15 (d, *J*=2.4 Hz, 2H), 3.76 (t, *J*=5.6 Hz, 2H), 2.41 (s, 2H), 1.81 (s, 3H), 1.73 (s, 3H); MS (ESI) m/z: 356.29 $[M+H]^+$; Chiral purity 98.76%. Compounds (**7-B**) and (**7-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 8

(*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-B**) and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-C**)



Preparation of ethyl 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**8-1**)

[0218] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.700 g, 1.84 mmol), pyridin-3-ylboronic acid (451 mg, 3.67 mmol) in THF (28 mL) and water (7 mL), was added potassium phosphate, tribasic (1.17 g, 5.51 mmol). The mixture was purged with nitrogen for 2 min, cataCXium-A-Pd-G3 (134 mg, 0.184 mmol) was added, and purged again for 1 min. The mixture was stirred at 80 °C for 16 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue purified by column chromatography (SiO_2, Ethyl acetate/petroleum ether gradient) to afford ethyl 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**8-1**) (500 mg, 71%). MS (ESI) 280.22 $[M+H]^+$.

Preparation of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**8-2**)

[0219] To a stirred solution of ethyl 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**8-1**) (0.500 g, 1.32 mmol) in THF (2.5 mL), water (2.5 mL), ethanol (2.5 mL), was added lithium hydroxide (0.221 g, 9.22 mmol) at rt. The mixture was stirred at 60 °C for 16 h, then concentrated and azeotropically dried with toluene (3 × 15 mL) to give 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**8-2**) (0.75 g, crude). MS (ESI) 352.19 $[M+H]^+$.

Preparation of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8A**)

[0220] To a stirred mixture of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**8-2**) (0.750 g, 2.14 mmol), ammonium chloride (2.28 g, 42.7 mmol), and dimethylformamide (7.5 mL) at rt, were added DIPEA (11.8 mL, 64.0 mmol), and HATU (4.06 g, 10.7 mmol). The mixture was stirred at rt for 16 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers dried over $MgSO_4$, filtered, and concentrated. The residue purified by column chromatography (SiO_2, methanol/dichloromethane gradient), followed by prep-HPLC (C18, ACN/ Ammonium bicarbonate in water) to afford 6-amino-1-(3-hydroxy-2,6-

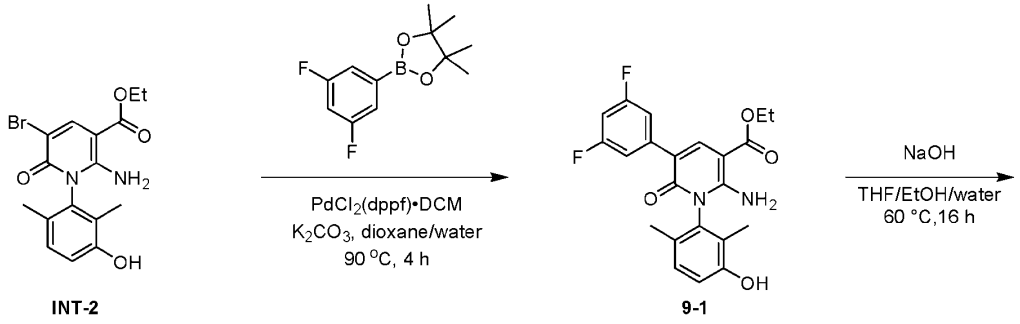
dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8A**) (160 mg, 34% over two steps). MS (ESI) 351.29 $[M+H]^+$.

(*S*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-B**) and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-C**)

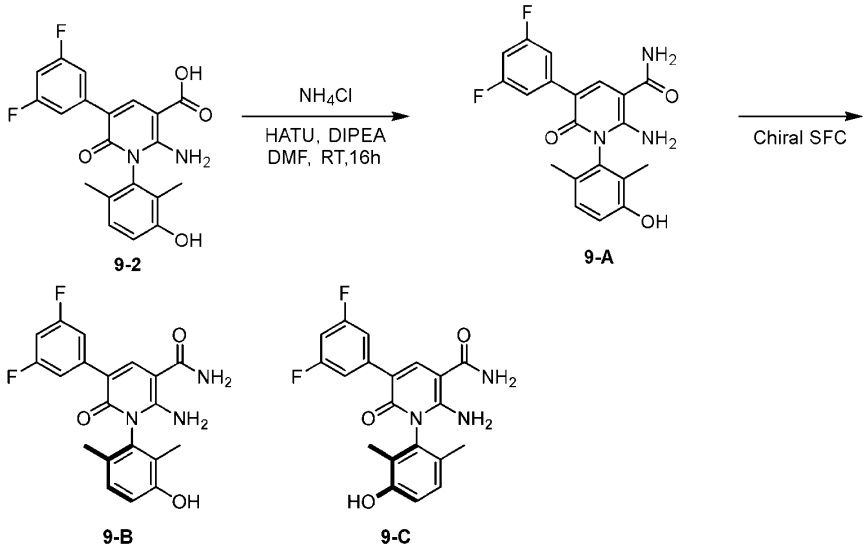
[0221] 6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-A**) (160 mg) was subjected to chiral SFC (CHIRALART -SA (30x250) mm, 5μ, CO_2/Methanol) to afford (*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-B**) (64 mg, 13%, 99.9% ee), and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**8-C**) (63 mg, 13%, 96.1% ee). **8-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.54 (s, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.39-8.37 (m, 1H), 8.29 (s, 1H), 8.13-8.10 (m, 1H), 8.19-7.54 (m, 2H), 7.48-6.75 (m, 2H), 7.34-7.32 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); MS (ESI) 351.34 $[M+H]^+$; HPLC: 99.22%. **8-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (s, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.39-8.37 (m, 1H), 8.29 (s, 1H), 8.20-7.54 (m, 2H), 8.13-8.10 (m, 1H), 7.35-7.32 (m 1H), 7.35-6.80 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); MS (ESI) 351.34 $[M+H]^+$; HPLC: 99.15%. Compounds (**8-B**) and (**8-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 9

(*S*)-2-Amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-B**) and (*R*)-2-Amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-C**)



INT-2 **9-1**



Preparation of ethyl 2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**9-1**)

[0222] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.300 g, 0.787 mmol), 2-(3,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.378 g, 1.57 mmol), dioxane (3.9 mL), and water (0.60 mL), was added potassium carbonate (0.326 g, 2.36 mmol). The mixture was purged with argon for 15 min, followed by the addition of $PdCl_2$(dppf)DCM (0.064 g, 0.079 mmol,), and purged again with argon for 5 min. The mixture was stirred at 90 °C for 4 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (40 × 2 mL). The combined organic layers dried over magnesium sulphate, filtered, and concentrated. The residue purified by column chromatography using 40% ethyl acetate in petroleum ether to give ethyl 2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**9-1**) (0.18 g, 55%). LCMS (ESI) 415.56 $[M+H]^+$.

Preparation of 2-Amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9-2**)

[0223] To a stirred mixture of ethyl 2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**9-1**) (0.180 g, 0.434 mmol) in THF (0.72 mL), ethanol (0.72 mL) and water (0.36 mL), was added sodium

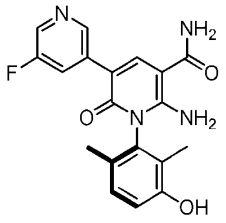
hydroxide (0.0520 g, 1.30 mmol). The mixture was stirred at 60 °C for 16 h. The mixture was acidified with 1N HCl solution (15 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, and concentrated to afford 2-Amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9-2**) (0.10 g), which was used directly for the next step without further purification. LCMS(ESI) 387.64 $[M+H]^+$

Preparation of (*S*)-2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-B**) and (*R*)-2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-C**)

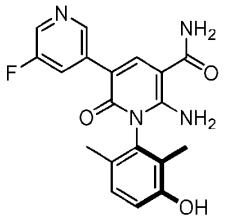
[0224] To a stirred mixture of 2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9-2**) (0.0900 g, 0.230 mmol), HATU (0.0970 g, 0.256 mmol), DIPEA (0.150 g, 1.17 mmol) in DMF (0.90 mL), was added ammonium chloride (0.0370 g, 0.699 mmol). The mixture was stirred at rt for 16 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue purified by prep-HPLC (Column/dimensions: XBRIDGE C18(19*150)5um; Mobile phase A: 10mM ammonium bicarbonate in water; Mobile phase B: Acetonitrile; Gradient (Time/%B): 0/15, 1/15, 8/40, 13.5/40, 13.6/100, 17/100, 17.1/15, 19/15; Flow rate: 17 mL/min.), followed by chiral separation via chiral SFC (Column/dimensions: CHIRALPAK AD-H (4.6x250) mm,5μ; $\%CO_2$: 80%; %Co-solvent: 20% (0.1% ammonia in MeOH); Flow: 100 mL/min.; Back Pressure: 100 bar; Temperature: 30 °C; UV: 210 nm) to afford (*S*)-2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-B**) (19 mg, 21%), and (*R*)-2-amino-5-(3,5-difluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**9-C**) (19 mg, 21%). **9-B**: LCMS (ESI) 386.27 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.59 (br s, 1H), 8.33 (s, 1H), 8.22-6.05 (m, 7H), 1.86 (s, 3H), 1.78 (s, 3H), two -N*H* protons are not visible in ^1H NMR. HPLC: 98.86%. Chiral purity: 99.55% ee. **9-C**: LCMS (ESI) 386.27 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (br s, 1H), 9.29 (br s, 2H), 8.33 (s, 1H), 7.90 (br s, 1H), 7.20-7.09 (m, 2H), 7.45-6.95 (m, 3H), 6.87 (d, J = 8.4 Hz, 1H), 1.86 (s, 3H), 1.78 (s, 3H). HPLC: 99.66%. Chiral purity: 99.78% ee. Compounds (**9-B**) and (**9-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 10

(*S*)-6-amino-5'-fluoro-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**10-B**) and (*R*)-6-amino-5'-fluoro-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**10-C**)



10-B

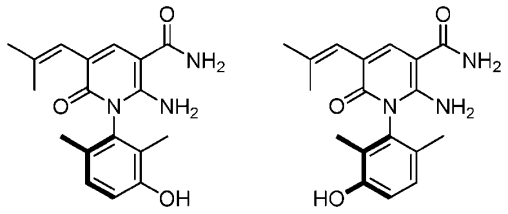


10-C

[0225] The racemic mixture of 6-amino-5'-fluoro-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**10-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid, and the crude product (40 mg) was subjected to chiral SFC purification, followed by prep-HPLC [Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 9% B to 39% B in 10 min; Wave Length: 254nm)] to afford (*S*)-6-amino-5'-fluoro-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**10-B**) (11 mg, 28%, 99.84% ee) and (*R*)-6-amino-5'-fluoro-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**10-C**) (13 mg, 32%, 99.88% ee). **10-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.54 (brs, 1H), 8.91 (s, 1H), 8.39 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 8.14-8.10 (m, 1H), 8.10-7.70 (brs, 1H), 7.40-6.90 (brs, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) 369.25 $[M+H]^+$; Purity by HPLC: 97.82%; **10-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.54 (brs, 1H), 8.91 (s, 1H), 8.39 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 8.14-8.10 (m, 1H), 8.08-7.70 (brs, 1H), 7.40-7.00 (brs, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) 369.25 $[M+H]^+$; Purity by HPLC: 98.82%. Compounds (**10-B**) and (**10-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 11

(*S*)-2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**11-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**11-C**)

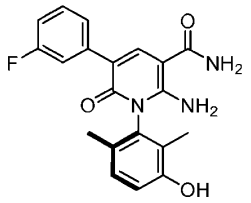


11-B **11-C**

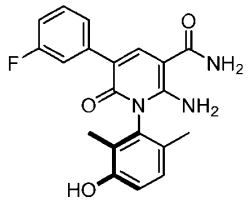
[0226] A mixture of racemic 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**11-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid, was subjected to chiral SFC (LUX-CELLULOSE-4 (4.6x250) mm, 5μ, 30% (0.2% 7N methanolic ammonia in MeOH) (1:1)), followed by prep-HPLC to give (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**11-B**) (32 mg, 24%, 99.84% ee), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**11-C**) (34 mg, 26%, 99.40% ee). **11-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.48 (s, 1H), 8.30-6.65 (bs, 4H), 7.75 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.97 (s, 1H), 1.81 (s, 6H), 1.77 (d, J = 0.8 Hz, 3H), 1.73 (s, 3H). MS (ESI) 328.32 $[M+H]^+$; HPLC: 99.37%. **11-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.49 (s, 1H), 8.30-6.65 (bs, 4H), 7.75 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.97 (s, 1H), 1.81 (s, 6H), 1.77 (d, J = 0.8 Hz, 3H), 1.73 (s, 3H).; MS (ESI) 328.31 $[M+H]^+$; HPLC: 99.68%. Compounds (**11-B**) and (**11-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 12

(*S*)-2-Amino-5-(3-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**12-B**) and (*R*)-2-amino-5-(3-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**12-C**)



12-B

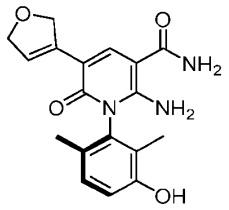


12-C

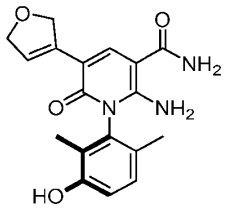
[0227] A mixture of racemic 2-amino-5-(3-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**12-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid, and subjected to prep-chiral-HPLC (CHIRALPAK AS-H 2*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 10; Wave Length: 254 nm) to afford (*S*)-2-amino-5-(3-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**12-B**) (40.5 mg, 36%), and (*R*)-2-amino-5-(3-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**12-C**) (38.3 mg, 34%). **12-B**: LCMS (MS, ESI): 368.10 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (s, 1H), 8.27 (s, 1H), 7.85 (brs, 1H), 7.69 -7.54 (m, 2H), 7.39-7.35 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.05-6.97 (m, 1H), 6.88 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.246. Chiral purity: 100%. **12-C**: LCMS (MS, ESI): 368.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (s, 1H), 8.27 (s, 1H), 7.85 (brs, 1H), 7.69 -7.58 (m, 2H), 7.39-7.33 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.05-6.96 (m, 1H), 6.88 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.245. Chiral purity: 99.6%. Compounds (**12-B**) and (**12-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 13

(*S*)-2-Amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-B**) and (*R*)-2-amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-C**)



13-B

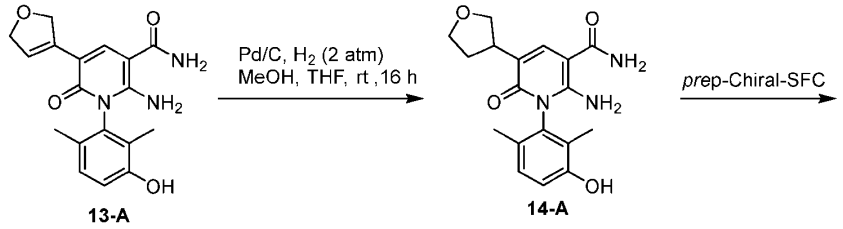


13-C

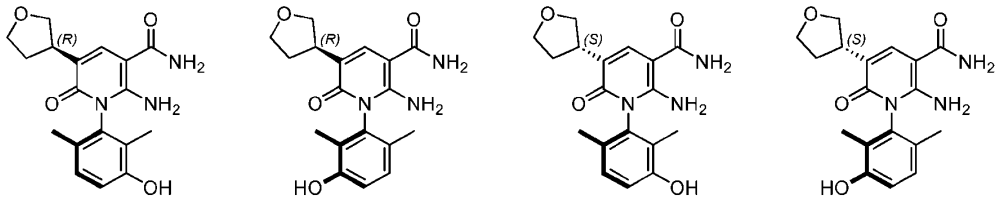
[0228] A mixture of racemic 2-amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid (ester), subjected to chiral prep-HPLC (Chiral ART Cellulose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 25; Wave Length: 254 nm) to afford (*S*)-2-amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-B**) (31 mg, 32%), and (*R*)-2-amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-C**) (28 mg, 29%) **13-B**: LCMS (MS, ESI): 342.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (s, 1H), 7.95-7.32 (m, 2H), 7.30-6.95 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.56 (t, J = 2.0 Hz, 1H), 4.84 (s, 2H), 4.66 (s, 2H), 1.82 (s, 3H), 1.74 (s, 3H). Chiral purity: 100%. **13-C**: LCMS (MS, ESI): 342.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (s, 1H), 7.94-7.32 (m, 2H), 7.24-6.96 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.56 (t, J = 2.0 Hz, 1H), 4.84 (s, 2H), 4.66 (s, 2H), 1.82 (s, 3H), 1.74 (s, 3H). Chiral purity: 98.9%. Compounds (**13-B**) and (**13-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 14

(*S*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-B**), (*R*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-C**), (*S*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-D**) and (*R*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-E**)



13-A **14-A**



14-B **14-C** **14-D** **14-E**

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-A**)

[0229] A mixture of 2-amino-5-(2,5-dihydrofuran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**13-A**) (0.300 g, 0.879 mmol) and Pd/C (0.30 g, 0.281 mmol) in methanol (10 mL) and THF (10 mL) was stirred under hydrogen (2 atm) at rt for 16 h. The mixture was filtered and concentrated. The residue purified by flash column chromatography (SiO_2, 10% MeOH/DCM) to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-A**) (0.28 g, 92%). LCMS (MS, ESI): 343.95 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 1H), 7.74 (s, 1H), 7.70-7.10 (m, 3H), 7.04-7.00 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 3.96-3.82 (m, 2H), 3.74 (q, J = 7.6 Hz, 1H), 3.46 (t, J = 8.0 Hz, 1H), 3.32-3.22 (m, 1H), 2.13-1.93 (m, 2H), 1.81 (s, 3H), 1.73 (s, 3H)

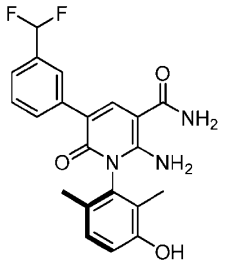
Chiral separation of (*S*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-B**), (*R*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-

carboxamide (**14-C**), (*S*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-D**), and (*R*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-E**)

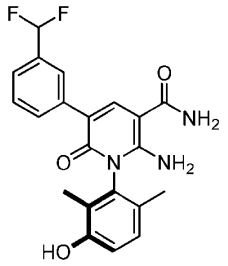
[0230] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-A**) (280 mg, 0.815 mmol) was subjected to prep-chiral-SFC (Column: CHIRAL ART Amylose-C NEO 3*25 cm, 5um; Mobile Phase A: CO_2, Mobile Phase B: EtOH(1%-2M-NH_3-MeOH); Flow rate: 90 mL/min; Gradient: isocratic 38% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm) to afford (*S*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-B**) (50 mg, 17%), (*R*, *R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-C**) (40 mg, 14%), (*S*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-D**) (45 mg, 15%), and (*R*, *S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(tetrahydrofuran-3-yl)-1,6-dihydropyridine-3-carboxamide (**14-E**) (58 mg, 20%). **14-B**: LCMS (MS, ESI): 344.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 7.74 (s, 1H), 7.55 (brs, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.03-3.80 (m, 2H), 3.74 (q, J = 7.6 Hz, 1H), 3.47 (t, J = 8.0 Hz, 1H), 3.32-3.22 (m, 1H), 2.16-1.95 (m, 2H), 1.82 (s, 3H), 1.73 (s, 3H); Chiral purity: 100% . **14-C**: LCMS (MS, ESI): 344.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 7.74 (s, 1H), 7.38 (brs, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 3.96-3.82 (m, 2H), 3.74 (q, J = 7.6 Hz, 1H), 3.46 (t, J = 8.0 Hz, 1H), 3.31-3.22 (m, 1H), 2.15-1.93 (m, 2H), 1.81 (s, 3H), 1.74 (s, 3H); Chiral purity: 100%. **14-D**: LCMS (MS, ESI): 344.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 7.74 (s, 1H), 7.55 (brs, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 3.97-3.82 (m, 2H), 3.74 (q, J = 7.6 Hz, 1H), 3.46 (t, J = 8.0 Hz, 1H), 3.31-3.21 (m, 1H), 2.16-1.95 (m, 2H), 1.81 (s, 3H), 1.74 (s, 3H); Chiral purity: 100% **14-E**: LCMS (MS, ESI): 344.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1H), 7.74 (s, 1H), 7.39 (brs, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 3.96-3.82 (m, 2H), 3.74 (q, J = 7.6 Hz, 1H), 3.47 (t, J = 8.0 Hz, 1H), 3.31-3.22 (m, 1H), 2.16-1.92 (m, 2H), 1.82 (s, 3H), 1.73 (s, 3H); Chiral purity: 100% Compounds (**14-B**), (**14-C**), (**14-D**) and (**14-E**) are diastereomers, and the stereochemistry may be the opposite of that depicted.

Example 15

(*S*)-2-Amino-5-(3-(difluoromethyl)phenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**15-B**) and (*R*)-2-Amino-5-(3-(difluoromethyl)phenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**15-C**)



15-B

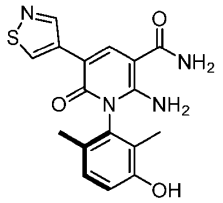


15-C

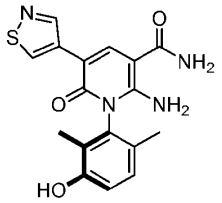
[0231] A mixture of racemic 2-Amino-5-(3-(difluoromethyl)phenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide(**15-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid (ester), and subjected to chiral SFC purification (Column/dimensions: LUX CELLULOSE-4 (30x250) mm,5µ; %CO_2: 70%; % Co-solvent: 30% (0.2% ammonia in ACN and MeOH)(1:1); Flow: 100 mL/min.; Back Pressure: 100 bar; Temperature: 30 °C; UV: 289 nm) to afford (*S*)-2-amino-5-(3-(difluoromethyl)phenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**15-B**) (33 mg) and (*R*)-2-amino-5-(3-(difluoromethyl)phenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**15-C**) (34 mg). **15-B**: LC-MS (ESI) 400.29 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.88-7.76 (br s, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.99 (t, J = 56 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); HPLC purity: 96.23%; Chiral purity: 99.97% HPLC: 96%. **15-C**: LC-MS (ESI) 400.29 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.88-7.76 (br s, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.99 (t, J = 56 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); HPLC purity: 99.40%; Chiral purity : 98.47%. HPLC: 98.7%. Compounds (**15-B**) and (**15-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 16

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(1,2-thiazol-4-yl)pyridine-3-carboxamide (**16-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(1,2-thiazol-4-yl)pyridine-3-carboxamide (**16-C**)



16-B

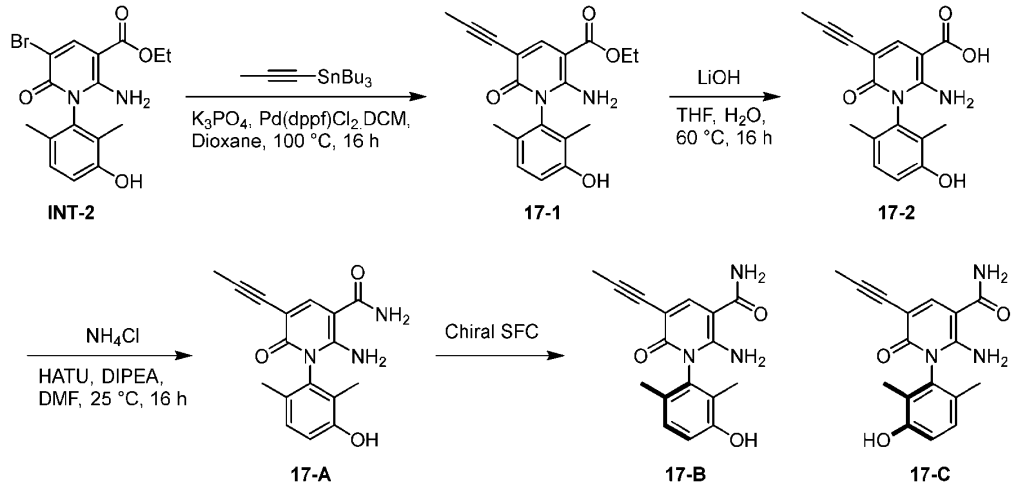


16-C

[0232] A mixture of racemic 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(1,2-thiazol-4-yl)pyridine-3-carboxamide (**16-A**) was prepared according to the procedure described in Example 9 using the corresponding boronic acid (ester), and subjected to prep-chiral-SFC chiral separation [Column: CHIRAL ART Cellulose-SJ 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (1%-2M-NH_3-MeOH); Flow rate: 85 mL/min; Gradient: isocratic 26% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm)] to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(1,2-thiazol-4-yl)pyridine-3-carboxamide (**16-B**) (36 mg), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(1,2-thiazol-4-yl)pyridine-3-carboxamide (**16-C**) (38 mg). **16-B**: LCMS (MS, ESI): 357.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 9.27 (s, 1H), 9.17 (s, 1H), 8.52 (s, 1H), 8.00-7.61 (brs, 1H), 7.31-6.95 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 1.86 (s, 3H), 1.78 (s, 3H); Chiral purity: 100% **16-C**: LCMS (MS, ESI): 357.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 9.27 (s, 1H), 9.17 (s, 1H), 8.52 (s, 1H), 7.99-7.68 (brs, 1H), 7.40-6.98 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H), 1.86 (s, 3H), 1.78 (s, 3H); Chiral purity: 98.71%. Compounds (**16-B**) and (**16-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 17

(*S*)-2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-C**)



Preparation of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylate (**17-1**).

[0233] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (1.00 g, 2.62 mmol), tributyl(prop-1-yn-1-yl)stannane (1.73 g, 5.25 mmol), 1,4-dioxane (20 mL), was added potassium phosphate tribasic monohydrate (1.51 g, 6.56 mmol), followed by $Pd(dppf)Cl_2$•DCM (0.214 g, 0.262 mmol). The mixture was purged with nitrogen for 10 min. The mixture was stirred at 100 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, ethyl acetate/petroleum ether) to afford ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylate (**17-1**) (0.42 g, 47%). MS (ESI) 341.23 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylic acid (**17-2**)

[0234] To a stirred mixture of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylate (**17-1**) (0.420 g, 1.23 mmol) in

water (2.1 mL) and ethanol (2.1 mL), was added lithium hydroxide monohydrate (0.362 g, 8.64 mmol) at 25 °C. The mixture was stirred at 60 °C for 16 h. The mixture was concentrated, and triturated with toluene (3 × 15 mL) to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylic acid (**17-2**) (0.40 g, crude), which was used directly for next step without further purification. MS (ESI) 313.17 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-A**)

[0235] To a stirred mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxylic acid (**17-2**) (0.400 g, 1.28 mmol) and ammonium chloride (1.37 g, 25.6 mmol) in dimethylformamide (8 mL), were added DIPEA (7.08 mL, 38.4 mmol) and HATU (2.44 g, 6.40 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers washed with brine, dried over magnesium sulphate, filtered, and concentrated. The residue purified by flash column chromatography (SiO_2, ethyl acetate/petroleum ether) to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-A**) (0.15 g, 39% over two steps). MS (ESI) 312.17 $[M+H]^+$.

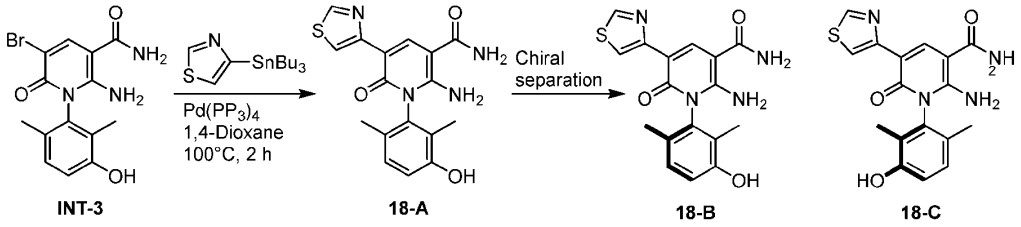
Separation of (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-B**) and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-C**)

[0236] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-A**) (0.150 g) were subjected to chiral SFC separation (Chiralpak AD-H (30x250) mm, 5μ, CO_2/0.1% ammonia in methanol) to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-B**) (0.045 g, 30%, 99.78% ee), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-yn-1-yl)-1,6-dihydropyridine-3-carboxamide (**17-C**) (0.042 g, 28%, 99.74% ee). **17-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (s, 1H), 8.11 (s, 1H), 7.64 (brs, 1H), 7.30-6.60 (brs, 1H), 7.19 (s, 2H), 7.05 (d, J = 8.40 Hz, 1H), 6.85 (d, J = 8.00 Hz, 1H), 1.97 (s, 3H), 1.81 (s, 3H), 1.73 (s, 3H); MS (ESI) 312.25 $[M+H]^+$; HPLC: 99.50%. **17-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.50 (s, 1H), 8.10 (s, 1H),7.90-6.90 (brs, 2H), 7.04 (d, J = 8.00 Hz, 1H), 6.85 (d, J = 8.40 Hz, 1H), 1.97 (s, 3H), 1.81 (s, 3H), 1.73

(s, 3H); MS (ESI) 312.28 $[M+H]^+$; HPLC: 98.33%. Compounds (**17-B**) and (**17-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 18

(S)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-B**) and *(R)*-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-C**)



Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-A**)

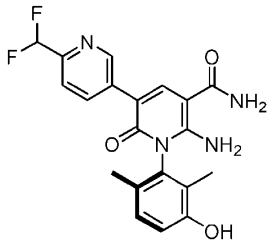
[0237] The stirred mixture of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**) (0.300 g, 0.852 mmol), 4-(tributylstannyl)thiazole (0.480 g, 1.28 mmol) and $Pd(PPh_3)_4$ (0.200 g, 0.170 mmol,) in 1,4-dioxane (10 mL), was degassed and backfilled with nitrogen five times, then stirred at 100 °C for 2 h. The mixture was cooled to rt, diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue purified by prep-HPLC [Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 8% B to 38% B in 10 min; Wave Length: 254 nm / 220 nm), to give 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-A**) (0.12 g, 39%). LCMS (MS, ESI): 357.05 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.87 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.95-7.25 (brs, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H).

Separation of *(S)*-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-B**), and *(R)*-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-C**)

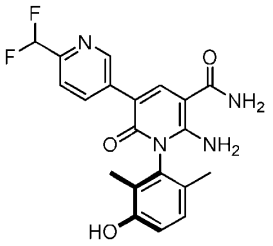
[0238] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-A**) (120 mg) was subjected to prep-chiral-HPLC [Column: Lux 5um Cellulose-4, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL / min; Gradient: isocratic 40; Wave Length: 254 nm / 220 nm] to afford *(S)*-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-B**) (53 mg, 44%), and *(R)*-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(thiazol-4-yl)-1,6-dihydropyridine-3-carboxamide (**18-C**) (53 mg, 44%). **18-B**: LCMS (MS, ESI): 357.15 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.87 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.05-7.30 (brs, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); Chiral purity: 100%. **18-C**: LCMS (MS, ESI): 357.20 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.87 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.98-7.30 (brs, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H): Chiral purity: 100%. Compounds (**18-B**) and (**18-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 19

(*S*)-6-amino-6'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**19-B**) and (*R*)-6-amino-6'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**19-C**)



19-B



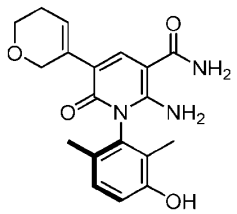
19-C

[0239] The racemic mixture of 6-amino-6'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**19-A**) was prepared

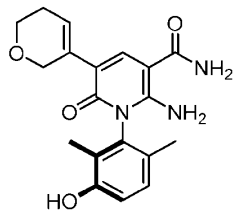
according to the procedures described in Example 2 using the corresponding boronic acid (ester), and subjected to chiral SFC separation (CHIRALPAK AD-H (30x250) mm, 5μ, CO_2/0.2% ammonia in methanol), followed by prep-HPLC, to afford (*S*)-6-amino-6'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**19-B**) (0.070 g, 99.76% ee), and (*R*)-6-amino-6'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**19-C**) (0.062 g, 97.86% ee). **19-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.55 (s, 1H), 9.06 (s, 1H), 8.39 (s, 1H), 8.34 (dd, *J* = 8.40, 2.40 Hz, 1H), 8.10-7.50 (brs, 1H), 7.65 (d, *J* = 8.40 Hz, 1H), 7.40-6.60 (m, 4H), 1.88 (s, 3H), 1.80 (s, 3H); MS (ESI) 401.33 $[M+H]^+$; HPLC: 99.26%. **19-C**: ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ ppm 9.48 (brs, 1H), 9.06 (s, 1H), 8.10-7.50 (brs, 1H), 7.65 (d, *J* = 8.40 Hz, 1H), 7.45-6.50 (m, 4H), 1.88 (s, 3H), 1.80 (s, 3H); MS (ESI) 401.33 $[M+H]^+$; HPLC: 99.28%. Compounds (**19-B**) and (**19-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 20

(*S*)-2-amino-5-(5,6-dihydro-2H-pyran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**20-B**) and (*R*)-2-amino-5-(5,6-dihydro-2H-pyran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**20-C**)



20-B



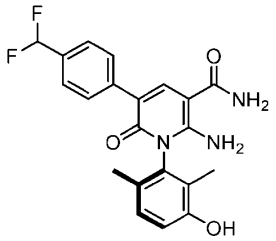
20-C

[0240] Racemic 2-Amino-5-(5,6-dihydro-2H-pyran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**20-A**) was prepared according to the procedures described in Example 9, and subjected to prep-chiral-HPLC [Column: JW-LUX-5UM Cellulose-4, 21.2*250mm, 5um; Mobile Phase A: EtOH--HPLC, Mobile Phase B: Hex(0.1% FA)--HPLC; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 15min; Wave Length: 220/254 nm] to afford (*S*)-2-amino-5-(5,6-dihydro-2H-pyran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**20-B**) (37 mg), and (*R*)-2-amino-5-(5,6-dihydro-2H-pyran-3-yl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide

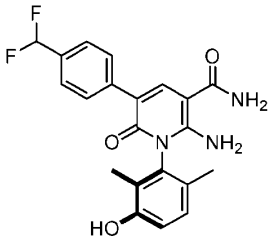
(**20-C**) (34 mg). **20-B**: LCMS (MS, ESI): 356.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (s, 1H), 7.80-7.50 (m, 2H), 7.06-7.03 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.38-6.36 (m, 1H), 4.36-4.35 (m, 2H), 3.70-3.67 (m, 2H), 2.19-2.18 (m, 2H), 1.82 (s, 3H), 1.74 (s, 3H); Chiral purity: 99.96%. **20-C**: LCMS (MS, ESI): 356.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (s, 1H), 7.83-7.60 (m, 2H), 7.02-6.91 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.38-6.36 (m, 1H), 4.36-4.35 (m, 2H), 3.70-3.67 (m, 2H), 2.19-2.18 (m, 2H), 1.82 (s, 3H), 1.74 (s, 3H); Chiral purity: 99.46%. Compounds (**20-B**) and (**20-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 21

(*S*)-2-amino-5-[4-(difluoromethyl)phenyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**21-B**) and (*R*)-2-amino-5-[4-(difluoromethyl)phenyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**21-C**)



21-B



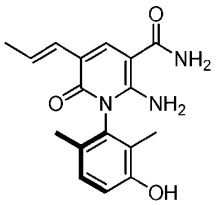
21-C

[0241] 2-Amino-5-[4-(difluoromethyl)phenyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**21-A**) was prepared according to the procedures described in Example 9 using the corresponding boronic acid (ester) (200 mg, 0.501 mmol) was subjected to p*rep*-chiral-HPLC [Column: JW-LUX-5UM Cellulose-4, 21.2*250mm, 5um; Mobile Phase A: EtOH--HPLC, Mobile Phase B: Hex(0.1% FA)--HPLC; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13min; Wave Length: 220/254 nm] to afford (*S*)-2-amino-5-[4-(difluoromethyl)phenyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**21-B**) (80 mg), and (*R*)-2-amino-5-[4-(difluoromethyl)phenyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**21-C**) (81 mg). **21-B**: LCMS (MS, ESI): 400.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 8.26 (s, 1H), 7.90-7.88 (m, 2H), 7.53-7.51 (m, 2H), 7.15-6.87 (m, 4H), 1.88 (s, 3H), 1.80 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -108.508; Chiral purity: 100%. **21-C**: LCMS (MS, ESI): 400.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 8.26 (s, 1H), 7.90-7.88

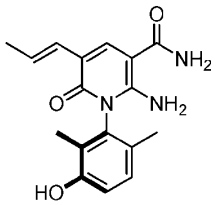
(m, 2H), 7.53-7.51 (m, 2H), 7.15-6.87 (m, 4H), 1.88 (s, 3H), 1.80 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -108.505; Chiral purity: 99.90%. Compounds (**21-B**) and (**21-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 22

(*S*)-(*E*)-2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-1-yl)-1,6-dihydropyridine-3-carboxamide (**22-B**) and (*R*)-(*E*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-1-yl)-1,6-dihydropyridine-3-carboxamide (**22-C**)



22-B

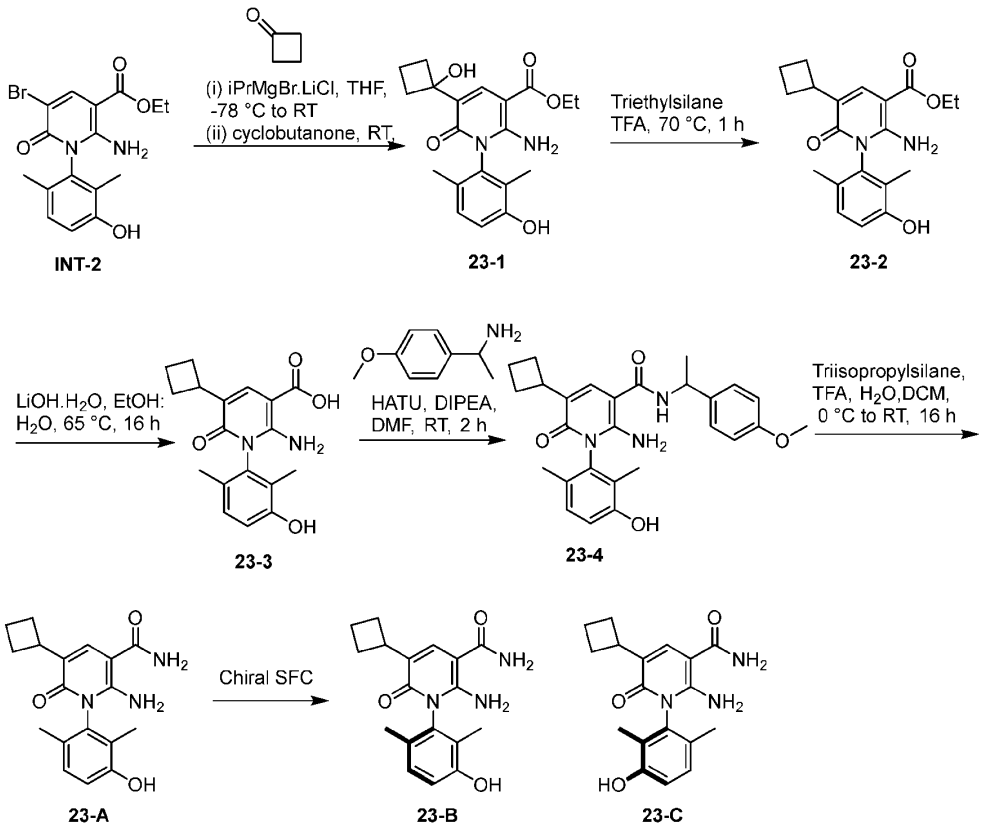


22-C

[0242] (*E*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-1-yl)-1,6-dihydropyridine-3-carboxamide (**22-A**), was prepared according to the experimental procedures described in Example 9 using the corresponding boronic acid (ester), and subjected to prep-chiral-HPLC separation [Column: JW-LUX-5UM Cellulose-4, 21.2*250mm, 5μm; Mobile Phase A: EtOH--HPLC, Mobile Phase B: Hex (0.1% FA)--HPLC; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 11min; Wave Length: 220/254 nm] to afford (*S*)-(*E*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-1-yl)-1,6-dihydropyridine-3-carboxamide (**22-B**) (50 mg), and (*R*)-(*E*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-1-yl)-1,6-dihydropyridine-3-carboxamide (**22-C**) (48 mg). **22-B**: LCMS (MS, ESI): 314.25 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (s, 1H), 8.00 (s, 1H), 7.91-7.11 (brs, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.48-6.11 (m, 2H), 1.81 (s, 3H), 1.78 (d, J = 6.0 Hz, 3H), 1.74 (s, 3H); Chiral purity: 100%. **22-C**: LCMS (MS, ESI): 314.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (s, 1H), 8.00 (s, 1H), 7.91-7.21 (brs, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.41-6.08 (m, 2H), 1.81 (s, 3H), 1.78 (d, J = 6.0 Hz, 3H), 1.74 (s, 3H); Chiral purity: 99.95%. Compounds (**22-B**) and (**22-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 23

(*S*)-2-Amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-B**) and (*R*)-2-Amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-C**)



Preparation of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-hydroxycyclobutyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-1**)

[0243] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (2.00 g, 5.25 mmol) in tetrahydrofuran (40.0 mL) at -78 °C, was added dropwise isopropyl magnesium chloride lithium chloride complex (1.3 M in THF) (109 mL, 142 mmol). The mixture was stirred at rt for 1.5 h. The mixture was cooled to -78 °C, then cyclobutanone (5.52 g, 78.7 mmol) was added. The mixture was stirred at -78 °C for 30 min, then warmed up to rt and stirred at rt for 1 h. The mixture was cooled down to 0 °C, and the reaction was quenched with aq. NH_4Cl. The mixture was extracted with EtOAc (150 mL), washed with aq. $NaHCO_3$ solution (2×50

mL) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue purified by silica gel flash column chromatography eluting with EtOAc in petroleum ether to afford ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-hydroxycyclobutyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-1**) (0.72 g, 36%). MS (ESI) *m/z* 371.18 $[M-H]^-$.

Preparation of ethyl 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-2**)

[0244] To a stirred mixture of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-hydroxycyclobutyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-1**) (0.720 g, 1.93 mmol) in triethylsilane (6.59 mL, 41.2 mmol) at 0 °C, was added trifluoroacetic acid (6.8 mL, 88.9 mmol). The mixture was stirred at 70 °C for 1 h. The mixture was quenched with ice-cold $NaHCO_3$ (50mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography eluting with EtOAc in petroleum ether, to afford ethyl 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-2**) (0.30 g, 43%). MS (ESI) *m/z* 357.21 $[M+H]^+$.

Preparation of 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**23-3**)

[0245] To a stirred mixture of ethyl 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**23-2**) (0.300 g, 0.842 mmol) in EtOH (3 mL) and water (3 mL) at rt, was added lithium hydroxide monohydrate (0.177 g, 4.21 mmol). The mixture was stirred at 65 °C for 16 h. The mixture was concentrated, diluted with water (10 mL) and acidified with 1N HCl to pH ~2. The obtained precipitated solid was filtered and dried under vacuum to afford 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**23-3**) (0.25 g, 90%), which was used directly for the next step without further purification. MS (ESI) *m/z* 329.18 $[M+H]^+$.

Preparation of 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-N-(1-(4-methoxyphenyl) ethyl) -6-oxo-1,6-dihydropyridine-3-carboxamide (**23-4**)

[0246] To a stirred mixture of 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**23-3**) (0.245 g, 0.746 mmol) in dimethylformamide (2.45 mL) at 0 °C, were added HATU (0.426 g, 1.12 mmol), *N,N*-diisopropylethylamine (0.650 mL, 3.73 mmol) and 1-(4-methoxyphenyl)ethan-1-amine

(0.135 g, 0.895 mmol). The mixture was stirred at rt for 2 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue purified by silica gel flash column chromatography eluting with EtOAc in petroleum ether to afford 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-*N*-(1-(4-methoxyphenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-4**) (0.20 g, 58%). MS (ESI) *m/z* 462.32 $[M+H]^+$.

Preparation of 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-A**)

[0247] To a stirred mixture of 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-*N*-(1-(4-methoxyphenyl)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-4**) (0.200 g, 0.433 mmol) in DCM (6 mL) at 0 °C, were added TFA (4.0 mL), water (0.60 mL) and triisopropylsilane (0.266 mL, 1.30 mmol). The mixture was stirred at rt for 30 min. The mixture was quenched with ice-cold $NaHCO_3$ (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue purified by silica gel flash column chromatography eluting with EtOAc in petroleum ether to afford 2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-A**) (0.090 g, 63%). MS (ESI) *m/z* 328.73 $[M+H]^+$.

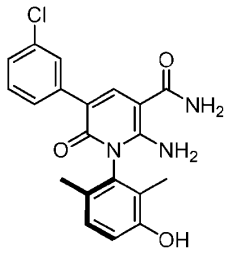
Separation of (*S*)-2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-B**), and (*R*)-2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-C**)

[0248] 2-Amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-A**) (0.090 g) was subjected to prep-chiral SFC [Column/dimensions: Chiral Pak ADH (30 × 250) mm,5μ; % CO_2: 75%, % Co-solvent: 25% (0.2% DEA in MeOH), Flow: 100 mL/min, Back Pressure: 100 bar, Temperature: 30 °C, UV: 220 nm] to afford (*S*)-2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-B**) (0.0273g, 30%), and (*R*)-2-amino-5-cyclobutyl-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**23-C**) (0.0259 g, 28%). **23-B**: MS (ESI) *m/z* 328.37 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 9.45 (s, 1H), 8.09-6.89 (m, 6H), 6.83 (d, J = 8.0 Hz, 1H), 3.48-3.33 (m, 1H), 2.18-1.96 (m, 4H), 1.94-

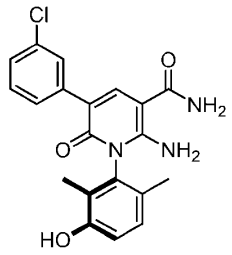
1.65 (m, 8H); Chiral purity: 99.85%. **23-C**: MS (ESI) *m/z* 328.37 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 9.45 (s, 1H), 7.93-7.18 (m, 4H), 7.03-6.79 (m, 3H), 3.45-3.36 (m, 1H), 2.19-1.98 (m, 4H), 1.94-1.84 (m, 1H), 1.82-1.67 (m, 7H); Chiral purity: 99.61%. Compounds (**23-B**) and (**23-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 24

(*S*)-2-amino-5-(3-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**24-B**) and (*R*)-2-amino-5-(3-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**24-C**)



24-B



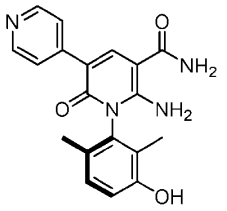
24-C

[0249] 2-Amino-5-(3-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**24-A**) (160 mg) was prepared according to the experimental procedures described in Example 9 using the corresponding boronic acid (ester), and subjected to prep-chiral-HPLC separation [Column: JW-LUX-5UM Cellulose-4, 21.2*250 mm, 5 μm; Mobile Phase A: EtOH--HPLC, Mobile Phase B: Hex (0.1% FA)--HPLC; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 12 min; Wave Length: 220/254 nm], to afford (*S*)-2-amino-5-(3-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**24-B**) (59 mg, 36%), and (*R*)-2-amino-5-(3-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**24-C**) (57 mg, 35%). **24-B**: LCMS (MS, ESI): 384.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (s, 1H), 8.25 (s, 1H), 8.03-7.78 (m, 2H), 7.75-7.73 (m, 1H), 7.37-7.30 (m, 1H), 7.25-7.23 (m, 1H), 7.20-6.93 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); Chiral purity: 100%. **24-C**: LCMS (MS, ESI): 384.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 (s, 1H), 8.26 (s, 1H), 8.00-7.81 (m, 2H), 7.75-7.73 (m, 1H), 7.37-7.33 (m, 1H), 7.25-7.23 (m, 1H), 7.20-6.96 (m, 2H),

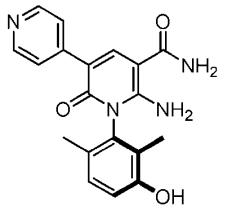
6.88 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); Chiral purity: 100%. Compounds (**24-B**) and (**24-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 25

(*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-[3,4'-bipyridine]-5-carboxamide (**25-B**) and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-[3,4'-bipyridine]-5-carboxamide (**25-C**)



25-B

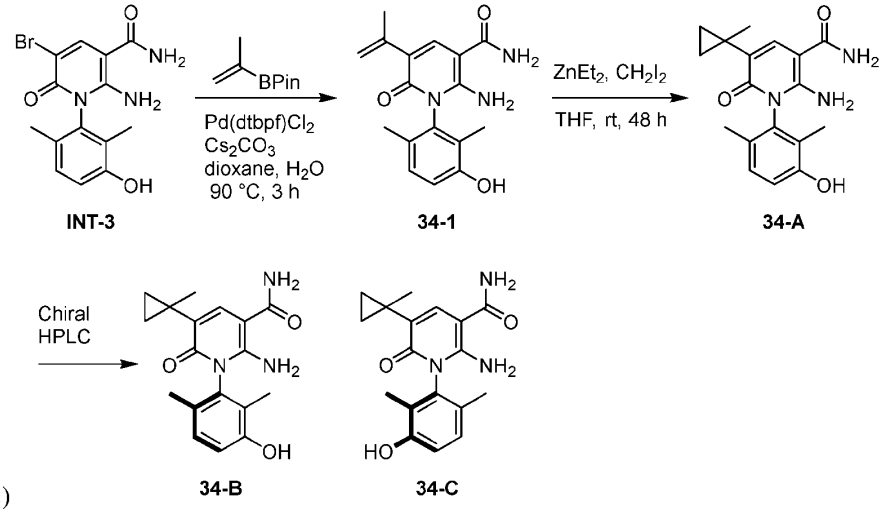


25-C

[0250] 6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-[3,4'-bipyridine]-5-carboxamide (**25-A**) (590 mg) was prepared according to the experimental procedures described in Example 2 using the corresponding boronic acid (ester), and subjected to prep-SFC separation [Column: CHIRAL ART Cellulose-SZ 3*25 cm, 5um; Mobile Phase A: CO_2, Mobile Phase B: MeOH(1%-2M-NH_3-MeOH); Flow rate: 85 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], to afford (*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-[3,4'-bipyridine]-5-carboxamide (**25-B**) (204 mg, 34%), and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-[3,4'-bipyridine]-5-carboxamide (**25-C**) (267 mg, 45%). **25-B**: LCMS (MS, ESI): 350.90 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 8.58-8.37 (m, 3H), 8.02-7.75 (m, 3H), 7.25-7.02 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); Chiral purity: 100%. **25-C**: LCMS (MS, ESI): 350.85 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 (s, 1H), 8.55-8.35 (m, 3H), 8.02-7.73 (m, 3H), 7.28-6.98 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); Chiral purity: 100%. Compounds (**25-B**) and (**25-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 26

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-C**)



INT-3 34-1 34-A 34-B 34-C

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**34-1**)

[0251] To a stirred mixture of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**INT-3**) (0.700 g, 1.99 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.400 g, 2.39 mmol) in dioxane (16 mL) and H_2O (4 mL), were added $Pd(dtbpf)Cl_2$ (0.130 g, 0.199 mmol) and Cs_2CO_3 (1.30 g, 3.98 mmol). After the reaction mixture was purged and backfilled with nitrogen five times, it was stirred at 90 °C for 3 h. The mixture was then cooled down to RT, diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether), to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**34-1**) (0.50 g, 81% yield). LCMS (MS, ESI): 314.15 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-A**)

[0252] To a stirred mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(prop-1-en-2-yl)-1,6-dihydropyridine-3-carboxamide (**34-1**) (0.430 g, 1.37 mmol) in THF

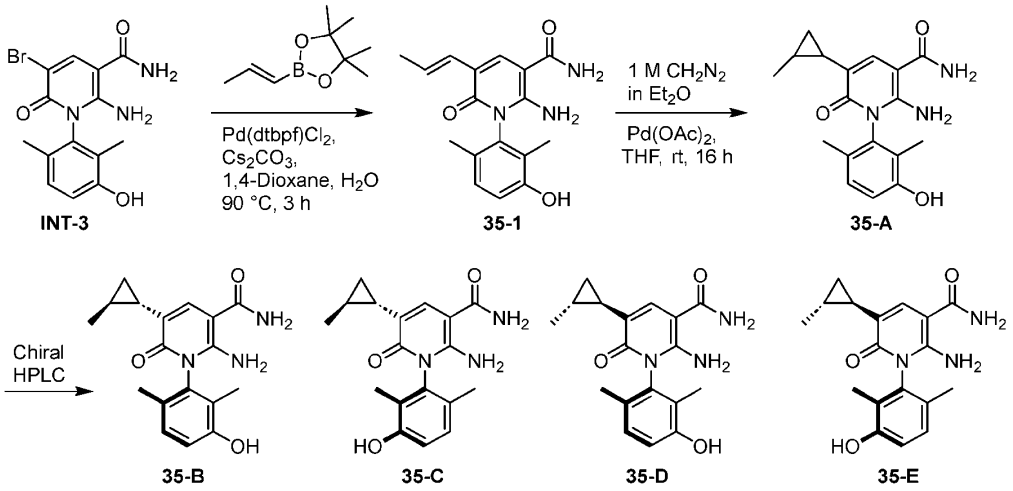
(14 mL) under nitrogen at 0 °C, were added $ZnEt_2$ (27.4 mL, 27.4 mmol) and diiodomethane (2.20 mL, 27.4 mmol. After stirring at 0 °C for 30 min then RT for 48 h, the reaction mixture was quenched with aqueous saturated NH_4Cl (15 mL), and then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by preparative achiral SFC [Column: DAICEL DCpak P4VP 3*25 cm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (1%-2M-NH_3-MeOH); Flow rate: 65 mL/min; Gradient: isocratic 34% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], followed by lyophilization to give 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-A**) (145 mg, 32% yield). LCMS (MS, ESI): 328.20 $[M+H]^+$.

Separation of (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-C**)

[0253] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-A**) (145 mg, 0.443 mmol), was subjected to preparative chiral HPLC [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 35; Wave Length: 254 / 220 nm], to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-B**) (61 mg, 42% yield), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methylcyclopropyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**34-C**) (60 mg, 41% yield). **34-B**: LCMS (MS, ESI): 328.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.73 (s, 1H), 7.70-7.12 (brs, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.21 (s, 3H), 0.74-0.57 (m, 2 H), 0.57-0.39 (m, 2H). Chiral purity: 100% ee. **34-C**: LCMS (MS, ESI): 328.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.73 (s, 1H), 7.69-7.11 (brs, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.21 (s, 3H), 0.76-0.56 (m, 2 H), 0.56-0.38 (m, 2H). Chiral purity: 99.9% ee. Compounds (**34-B**) and (**34-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 27

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-B**), (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-C**), (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-D**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-E**)



Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-prop-1-en-1-yl]pyridine-3-carboxamide (**35-1**)

[0254] To a stirred mixture of 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**INT-3**) (0.800 g, 2.27 mmol), 4,4,5,5-tetramethyl-2-[(1*E*)-prop-1-en-1-yl]-1,3,2-dioxaborolane (0.460 g, 2.73 mmol), dioxane (16 mL), and H_2O (4 mL), were added $Pd(dtbpf)Cl_2$ (0.150 g, 0.227 mmol) and Cs_2CO_3 (1.48 g, 4.54 mmol). After the reaction mixture was degassed and backfilled with nitrogen five times. The mixture was stirred at 90 °C for 3 h, then cooled down to RT, diluted with water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, $MeOH/CH_2Cl_2$), to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-prop-1-en-1-yl]pyridine-3-carboxamide (**35-1**) (0.40 g, 56% yield). LCMS (MS, ESI): 314.85 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylcyclopropyl)-6-oxopyridine-3-carboxamide (**35-A**)

[0255] To a stirred mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-prop-1-en-1-yl]pyridine-3-carboxamide (**35-1**) (0.260 g, 0.830 mmol) in THF (8 mL) at 0 °C, were added $Pd(OAc)_2$ (0.0400 g, 0.166 mmol) and 1 M diazomethane in Et_2O (41.5 mL, 41.500 mmol) under nitrogen. After stirring at RT for 16 h, the reaction mixture was filtered through a pad of Celite, and the filter cake washed with ethyl acetate (3 × 10 mL). The combined filtrates were concentrated, and the obtained residue purified by preparative HPLC [Column: DAICEL DCPAK P4VP 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (1%-2M-NH_3-MeOH); Flow rate: 65 mL/min; Gradient: isocratic 38% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], followed by lyophilization, to give 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylcyclopropyl)-6-oxopyridine-3-carboxamide (**35-A**) (120 mg, 44% yield). LCMS (MS, ESI): 328.20 $[M+H]^+$.

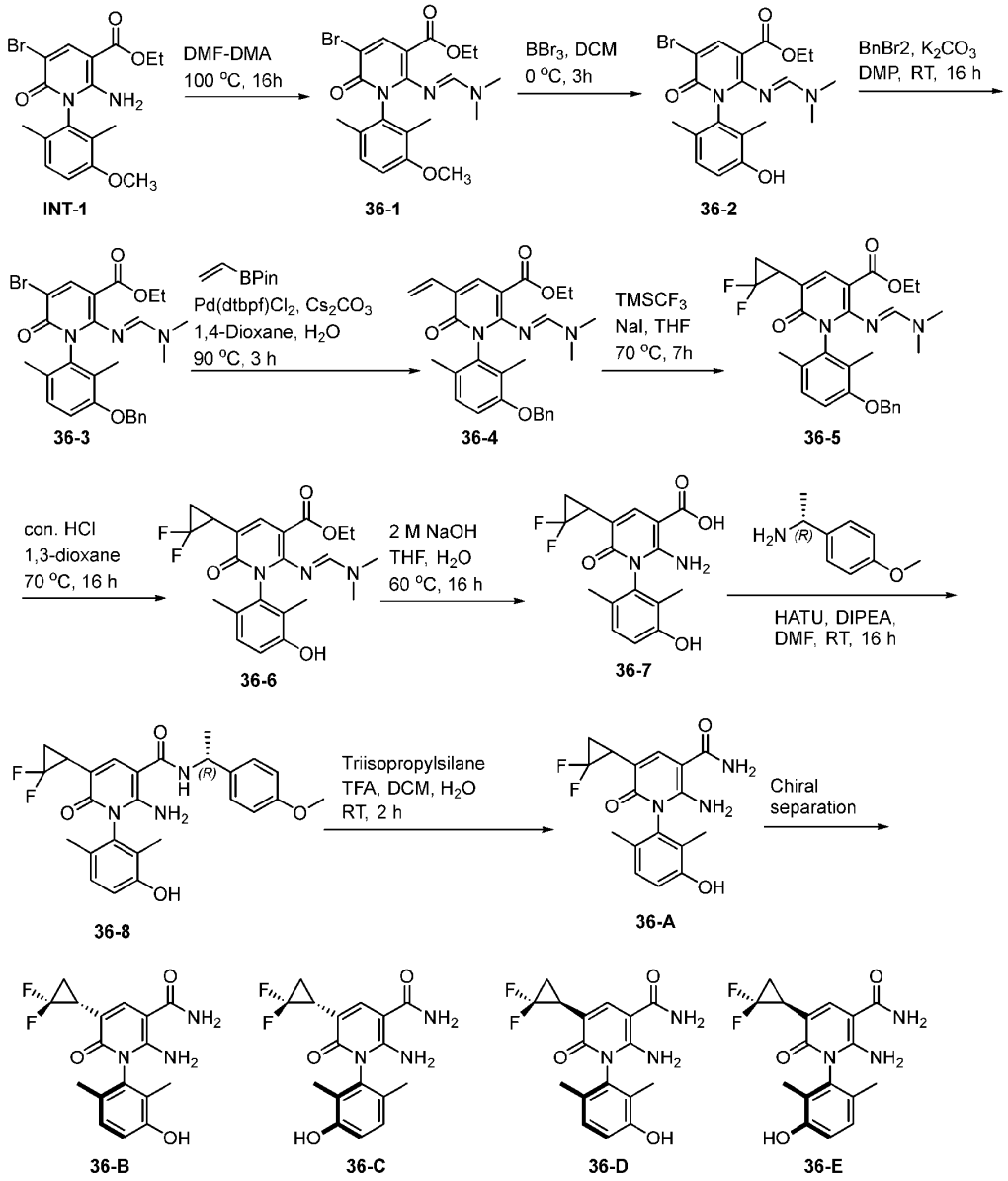
Separation of (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-B**), (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-C**), (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-D**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-E**)

[0256] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(2-methylcyclopropyl)-6-oxopyridine-3-carboxamide (**35-A**) (120 mg, 0.359 mmol), was subjected to preparative chiral HPLC [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford Fraction A then Fraction B. Fraction A was further subjected to preparative SFC [Column: (S,S)-WHELK-O1 3*25 cm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: IPA (1%-2M-NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 22% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-B**) (17 mg, 14% yield), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*S*,2*S*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-C**) (20

mg, 16% yield). Fraction B was further purified by preparative chiral HPLC [Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 15; Wave Length: 254/220 nm], to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-D**) (16 mg, 13% yield), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-[(1*R*,2*R*)-2-methylcyclopropyl]-6-oxopyridine-3-carboxamide (**35-E**) (17 mg, 14% yield). **35-B**: LCMS (MS, ESI): 326.15 $[M-H]^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.61- 7.17 (m, 3H), 7.04 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 1.81 (s, 3H), 1.73 (s, 3H), 1.55-1.44 (m, 1H), 1.15-1.06 (m, 3H), 1.02-0.91 (m, 1H), 0.86-0.72 (m, 1H), 0.58-0.44 (m, 1H). Chiral purity: 100% ee. **35-C**: LCMS (MS, ESI): 328.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.95- 7.03 (m, 3H), 7.04 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.58-1.44 (m, 1H), 1.18-1.05 (m, 3H), 1.05-0.92 (m, 1H), 0.87-0.72 (m, 1H), 0.57-0.47 (m, 1H). Chiral purity: 100% ee. **35-D**: LCMS (MS, ESI): 328.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.59- 7.22 (m, 3H), 7.04 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 1.81 (s, 3H), 1.73 (s, 3H), 1.57-1.42 (m, 1H), 1.24-1.05 (m, 3H), 1.02-0.88 (m, 1H), 0.88-0.61 (m, 1H), 0.57-0.38 (m, 1H). Chiral purity: 99.7% ee. **35-E**: LCMS (MS, ESI): 328.25 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.68- 7.04 (m, 3H), 7.04 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.57-1.46 (m, 1H), 1.21-1.06 (m, 3H), 1.06-0.89 (m, 1H), 0.89-0.71 (m, 1H), 0.61-0.44 (m, 1H). Chiral purity: 98.05% ee. Compounds (**35-B**), (**35-C**) (**35-D**) and (**35-E**) are diastereomers, and the stereochemistry may be the opposite of that depicted.

Example 28

(*S*)-2-amino-5-[(1*R*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-B**), (*R*)-2-amino-5-[(1*R*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-C**), (*S*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-D**), (*R*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-E**)



Preparation of ethyl 5-bromo-2-[(*E*)-[(dimethylamino)methylidene] amino]-1-(3-methoxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**36-1**)

[0257] A stirred mixture of ethyl 2-amino-5-bromo-1-(3-methoxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**INT-1**) (1.00 g, 2.53 mmol) in DMF-DMA (15 mL), was heated at 100 °C for 16 h. The mixture was cooled down to RT, concentrated, and the residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether), to afford ethyl 5-bromo-2-[(*E*)-[(dimethylamino)methylidene]amino]-1-(3-methoxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**36-1**) (0.80 g, 70% yield). LCMS (MS, ESI): 450.05, 452.05 $[M+H]^+$.

Preparation of ethyl (*E*)-5-bromo-2-(((dimethylamino)methylene)amino)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-2**)

[0258] To a stirred mixture of ethyl (*E*)-5-bromo-2-(((dimethylamino)methylene)amino)-1-(3-methoxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-1**) (5.00 g, 11.1 mmol) in DCM (100 mL) at 0 °C, was added BBr_3 (44.4 mL, 44.4 mmol) slowly under nitrogen. After stirring at 0 °C for 3 h, the reaction mixture was basified to pH 8 with aq. saturated $NaHCO_3$, then extracted with ethyl acetate (4 × 150 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by flash column chromatography (SiO_2, EtOAc/DCM), to afford ethyl (*E*)-5-bromo-2-(((dimethylamino)methylene)amino)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-2**) (3.17 g, 65% yield). LCMS (MS, ESI): 436.05, 438.05 $[M+H]^+$.

Preparation of ethyl (*E*)-1-(3-(benzyloxy)-2,6-dimethylphenyl)-5-bromo-2-(((dimethylamino)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-3**)

[0259] To a stirred mixture of ethyl (*E*)-5-bromo-2-(((dimethylamino)methylene)amino)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-2**) (3.00 g, 6.88 mmol) in DMF (60 mL), were added K_2CO_3 (2.85 g, 20.6 mmol) and benzyl bromide (1.76 g, 10.3 mmol). After stirring at RT for 16 h, the reaction mixture was quenched with water (250 mL), and then extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by flash

column chromatography (SiO_2, EtOAc/petroleum ether), to afford ethyl (*E*)-1-(3-(benzyloxy)-2,6-dimethylphenyl)-5-bromo-2-(((dimethylamino)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate (**36-3**) (3.10 g, 85% yield). LCMS (MS, ESI): 526.00, 528.00 $[M+H]^+$.

Preparation of ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-2-[(*E*)-[(dimethylamino)methylidene]amino]-5-ethenyl-6-oxopyridine-3-carboxylate (**36-4**)

[0260] To a stirred mixture of ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-5-bromo-2-[(*E*)-[(dimethylamino)methylidene] amino]-6-oxopyridine-3-carboxylate (**36-3**) (1.34 g, 2.54 mmol), 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.470 g, 3.05 mmol) in dioxane (12 mL) and H_2O (3 mL), were added $Pd(dtbpf)Cl_2$ (0.170 g, 0.255 mmol) and Cs_2CO_3 (1.66 g, 5.09 mmol). After the reaction mixture was degassed and backfilled with nitrogen five times, it was stirred at 90 °C for 3 h. The mixture was cooled down to RT, diluted with water (15 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, EtOAc/CH_2Cl_2), to afford ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-2-[(*E*)-[(dimethylamino)methylidene] amino]-5-ethenyl-6-oxopyridine-3-carboxylate (**36-4**) (1.00 g, 82% yield). LCMS (MS, ESI): 474.05 $[M+H]^+$.

Preparation of ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-5-(2,2-difluorocyclopropyl)-2-[(*E*)-[(dimethylamino)methylidene]amino]-6-oxopyridine-3-carboxylate (**36-5**)

[0261] To a stirred mixture of ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-2-[(*E*)-[(dimethylamino)methylidene]amino]-5-ethenyl-6-oxopyridine-3-carboxylate (**36-4**) (1.00 g, 2.11 mmol) in THF (20 mL) at RT, were added trimethyl(trifluoromethyl)silane (1.50 g, 10.6 mmol) and NaI (0.630 g, 4.22 mmol). After stirring at 70 °C for 7 h, the reaction mixture was cooled down to RT, quenched with water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by flash column chromatography (SiO_2, EtOAc/CH_2Cl_2), to afford ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-5-(2,2-difluorocyclopropyl)-2-[(*E*)-[(dimethylamino)methylidene] amino]-6-oxopyridine-3-carboxylate (**36-5**) (0.90 g, 81% yield). LCMS (MS, ESI): 524.05 $[M+H]^+$.

Preparation of ethyl 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**36-6**)

[0262] To a stirred mixture of ethyl 1-[3-(benzyloxy)-2,6-dimethylphenyl]-5-(2,2-difluorocyclopropyl)-2-[(*E*)-[(dimethylamino)methylidene] amino]-6-oxopyridine-3-carboxylate (**36-5**) (0.810 g, 1.55 mmol) in dioxane (10 mL), was added conc. HCl (5 mL) at RT. After stirring at 70 °C for 16 h, the reaction mixture was cooled down to 0 °C, basified to pH 8 with aq. saturated $NaHCO_3$, and the extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by flash column chromatography (SiO_2, EtOAc/CH_2Cl_2), to afford ethyl 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**36-6**) (0.50 g, 85% yield). LCMS (MS, ESI): 379.15 $[M+H]^+$.

Preparation of 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylic acid (**36-7**)

[0263] To a stirred mixture of ethyl 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**36-6**) (0.450 g, 1.19 mmol) in THF (12 mL) and H_2O (3 mL) at RT, was added 2 M NaOH (3.0 mL, 5.9 mmol). After stirring at 60 °C for 16 h, the reaction mixture was cooled down to RT, concentrated, and acidified to pH 6 with 1 M HCl at 0 °C. The resulting precipitate was collected, washed with water (2 × 5 mL), and then dried under vacuum to afford 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylic acid (**36-7**) (0.36 g, 86% yield). LCMS (MS, ESI): 350.90 $[M+H]^+$.

Preparation of 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-*N*-[(1*R*)-1-(4-methoxyphenyl) ethyl]-6-oxopyridine-3-carboxamide (**36-8**)

[0264] To a stirred mixture of 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylic acid (**36-7**) (0.350 g, 0.999 mmol) and (1*R*)-1-(4-methoxyphenyl)ethanamine (0.230 g, 1.50 mmol) in DMF (10 mL), were added HATU (0.600 g, 1.50 mmol) and DIPEA (0.90 mL, 5.0 mmol) at 0 °C. After stirring at RT for 16 h, the reaction mixture was diluted with water (20 mL), and then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by flash column

chromatography (SiO_2, MeOH/CH_2Cl_2), to afford 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-*N*-[(1*R*)-1-(4-methoxyphenyl) ethyl]-6-oxopyridine-3-carboxamide (**36-8**) (0.50 g, 97% yield). LCMS (MS, ESI): 484.00 $[M+H]^+$.

Preparation of 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-A**)

[0265] To a stirred mixture of 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-*N*-[(1*R*)-1-(4-methoxyphenyl) ethyl]-6-oxopyridine-3-carboxamide (**36-8**) (0.450 g, 0.931 mmol) in DCM (9 mL) at 0 °C, were added TFA (9 mL), H_2O (1.8 mL) and triisopropylsilane (0.440 g, 2.79 mmol). After stirring at RT for 2 h, the reaction mixture was cooled to 0 °C, basified to pH 8 with aq. saturated $NaHCO_3$, and then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, MeOH/CH_2Cl_2), to afford 2-amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-A**) (200 mg, 67% yield). LCMS (MS, ESI): 349.90 $[M+H]^+$.

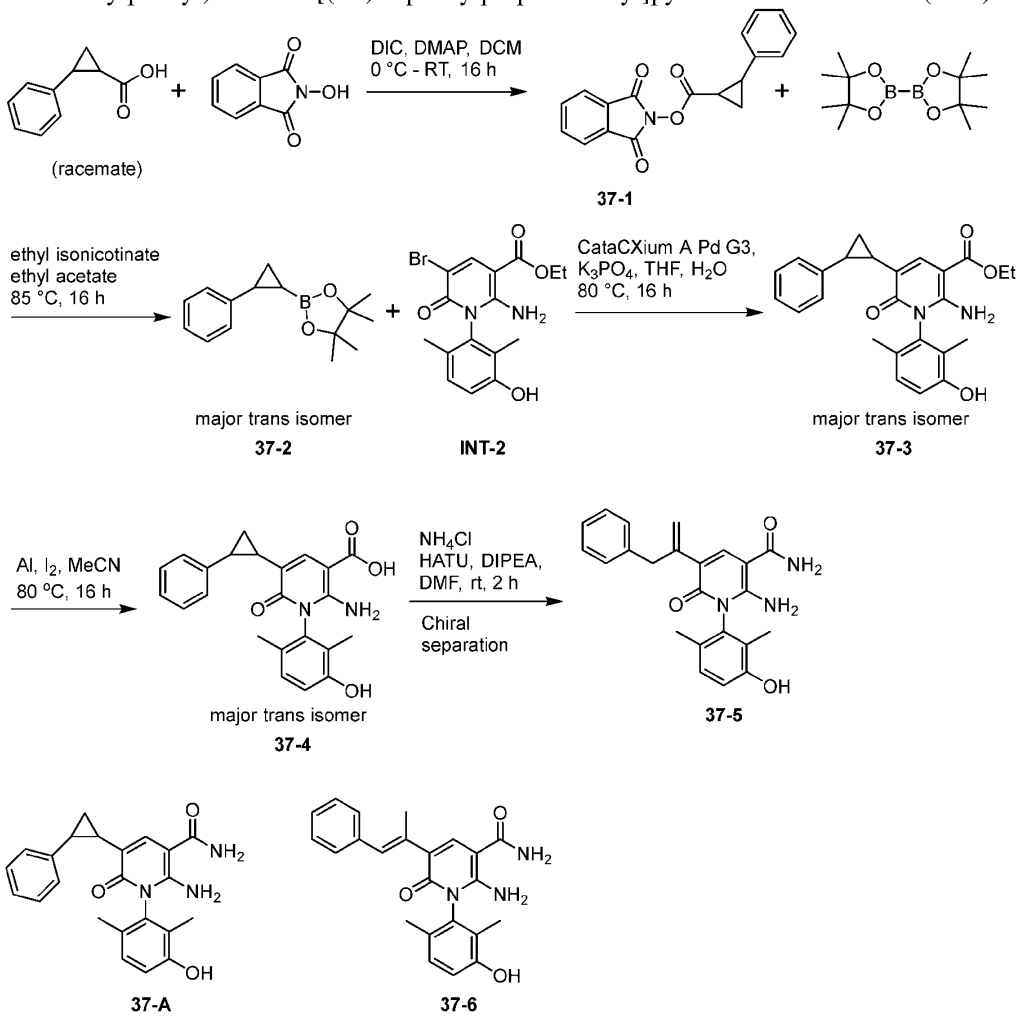
Separation of (*S*)-2-amino-5-[(1*R*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-B**), (*R*)-2-amino-5-[(1*R*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-C**), (*S*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-D**), (*R*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-E**)

[0266] 2-Amino-5-(2,2-difluorocyclopropyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-A**) (200 mg, 0.570 mmol), was first purified by preparative chiral-HPLC [Column: CHIRAL ART Cellulose-SJ 3*25 cm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (1%-2M-NH_3-MeOH); Flow rate: 85 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], to afford Fraction A then Fraction B. Fraction A was further purified by preparative chiral HPLC [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 15; Wave Length: 254/220 nm], to afford (*S*)-2-amino-5-[(1*R*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-B**) (19 mg, 9% yield), and (*R*)-2-amino-5-[(1*R*)-2,2-

difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-C**) (27 mg, 13% yield). Fraction B was further purified by preparative chiral HPLC [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 254/220 nm], to afford (*S*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-D**) (22 mg, 10% yield), and (*R*)-2-amino-5-[(1*S*)-2,2-difluorocyclopropyl]-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**36-E**) (26 mg, 13% yield). **36-B**: LCMS (MS, ESI): 350.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.70 (s, 1H), 7.66-7.21 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 2.71-2.58 (m, 1H), 2.09-1.89 (m, 1H), 1.88-1.61 (m, 7H). ^{19}F NMR (376 MHz, DMSO) δ -126.76 (d, J = 148 Hz, 1F), -142.58 (d, J = 149 Hz, 1F). Chiral purity: 100% ee. **36-C**: LCMS (MS, ESI): 350.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.78 (s, 1H), 7.68-7.11 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.70-2.59 (m, 1H), 2.04-1.91 (m, 1H), 1.84 (s, 3H), 1.82-1.73 (m, 1H), 1.72 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -126.73 (d, J = 149 Hz, 1F), -142.55 (d, J = 149 Hz, 1F). Chiral purity: 98.9% ee. **36-D**: LCMS (MS, ESI): 350.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.75 (s, 1H), 7.68-7.11 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 2.69-2.59 (m, 1H), 2.08-1.91 (m, 1H), 1.84 (s, 3H), 1.82-1.72 (m, 1H), 1.73 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -126.54 (d, J = 148 Hz, 1F), -142. 55 (d, J = 148 Hz, 1F). Chiral purity: 99.7% ee. **36-E**: LCMS (MS, ESI): 350.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.70 (s, 1H), 7.69-7.11 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.69-2.58 (m, 1H), 2.08-1.89 (m, 1H), 1.83-1.69 (m, 7H). ^{19}F NMR (376 MHz, DMSO) δ -126.72 (d, J = 149 Hz, 1F), -142. 54 (d, J = 149 Hz, 1F). Chiral purity: 99.85% ee. Compounds (**36-B**), (**36-C**) (**36-D**) and (**36-E**) are diastereomers, and the stereochemistry may be the opposite of that depicted.

Example 29

2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(3-phenylprop-1-en-2-yl)pyridine-3-carboxamide (**37-5**), 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)pyridine-3-carboxamide (**37-A**), 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-1-phenylprop-1-en-2-yl]pyridine-3-carboxamide (**37-6**)



Preparation of 1,3-dioxoisoindol-2-yl 2-phenylcyclopropane-1-carboxylate (**37-1**)

[0267] To a stirred mixture of 2-phenylcyclopropane-1-carboxylic acid (2.50 g, 15.4 mmol), DMAP (0.380 g, 3.09 mmol) and *N*-hydroxyphthalimide (2.77 g, 17.0 mmol) in DCM (25 mL) at 0 °C, was added DIC (2.24 g, 17.7 mmol) portion wise under nitrogen. After stirring at RT for 16 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed

with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether), to afford 1,3-dioxoisoindol-2-yl 2-phenylcyclopropane-1-carboxylate (**37-1**) (2.00 g, 42% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94-7.88 (m, 2H), 7.84-7.78 (m, 2H), 7.39-7.32 (m, 2H), 7.29-7.25 (m, 1H), 7.24-7.16 (m, 2H), 2.86-2.75 (m, 1H), 2.29-2.21 (m, 1H), 1.89-1.81 (m, 1H), 1.71-1.63 (m, 1H).

Preparation of 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (**37-2**)

[0268] To a stirred mixture of 1,3-dioxoisoindol-2-yl 2-phenylcyclopropane-1-carboxylate (**37-1**) (2.00 g, 6.51 mmol) and bis(pinacolato)diboron (3.31 g, 13.0 mmol) in ethyl acetate (40 mL), was added ethyl isonicotinate (0.200 g, 1.30 mmol) portion wise at RT under nitrogen. After stirring at 85 °C for 16 h, the reaction mixture was cooled down to RT, diluted with water (40 mL), and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether), to afford 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (**37-2**) (0.50 g, 32% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30-7.22 (m, 2H), 7.18-7.12 (m, 1H), 7.12-7.07 (m, 2H), 2.18-2.08 (m, 1H), 1.30-1.24 (m, 12H), 1.20-1.14 (m, 1H), 1.06-0.99 (m, 1H), 0.36-0.27 (m, 1H).

Preparation of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylate (**37-3**)

[0269] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxylate (**INT-2**) (0.200 g, 0.525 mmol) and 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (**37-2**) (0.260 g, 1.05 mmol) in THF (4 mL) and H_2O (1 mL) at RT, were added CataCXium A Pd G3 (0.040 g, 0.053 mmol) and K_3PO_4 (0.330 g, 1.58 mmol) under nitrogen. After stirring at 80 °C for 16 h, the reaction mixture was cooled down to RT, diluted with water (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, EtOAc/petroleum ether), to afford ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylate (**37-3**) (0.150 g, 68% yield). LCMS (MS, ESI): 418.95 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylic acid (**37-4**)

[0270] To a stirred mixture of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylate (**37-3**) (0.130 g, 0.311 mmol) and iodine (0.160 g, 0.622 mmol) in MeCN (10 mL) at 0 °C, was added aluminum (0.080 g, 3.1 mmol) portion wise under nitrogen. The reaction mixture was stirred at 80 °C for 16 h. The mixture was cooled down to RT, filtered, concentrated, and the residue purified by flash column chromatography (SiO_2, MeOH/CH_2Cl_2), to afford a mixture of desired 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylic acid (**37-4**), and some ring-opening side products (0.200 g, crude). LCMS (MS, ESI): 391.15 $[M+H]^+$.

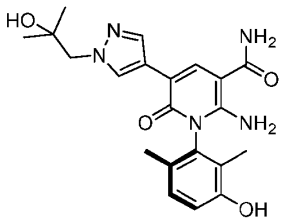
Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(3-phenylprop-1-en-2-yl)pyridine-3-carboxamide (**37-5**), 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)pyridine-3-carboxamide (**37-A**), 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-1-phenylprop-1-en-2-yl]pyridine-3-carboxamide (**37-6**)

[0271] To a stirred crude mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)-1,6-dihydropyridine-3-carboxylic acid (**37-4**) (0.200 g, 0.513 mmol) in DMF (6 mL) at 0 °C, were added ammonium chloride (0.550 g, 10.3 mmol), HATU (0.970 g, 2.56 mmol) and DIPEA (0.660 g, 5.13 mmol) under nitrogen. After stirring at RT for 2 h, the reaction mixture was diluted with water (15 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue purified by preparative-HPLC [Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 40% B in 10 min; Wave Length: 254 nm / 220 nm], followed by further purification by preparative achiral SFC [Column: DAICEL DCpak P4VP 3*25 cm, 5 um; Mobile Phase A: CO_2, Mobile Phase B: MeOH(1%-2M-NH_3-MeOH); Flow rate: 65 mL/min; Gradient: isocratic 42% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm], to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(3-phenylprop-1-en-2-yl)pyridine-3-carboxamide (**37-5**) (6 mg, 10% yield), 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-(2-phenylcyclopropyl)pyridine-3-carboxamide (**37-A**) (17 mg, 8%

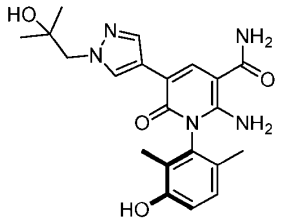
yield), and 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-5-[(1*E*)-1-phenylprop-1-en-2-yl]pyridine-3-carboxamide (**37-6**) (1.6 mg, 2% yield). **37-5**: LCMS (MS, ESI): 390.00 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.51 (brs, 1H), 7.83 (s, 1H), 7.76-7.40 (m, 2H), 7.40-7.34 (m, 2H), 7.32-7.29 (m, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.47-6.32 (m, 2H), 3.22 (d, J = 5.2 Hz, 2H), 1.83 (s, 3H), 1.76 (s, 3H). **37-A**: LCMS (MS, ESI): 390.00 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.48 (brs, 1H), 7.82-7.31 (m, 3H), 7.29-7.20 (m, 2H), 7.20-7.08 (m, 3H), 7.08-6.98 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 2.08 (t, J = 7.2 Hz, 2H), 1.82 (d, J = 7.6 Hz, 3H), 1.74 (d, J = 7.2 Hz, 3H), 1.54-1.45 (m, 1H), 1.26-1.16 (m, 1H). **37-6**: LCMS (MS, ESI): 389.95 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.56 (brs, 1H), 7.99 (s, 1H), 7.92-7.53 (m, 1H), 7.52-7.43 (m, 2H), 7.38-7.31 (m, 2H), 7.29-7.14 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.87 (d, J =7.6 Hz, 1H), 6.65 (s, 1H), 2.22 (s, 3H), 1.86 (s, 3H), 1.78 (s, 3H).

Example 30

(*S*)- 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**40-B**), and (*R*)- 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**40-C**)



40-B



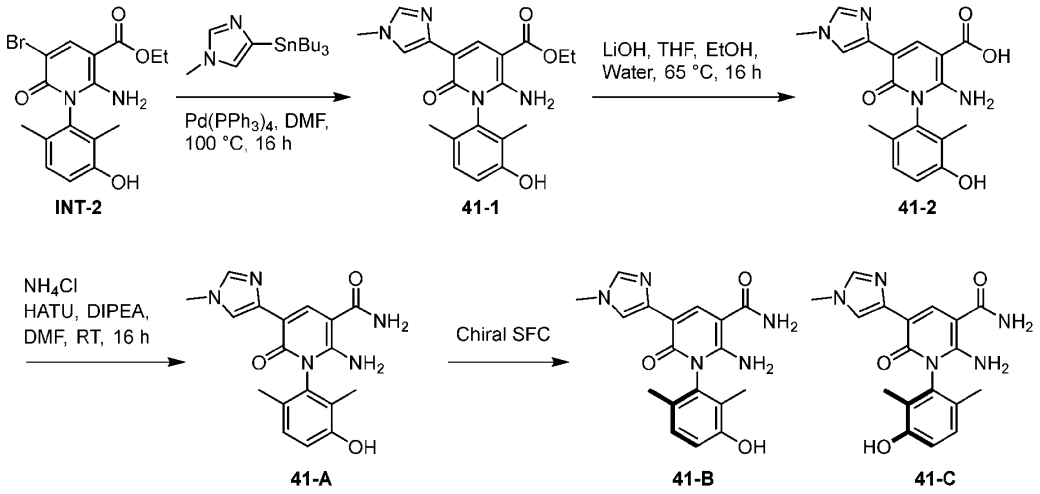
40-C

[0272] The racemic mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**40-A**) was prepared according to the procedure described in Example 5, and subjected to chiral SFC separation [column: LUX CELLULOSE-4 (30x250) mm, 5μm; % CO2: 67%; % Co-solvent: 33% (0.1% 7N Methanolic ammonia in ACN-MeOH); Flow: 100 mL/min.; Back Pressure: 100 bar; Temperature: 30 °C; UV: 220 nm], followed by lyophilization, to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**40-B**) (0.0106 g, 31% yield), and

(*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**40-C**) (0.0113 g, 34% yield). **40-B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.25 (s, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.80 – 7.10 (br s, 5H), 6.88 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 3.96 (s, 2H), 1.83 (s, 3H), 1.76 (s, 3H). MS (ESI) 412.35 $[M+H]^+$. HPLC Purity: 98.16%. Chiral purity: 99.48% ee. **40-C**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.25 (s, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.80 – 7.10 (br s, 5H), 6.88 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 3.96 (s, 2H), 1.83 (s, 3H), 1.76 (s, 3H). MS (ESI) 412.34 $[M+H]^+$. HPLC Purity: 99.82%. Chiral purity: 98.10% ee. Compounds (**40-B**) and (**40-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 31

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-C**)



Preparation of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**41-1**)

[0273] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (0.700 g, 1.84 mmol) in

DMF (17 mL), was added 1-methyl-4-(tributylstannyl)-1*H*-imidazole (1.36 g, 3.67 mmol), followed by degassing the reaction mixture with nitrogen for 2 min, and then adding $Pd(PPh_3)_4$ (0.637 g, 0.551 mmol). After degassing again for 2 min, the reaction mixture was stirred at 100 °C for 16 h, then cooled down to RT, diluted with water (30 mL), and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, Ethyl acetate: petroleum ether), to afford ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**41-1**) (800 mg, 99% yield, LCMS: 87% purity). MS (ESI) 383.26 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**41-2**).

[0274] To a stirred mixture of ethyl 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**41-1**) (0.800 g, 2.09 mmol) in THF (4 mL), water (4 mL), and ethanol (4 mL), was added lithium hydroxide (0.351 g, 14.6 mmol) at RT. The mixture was stirring at 65 °C for 16 h, then reaction mixture was concentrated and triturated with toluene (15 mL × 3). The resulting solids were collected by filtration and dried under vacuum, to afford 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**41-2**) (0.800 g), which was used directly for the next step without further purification. MS (ESI) 355.34 $[M+H]^+$.

Preparation of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-A**).

[0275] To a stirred mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**41-2**) (0.800 g, 2.26 mmol) and ammonium chloride (2.42 g, 452 mmol) in DMF (16 mL) at RT, were added DIPEA (12.5 mL, 67.7 mmol) and HATU (4.29 g, 11.3 mmol). The reaction mixture was stirred at RT for 16 h. The mixture was diluted with water (30 mL), and extracted with 20% methanol in dichloromethane (3 × 30 mL). The combined organic layers was dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash column chromatography (methanol/dichloromethane), followed by prep-HPLC (C18, ACN/ammonium bicarbonate in water), to give 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-

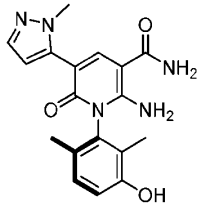
6-oxo-1,6-dihydropyridine-3-carboxamide (**41-A**) (120 mg, 15% yield). MS (ESI) 354.24 $[M+H]^+$.

Separation of (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-C**).

[0276] 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-A**) (120 mg), was subjected to preparative chiral SFC separation [CHIRALPAK AD-H (30x250) mm, 5µm, CO_2/0.1% ammonia in ACN:MeOH], to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-B**) (45 mg, 5% yield), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**41-C**) (45 mg, 5% yield). **41-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.48 (s, 1H), 8.53 (s, 1H), 8.00-7.18 (brs, 3H), 7.57 (d, J = 0.8 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.17-6.75 (brs, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.63 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H); MS (ESI) 354.31 $[M+H]^+$; HPLC purity : 98.81%; Chiral purity: 99.3% ee. **41-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.47 (s, 1H), 8.53 (s, 1H), 8.15-7.21 (brs, 3H), 7.57 (s, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.17-6.70 (brs, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.63 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H); MS (ESI) 354.31 $[M+H]^+$; HPLC purity: 99.62%; Chiral purity: 98.6% ee. Compounds (**41-B**) and (**41-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 32

(*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**42-B**), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**42-C**)



42-B

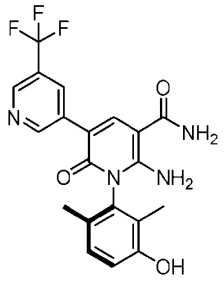


42-C

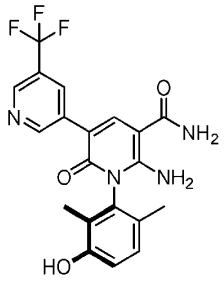
[0277] The racemic mixture of 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**42-A**) was prepared according to the procedure described in Example 5, and subjected to preparative chiral HPLC [Column: CHIRALPAK AD-H, 2*25 cm, 5μm; Mobile Phase A: Hex (0.1% FA), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford (*S*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**42-B**) (56 mg, 40% yield), and (*R*)-2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**42-C**) (39 mg, 28% yield). **42-B**: LCMS (MS, ESI): 354.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.06 (s, 1H), 7.86-7.48 (brs, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.25-6.93 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.26 (d, J = 1.6 Hz, 1H), 3.64 (s, 3H), 1.89 (s, 3H), 1.81 (s, 3H); Chiral purity: 100% ee. **42-C**: LCMS (MS, ESI): 354.25 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.07 (s, 1H), 7.90-7.50 (brs, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.35-6.97 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 3.64 (s, 3H), 1.89 (s, 3H), 1.81 (s, 3H); Chiral purity: 98.76% ee. Compounds (**42-B**) and (**42-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 33

(*S*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-5'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**43-B**), and (*R*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-5'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**43-C**)



43-B

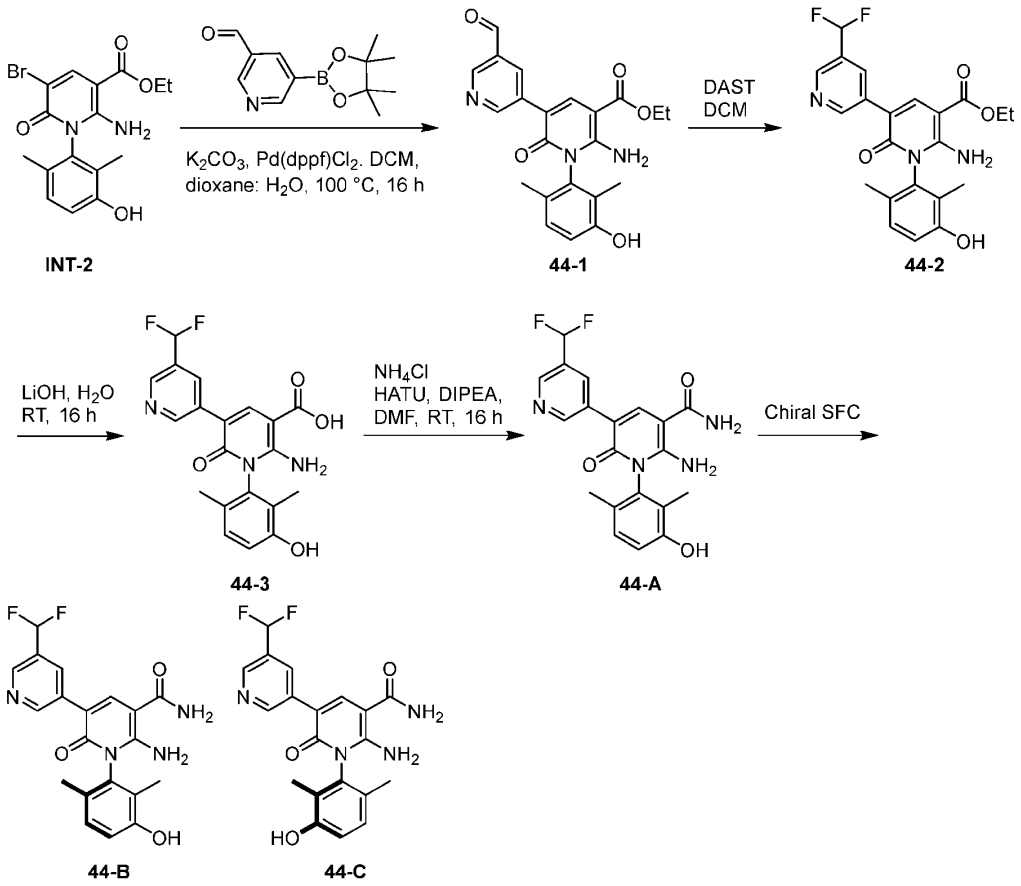


43-C

[0278] The racemic mixture of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-5'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**43-A**), was prepared according to the procedure described in Example 5, and subjected to preparative chiral SFC separation [column: CHIRALPAK-IH (30x250) mm, 5μm; % CO_2: 60%; % Co-solvent: 40% (0.2% ammonia in ACN-MeOH) (1:1)); Flow: 100 mL/min.; Back Pressure: 100 bar; Temperature: 30 °C; UV: 290 nm], followed by lyophilization, to afford (*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-5'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**43-B**) (0.0281 g, 28% yield), and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-5'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**43-C**) (0.0192 g, 19% yield). **43-B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01-8.95 (m, 2H), 8.75 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 7.90 (br s, 1H), 7.20 (br s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H). MS (ESI) 419.33 $[M+H]^+$. HPLC purity: 95.10%; Chiral purity: 99.88% ee. **43-C**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (br s, 1H), 9.30 (s, 1H), 8.76 (s, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 7.94 (br s, 1H), 7.20 (br s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 1.88 (s, 3H), 1.81 (s, 3H). MS (ESI) 419.30 $[M+H]^+$; HPLC purity: 99.06%; Chiral purity: 98.24% ee. Compounds (**43-B**) and (**43-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 34

(*S*)-6-Amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-B**), and (*R*)-6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-C**)



Preparation of ethyl 6-amino-5'-formyl-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-1**)

[0279] To a stirred mixture of ethyl 2-amino-5-bromo-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**INT-2**) (3.00 g, 7.87 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinaldehyde (2.20 g, 9.44 mmol) in 1,4-dioxane (24 mL) and water (6 mL), were added potassium carbonate (3.26 g, 23.6 mmol). The mixture was degassed with nitrogen for 2 min, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.643 g, 0.787 mmol) was added, then the resulting mixture was degassed again for 1 min. The mixture was stirred at 100 °C for 16 h, cooled down to RT, diluted with water (150 mL), and extracted

with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine, dried over magnesium sulphate, filtered, and concentrated to afford ethyl 6-amino-5'-formyl-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-1**) (3.30 g), which was used directly for the next step without further purification. MS (ESI) 408.22 $[M+H]^+$.

Preparation of ethyl 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-2**)

[0280] To a stirred mixture of ethyl 6-amino-5'-formyl-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-1**) (3.20 g, 7.85 mmol) in dichloromethane (64 mL) at 0 °C, was added diethylaminosulfur trifluoride (5.19 mL, 39.3 mmol). After stirring at RT for 16 h, the reaction mixture was quenched with ice cold sodium bicarbonate solution and extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine, dried over magnesium sulphate, filtered, concentrated, and residue purified by flash column chromatography (SiO_2, ethyl acetate/petroleum ether), to afford ethyl 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-2**) (2.00 g, 59% yield). MS (ESI) 430.41 $[M+H]^+$.

Preparation of 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**44-3**)

[0281] To a stirred mixture of ethyl 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (**44-2**) (2.00 g, 4.66 mmol) in water (10 mL) and ethanol (10 mL), was added lithium hydroxide monohydrate (0.977 g, 23.3 mmol) at RT. After stirring at RT for 16 h, the reaction mixture was concentrated, and the residue was triturated with toluene (50 mL × 4). The resulting solids were collected via filtration, then dried under vacuum to afford 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**44-3**) (2.00g), which was used directly for the next step without further purification. MS (ESI) 402.34 $[M+H]^+$.

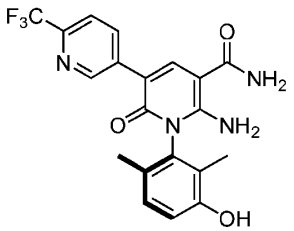
Preparation of 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridinc]-5-carboxamidc (**44-A**)

[0282] To a stirred mixture of 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylic acid (**44-3**) (1.00 g, 2.49 mmol) and ammonium chloride (1.33 g, 24.9 mmol) in dimethylformamide (20 mL), were added DIPEA (4.59 mL, 24.9 mmol) and HATU (4.74 g, 12.4 mmol) at RT. After stirring at RT for 16 h, the reaction mixture was quenched with ice-cold sodium bicarbonate solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over magnesium sulphate, filtered, concentrated, and residue purified by preparative HPLC [X BRIDGE PHENYL (19*250*5µm), ACN+THF+WATER], to afford 6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-A**) (0.140 g, 14% yield). MS (ESI) 401.4 $[M+H]^+$.
Separation of (*S*)-6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-B**), and (*R*)-6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-C**)

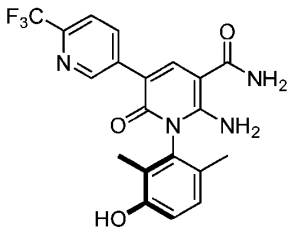
[0283] 6-Amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-A**) (0.140 g), was subjected to chiral SFC separation [Chiralpak ADH (30*250) mm, 5µm, CO_2/0.1% diethylamine in methanol], to afford (*S*)-6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-B**) (0.0566 g, 40% yield), and (*R*)-(6-amino-5'-(difluoromethyl)-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**44-C**) (0.0591 g, 42% yield). **44-B**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.55 (s, 1H), 9.11 (s, 1H), 8.57 (s, 1H), 8.41-8.40 (m, 2H), 7.89 (bs, 1H), 7.42-7.00 (bs, 1H), 7.13 (t, J = 55.2 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H) 1.88 (s, 3H), 1.80 (s, 3H); MS (ESI) 401.28 $[M+H]^+$; HPLC purity: 99.34%; Chiral purity: 99.98% ee. **44-C**: ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.54 (s, 1H), 9.11 (s, 1H), 8.57 (s, 1H), 8.41-8.40 (m, 2H), 7.88 (bs, 1H), 7.42-7.00 (bs, 1H), 7.13 (t, J = 55.2 Hz, 1H), 7.09 (d, J =8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H); MS (ESI) 401.28 $[M+H]^+$; HPLC purity: 98.34%: Chiral purity: 99.74% ee. Compounds (**44-B**) and (**44-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 35

(*S*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-6'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**45-B**), and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-6'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**45-C**)



45-B

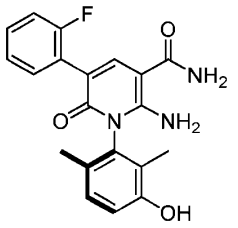


45-C

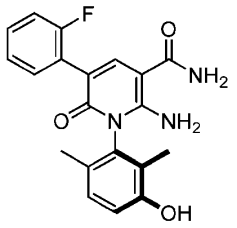
[0284] The racemic mixture of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-6'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**45-A**), was prepared according to the procedure described in Example 5, and subjected to chiral SFC separation [Column/dimensions: LUX I AMYLOSE-3 (30x250) mm,5µm, %CO_2: 65%, %Co-solvent: 35% (0.2% ammonia in methanol), Flow: 100 mL/min, Back Pressure: 100 bar, Temperature: 30 °C, UV: 290 nm], followed by lyophilization, to afford (*S*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-6'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**45-B**) (0.0401g, 48% yield), and (*R*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-2-oxo-6'-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**45-C**) (0.0435 g, 43% yield). **45-B**: MS (ESI) *m/z* 419.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 9.15 (d, *J* = 1.2 Hz, 1H), 8.51 – 8.42 (m, 2H), 8.01 – 7.05 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); Chiral purity: 99.78% ee. **45-C**: MS (ESI) *m/z* 419.26 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 9.15 (s, 1H), 8.45 (d, *J* = 4.8 Hz, 2H), 8.10 – 7.62 (m, 2H), 7.46 – 6.96 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 1.88 (s, 3H), 1.80 (s, 3H); Chiral purity: 99.94% ee. Compounds (**45-B**) and (**45-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 36

(*S*)-2-Amino-5-(2-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**46-B**), and (*R*)-2-amino-5-(2-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**46-C**)



46-B

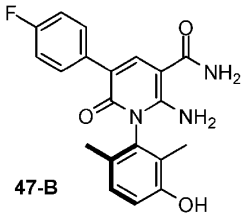


46-C

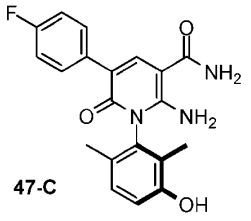
[0285] The racemic mixture of 2-amino-5-(2-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**46-A**), was prepared according to the procedure described in Example 5, and subjected to preparative chiral-HPLC separation [Column: Lux 5 μm Cellulose-4, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford (*S*)-2-amino-5-(2-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**46-B**) (34 mg, 19 % yield), and (*R*)-2-amino-5-(2-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**46-C**) (35 mg, 19% yield). **46-B**: LCMS (MS, ESI): 368.25 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.05 (s, 1H), 7.78-7.50 (br s, 1H), 7.47-7.43 (m, 1H), 7.32-7.29 (m, 1H), 7.21-7.14 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 1.89 (s, 3H), 1.81 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.066. Chiral purity: 100% ee. **46-C**: LCMS (MS, ESI): 368.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.05 (s, 1H), 7.78-7.50 (br s, 1H), 7.47 – 7.43 (m, 1H), 7.32-7.29 (m, 1H), 7.21-7.14 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 1.89 (s, 3H), 1.81 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.065. Chiral purity: 100% ee. Compounds (**46-B**) and (**46-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 37

(*S*)-2-Amino-5-(4-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**47-B**), and (*R*)-2-amino-5-(4-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**47-C**)



47-B

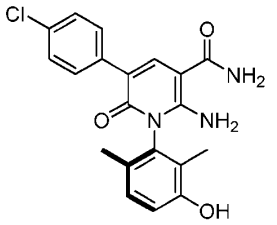


47-C

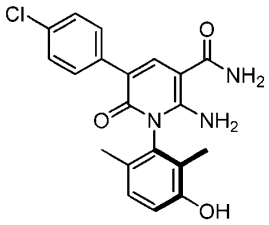
[0286] The racemic mixture of 2-amino-5-(4-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**47-A**), was prepared according to the procedure described in Example 5, and subjected to preparative chiral HPLC separation [Column: Lux 5 μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex(0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford (*S*)-2-Amino-5-(4-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**47-B**) (49 mg, 22% yield), and (*R*)-2-amino-5-(4-fluorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**47-C**) (44 mg, 19% yield). **47-B**: LCMS (MS, ESI): 368.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.16 (s, 1H), 7.92-7.37 (m, 3H), 7.17-7.13 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H). ^{19} F NMR (376 MHz, DMSO-d_6) δ -116.864. Chiral purity: 100% ee. **47-C**: LCMS (MS, ESI): 368.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.16 (s, 1H), 7.88-7.28 (m, 3H), 7.17-7.13 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H). ^{19} F NMR (376 MHz, DMSO-d_6) δ -116.864. Chiral purity: 99.87% ee. Compounds (**47-B**) and (**47-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 38

(*S*)-2-Amino-5-(4-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**48-B**), and (*R*)-2-amino-5-(4-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**48-C**)



48-B

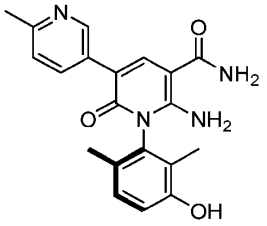


48-C

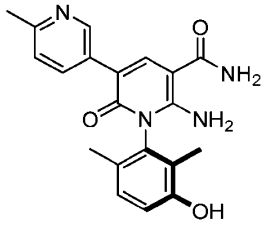
[0287] The racemic mixture of amino-5-(4-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**48-A**), was prepared according to the procedure described in Example 5, and subjected to preparative chiral HPLC separation [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex(0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford (*S*)-2-amino-5-(4-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**48-B**) (65 mg, 29% yield), and (*R*)-2-amino-5-(4-chlorophenyl)-1-(3-hydroxy-2,6-dimethylphenyl)-6-oxopyridine-3-carboxamide (**48-C**) (65 mg, 29% yield). **48-B**: LCMS (MS, ESI): 384.15 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.21 (s, 1H), 8.02-7.77 (m, 2H), 7.60 (brs, 1H), 7.38-7.36 (m, 2H), 7.21-6.92 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H). Chiral purity: 100% ee. **48-C**: LCMS (MS, ESI): 384.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.21 (s, 1H), 7.98-7.78 (m, 2H), 7.60 (brs, 1H), 7.38-7.36 (m, 2H), 7.32-6.94 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 1.87 (s, 3H), 1.79 (s, 3H). Chiral purity: 100% ee. Compounds (**48-B**) and (**48-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 39

(*S*)-6-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6'-methyl-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**39-B**), and *(R)*-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6'-methyl-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**39-C**)



39-B

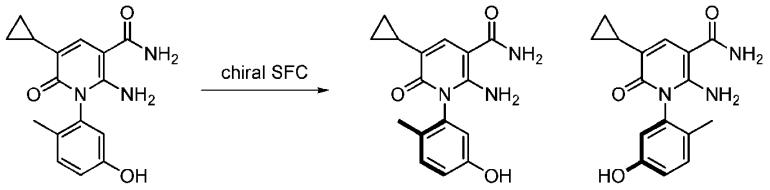


39-C

[0288] The racemic mixture of 6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6'-methyl-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**39-A**), was prepared according to the procedure described in Example 5, and subjected to preparative chiral HPLC separation [Column: Lux 5μm Cellulose-4, 2.12*25 cm; Mobile Phase A: Hex(0.1% FA), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 40; Wave Length: 254/220 nm], to afford (*S*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6'-methyl-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**39-B**) (29 mg, 29% yield), and (*R*)-6-amino-1-(3-hydroxy-2,6-dimethylphenyl)-6'-methyl-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxamide (**39-C**) (31 mg, 31% yield). **39-B**: LCMS (MS, ESI): 365.25 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (brs, 1H), 8.79 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.00 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 7.80 (brs, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15-7.00 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 2.45 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H). Chiral purity: 100% ee. **39-C**: LCMS (MS, ESI): 365.25 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (brs, 1H), 8.79 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.00 (dd, J = 8.0, 2.4 Hz, 1H), 7.80 (brs, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15-7.00 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 2.45 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H). Chiral purity: 100% ee. Compounds (**39-B**) and (**39-C**) are atropisomers, and the stereochemistry may be the opposite of that depicted.

Example 40

(*R*)-2-amino-5-cyclopropyl-1-(5-hydroxy-2-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**57-B**) and (*S*)-2-amino-5-cyclopropyl-1-(5-hydroxy-2-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**57-C**)

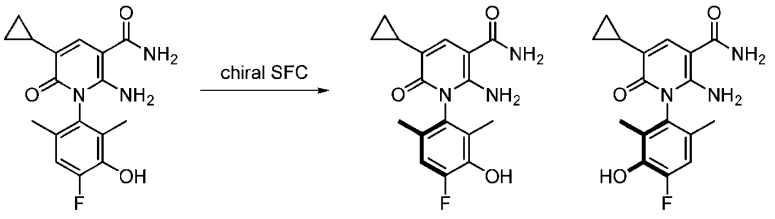


57-A **57-B** **57-C**

[0289] The racemic mixture of 2-amino-5-cyclopropyl-1-(5-hydroxy-2-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**57-A**) was prepared according to the procedure described in Example 2 (reversing the sequence of the BBr_3 deprotection with the hydrolysis/amidation steps) and was subjected to chiral SFC purification (Chiral OJ, 30 x 250 mm column), 50% MeOH with 0.1% 7M NH_3 in MeOH to afford the title compounds. From Peak 1: (*R*)-2-amino-5-cyclopropyl-1-(5-hydroxy-2-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**57-B**) (2.47 mg, 31%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.60 (br, 1H), 7.72 (s, 1H), 7.21 (d, *J*=8.3 Hz, 1H), 6.81 (dd, *J*=8.3, 2.5 Hz, 1H), 6.48 (d, *J*=2.5 Hz, 1H), 5.93 (m, 1H), 4.99 (m, 2H), 3.03 (d, *J*=6.4 Hz, 2H), 1.82 (s, 3H), 1.25 (m, 1H). MS (ESI) m/z: 300.1 $[M+H]^+$. From Peak 2: (*S*)-2-amino-5-cyclopropyl-1-(5-hydroxy-2-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**57-C**) (2.64 mg, 33%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.60 (br, 1H), 7.72 (s, 1H), 7.21 (d, *J*=8.3 Hz, 1H), 6.81 (dd, *J*=8.3, 2.5 Hz, 1H), 6.48 (d, *J*=2.5 Hz, 1H), 5.93 (m, 1H), 4.99 (m, 2H), 3.03 (d, *J*=6.4 Hz, 2H), 1.82 (s, 3H), 1.25 (m, 1H). MS (ESI) m/z: 300.1 $[M+H]^+$. Compounds **57-B** and **57-C** are atropisomers, and the shown stereochemistry may be the opposite of that depicted.

Example 41

(*S*)-2-amino-5-cyclopropyl-1-(4-fluoro-3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**58-B**) and (*R*)-2-amino-5-cyclopropyl-1-(4-fluoro-3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**58-C**)

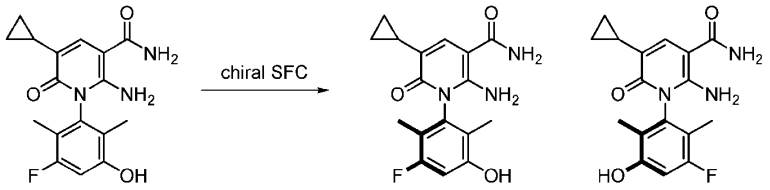


58-A **58-B** **58-C**

[0290] The racemic mixture of 2-amino-5-cyclopropyl-1-(4-fluoro-3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**58-A**) was prepared according to the procedure described in Example 40 and was subjected to chiral SFC purification (Chiral OJ, 30 x 250 mm column), 30% MeOH with 0.1% 7M NH_3 in MeOH to afford the title compounds. From Peak 1: (*S*)-2-amino-5-cyclopropyl-1-(4-fluoro-3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**58-B**) (8.99 mg, 37%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (s, 1H), 7.75 (s, 1H), 7.08 (d, *J*=11.5 Hz, 1H), 5.92 (m, 1H), 4.98 (m, 2H), 3.04 (d, *J*=6.2 Hz , 2H), 1.82 (s, 3H), 1.77 (s, 3H), 1.23 (m, 1H). MS (ESI) m/z: 332.1 $[M+H]^+$. From Peak 2: (*R*)-2-amino-5-cyclopropyl-1-(4-fluoro-3-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**58-C**) (8.86 mg, 37%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.53 (s, 1H), 7.75 (s, 1H), 7.08 (d, *J*=11.5 Hz, 1H), 5.92 (m, 1H), 4.98 (m, 2H), 3.04 (d, *J*=6.2 Hz , 2H), 1.82 (s, 3H), 1.77 (s, 3H), 1.23 (m, 1H). MS (ESI) m/z: 332.1 $[M+H]^+$. Compounds **58-B** and **58-C** are atropisomers, and the shown stereochemistry may be the opposite of that depicted.

Example 42

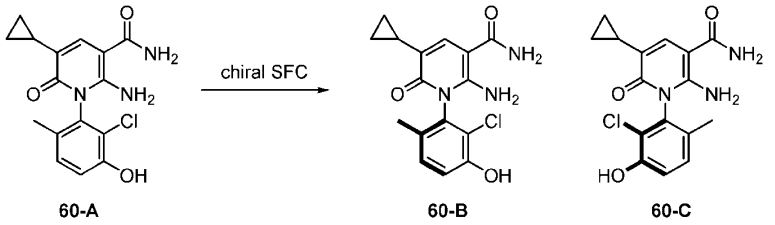
(*R*)- 2-amino-5-cyclopropyl-1-(3-fluoro-5-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**59-B**) and (*S*)- 2-amino-5-cyclopropyl-1-(3-fluoro-5-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**59-C**)



[0291] The racemic mixture of 2-amino-5-cyclopropyl-1-(3-fluoro-5-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**59-A**) was prepared according to the procedure described in Example 40 and subjected to chiral SFC purification (Chiral OJ, 30 x 250 mm column), 15% MeOH with 0.1% 7M NH_3 in MeOH to afford the title compounds. From Peak 1: (*R*)-2-amino-5-cyclopropyl-1-(3-fluoro-5-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**59-B**) (3.94 mg, 39%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.95 (s, 1H), 7.77 (s, 1H), 6.72 (d, *J*=11.3 Hz, 1H), 5.92 (m, 1H), 4.99 (m, 2H), 3.04 (d, *J*=6.4 Hz , 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.23 (m, 1H). MS (ESI) m/z: 332.1 $[M+H]^+$. From Peak 2: (*S*)-2-amino-5-cyclopropyl-1-(3-fluoro-5-hydroxy-2,6-dimethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**59-C**) (2.59 mg, 26%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.95 (s, 1H), 7.77 (s, 1H), 6.72 (d, *J*=11.3 Hz, 1H), 5.92 (m, 1H), 4.99 (m, 2H), 3.04 (d, *J*=6.4 Hz , 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.23 (m, 1H). MS (ESI) m/z: 332.1 $[M+H]^+$. Compounds **59-B** and **59-C** are atropisomers, and the shown stereochemistry may be the opposite of that depicted.

Example 43

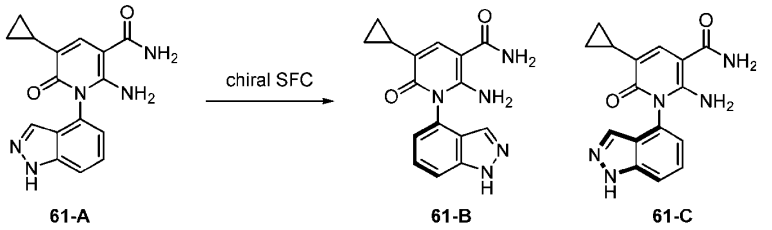
(*S*)-2-amino-1-(2-chloro-3-hydroxy-6-methylphenyl)-5-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**60-B**) and (*R*)-2-amino-1-(2-chloro-3-hydroxy-6-methylphenyl)-5-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**60-C**)



[0292] The racemic mixture of 2-amino-1-(2-chloro-3-hydroxy-6-methylphenyl)-5-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**60-A**) was prepared according to the procedure described in Example 40 and was subjected to chiral SFC purification (Chiral OJ, 30 x 250 mm column), 30% MeOH with 0.1% 7M NH_3 in MeOH to afford the title compounds. From Peak 1: (*S*)-2-amino-1-(2-chloro-3-hydroxy-6-methylphenyl)-5-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**60-B**) (4.06 mg, 40%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.25 (br, 1H), 7.75 (s, 1H), 7.18 (d, *J*=8.4 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 1H), 5.93 (m, 1H), 4.99 (m, 2H), 3.04 (m, 2H), 1.87 (s, 3H). MS (ESI) m/z: 334.1 $[M+H]^+$. From Peak 2: (*R*)-2-amino-1-(2-chloro-3-hydroxy-6-methylphenyl)-5-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**60-C**) (3.85 mg, 39%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.25 (br, 1H), 7.75 (s, 1H), 7.18 (d, *J*=8.4 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 1H), 5.93 (m, 1H), 4.99 (m, 2H), 3.04 (m, 2H), 1.87 (s, 3H). MS (ESI) m/z: 334.1 $[M+H]^+$. Compounds **60-B** and **60-C** are atropisomers, and the shown stereochemistry may be the opposite of that depicted.

Example 44

(*S*)-2-amino-5-cyclopropyl-1-(1H-indazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**61-B**) and (*R*)-2-amino-5-cyclopropyl-1-(1H-indazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**61-C**)



61-A **61-B** **61-C**

[0293] The racemic mixture of 2-amino-5-cyclopropyl-1-(1H-indazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**61-A**) was subjected to chiral SFC purification (Chiral OJ, 30 x 250 mm column), 30% MeOH with 0.1% 7M NH_3 in MeOH to afford the title compounds. From Peak 1: (*S*)-2-amino-5-cyclopropyl-1-(1H-indazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**61-B**) (8.10 mg, 41%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.33 (br, 1H), 7.75 (s, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.50 (dd, *J*=8.4, 7.3 Hz, 1H), 7.43 (s, 1H), 7.02 (d, *J*=7.3 Hz, 1H), 1.79-1.76 (m, 1H), 0.71-0.58 (comp, 4H). MS (ESI) m/z: 310.1 $[M+H]^+$. From Peak 2: (*R*)-2-amino-5-cyclopropyl-1-(1H-indazol-4-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (**61-C**) (7.80 mg, 39%) was isolated. Chiral purity 100% (Chiralpak OJ-H (4.6 x 250 mm column), 35%-95% MeCN in H_2O with 0.1% formic acid); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.33 (br, 1H), 7.75 (s, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.50 (dd, *J*=8.4, 7.3 Hz, 1H), 7.43 (s, 1H), 7.02 (d, *J*=7.3 Hz, 1H), 1.79-1.76 (m, 1H), 0.71-0.58 (comp, 4H). MS (ESI) m/z: 310.1 $[M+H]^+$. Compounds **61-B** and **61-C** are atropisomers, and the shown stereochemistry may be the opposite of that depicted.

Example 45

Kinase binding assay

[0294] Test compound IC_{50} values for PKMYT1 and WEE1 were determined by LanthaScreen® Eu Kinase Binding Assay (Thermo Fisher Scientific), based on the binding and displacement of a proprietary, AlexaFluor 647-labeled ATP-competitive kinase inhibitor scaffold (kinase tracer) to the kinase of interest. Binding of the tracer to the kinase is detected

using a europium-labeled anti-GST antibody, which binds to the fused tag on the kinase protein. A high degree of FRET (Förster Resonance Energy Transfer) from the europium (Eu) donor fluorophore to the Alexa Fluor® 647 acceptor fluorophore on the kinase tracer results from concurrent binding of both the tracer and antibody to the kinase. Inhibitor binding to the kinase competes with tracer binding, resulting in loss of FRET from the donor/acceptor pairs.

[0295] Test compounds and positive control RP-6306 (Lunresertib) were screened in 1% DMSO (final concentration) in each well typically in 10-point titrations by 3-fold serial dilutions conducted from starting/top concentration of 10 mM. LanthaScreen® assay conditions for both PKMYT1 and WEE1 were conducted similarly in buffer comprised of 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, and 1 mM EGTA using AlexaFluor Tracer 178. Kinase/Antibody Mixtures and Tracer are diluted to a 2X and 4X working concentration, respectively in this same buffer. The final concentrations for the kinase, antibody, and tracer for PKMYT1 LanthaScreen® assay were 2.5, 2, and 1 nM, respectively and for the WEE1 LanthaScreen® assay these values were 5, 2, and 50 nM, respectively. Test compounds, kinase buffer, kinase/antibody mixtures, and tracer were added to individual wells of a bar-coded, low volume, white 384-well plates (Greiner Cat. #784297 or Corning Cat. #4513) to a final volume of 16 uL, shaken for 30 seconds, and incubated for 60 minutes at rt prior to reading on a suitable fluorescent plate reader and subsequent data analysis. 0% displacement (no known inhibitor) and 100% displacement (highest concentration of known inhibitor) controls were included on each plate for maximum and minimum Emission Ratio determination, respectively. Dasatinib was used for both PKMYT1 and WEE1 as the known inhibitor.

[0296] IC_{50} determination was performed using a non-linear regression, variable slope (four parameter), inhibitor v. response equation (Prism 9.0). IC_{50} values are provided in Table 2. In Table 2: A = 0 nM < $IC_{50} \leq$ 10 nM; B = 10 nM < $IC_{50} \leq$ 100 nM; C = 100 nM < $IC_{50} \leq$ 1000 nM; D = 1000 nM < IC_{50}; ND = Not Determined.

[0297] Based on the kinase activity data provided in Table 2, compounds of Formula (I) provided herein are expected to exhibit excellent kinome selectivity which is a highly desirable property for a DNA damage response (DDR) kinase inhibitor to ensure a favorable *in vivo* safety profile.

Table 2. PKMYT1 and WEE1 IC_{50} values.

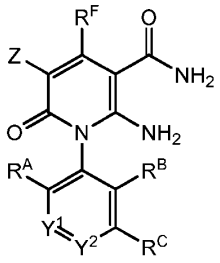
No.	PKMYT1 IC_{50} (nM)	WEE1 IC_{50} (nM)
RP-6306	A	B
1-B	A	D
2-B	A	C
3-B	A	D
4-B	A	D
5-B	A	C
6-B	A	D
7-B	A	D
8-B	A	C
9-B	A	C
10-B	A	C
11-B	A	D
12-B	A	C
13-B	A	C
14-B	A	D
15-B	A	D
16-B	A	C
17-B	A	D
18-B	A	C
19-B	A	C
20-B	A	D
21-B	A	C
22-B	A	D
23-B	A	D
24-B	A	C
25-B	A	C
26-B	A	D
28-B	B	D
29-B	A	C
30-B	A	D
31-B	A	D
32-B	A	D
34-B	B	D
35-B	A	D
36-B	A	D
38-B	A	C
39-B	A	C
40-B	A	C
41-B	A	D
42-B	B	D
43-B	A	D

No.	PKMYT1 IC_{50} (nM)	WEE1 IC_{50} (nM)
44-B	A	D
45-B	B	C
46-B	A	C
47-B	A	C
48-B	A	B
57-B	B	ND
58-B	A	ND
59-B	A	ND
60-B	A	ND
61-B	A	D

[0298] All patents, published patent applications, and other non-patent documents referenced herein are each incorporated herein by reference in their entirety. Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the disclosure.

WHAT IS CLAIMED IS:

1. A compound represented by the following Formula (I'):

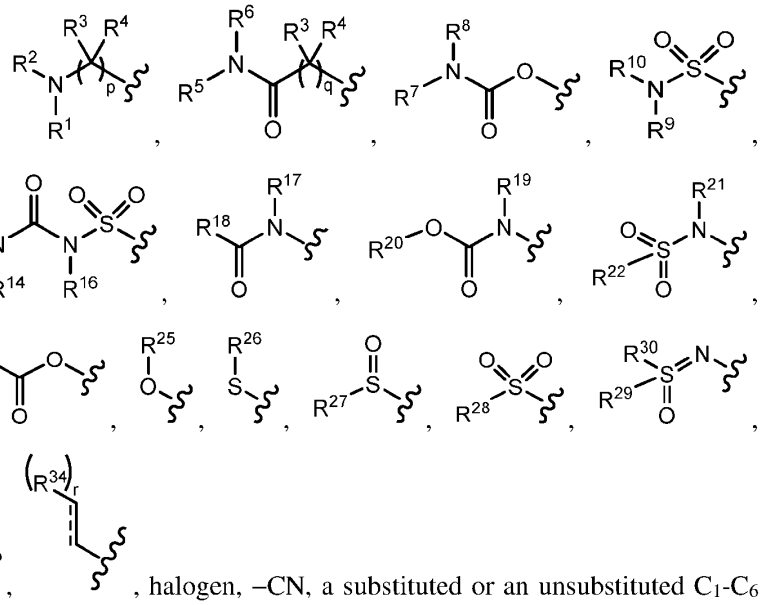


Formula (I')

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

≡ is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or

an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{A}}$, $\mathbf{R^{D}}$ and $\mathbf{R^{E}}$ are each independently hydrogen, halogen, –CN, –OH, –O$\mathbf{R^{35}}$, –S$\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and

$\mathbf{R^{B}}$ and $\mathbf{R^{C}}$ are each independently hydrogen, halogen, –CN, –OH, –O$\mathbf{R^{35}}$, –S$\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, or a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

$\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^F}$ is hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{37}}$, $-S\mathbf{R^{38}}$, $-N\mathbf{R^{39}R^{40}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

$\mathbf{R^{37}}$ and $\mathbf{R^{38}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

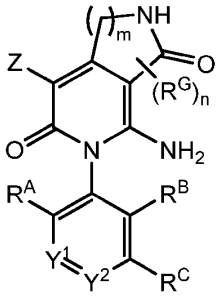
$\mathbf{R^{39}}$ and $\mathbf{R^{40}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{Z}$ and $\mathbf{R^F}$, together with the carbon atom that each of $\mathbf{Z}$ and $\mathbf{R^F}$ is respectively connected thereto, form a substituted or an unsubstituted C_7 cycloalkyl, a substituted or an unsubstituted 7-membered heterocyclyl or a substituted or an unsubstituted 7-membered heteroaryl; or

$\mathbf{R^F}$ and the $-CONH_2$ shown in Formula (I'), together with the carbon atom that each of $\mathbf{R^F}$ and the $-CONH_2$ is respectively connected thereto, form a substituted or an unsubstituted 5- to 7-membered lactam ring.

2. The compound of claim 1, wherein $\mathbf{R^F}$ is hydrogen, F, Cl, methyl or methoxy.

3. A compound represented by the following Formula (I'a):



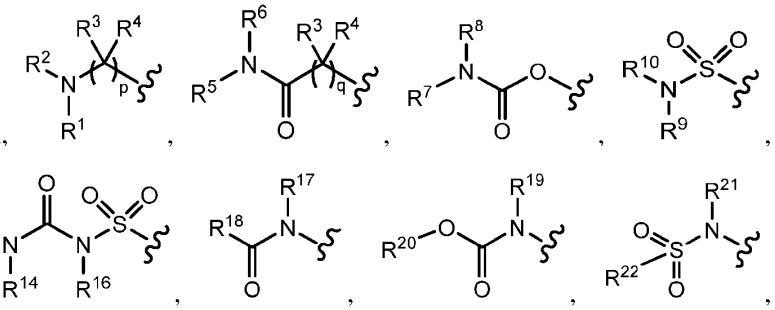
Formula (I'a)

or a pharmaceutically acceptable salt thereof, wherein:

m is 1, 2 or 3;

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

≡ is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, $\mathbf{R^5}$ and $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$, $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$, together with the respective nitrogen atom connected thereto, each independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted

C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{A}}$, $\mathbf{R^{D}}$, and $\mathbf{R^{E}}$ are each independently hydrogen, halogen, –CN, –OH, –O$\mathbf{R^{35}}$, –S$\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{B}}$ and $\mathbf{R^{C}}$ are each independently hydrogen, halogen, –CN, –OH, –O$\mathbf{R^{35}}$, –S$\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a

substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

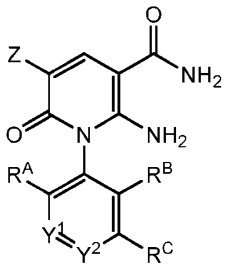
$\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^G}$, for each instance, is independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl and C_1-C_6 alkoxy; and

n is 0, 1 or 2.

4. A compound represented by the following Formula (I):

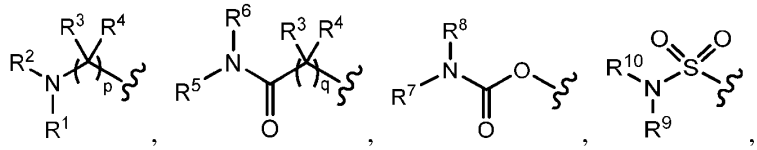
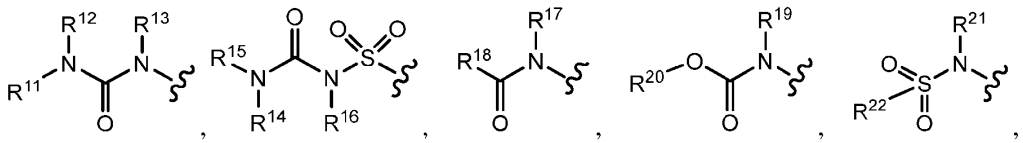


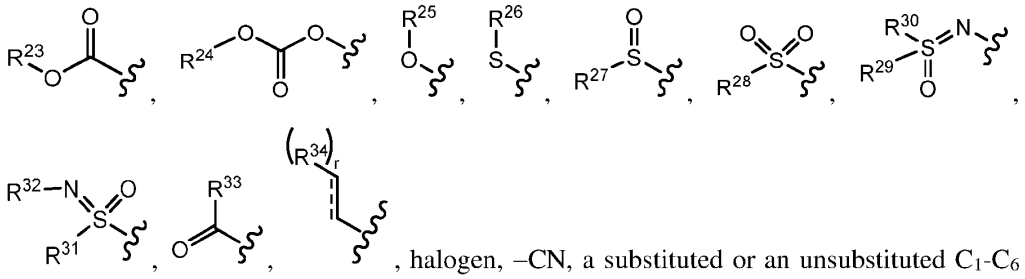
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{Y^1}$ is $-C\mathbf{R^D}$ or N (nitrogen);

$\mathbf{Y^2}$ is $-C\mathbf{R^E}$ or N (nitrogen), provided that $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are not both N;

Z is hydrogen, , 



, halogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

--- is a double bond or a triple bond;

p and **q** are each independently 0 or 1;

r is 1 or 2;

R^1, **R^2**, **R^5**, **R^6**, **R^7**, **R^8**, **R^9**, **R^{10}**, **R^{11}**, **R^{12}**, **R^{14}** and **R^{15}** are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

R^1 and **R^2**, **R^5** and **R^6**, **R^7** and **R^8**, **R^9** and **R^{10}**, **R^{11}** and **R^{12}**, or **R^{14}** and **R^{15}**, together with the respective nitrogen atom connected thereto, each independently form a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

R^3 and **R^4** are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted

4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl; or alternatively

$\mathbf{R^3}$ and $\mathbf{R^4}$, together with the carbon atom connected thereto, form a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl;

$\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl;

$\mathbf{R^{18}}$, $\mathbf{R^{20}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ and $\mathbf{R^{26}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{22}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{32}}$ is hydrogen, –CN, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a

substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 6- or 10-membered aryl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl;

$\mathbf{R^A}$, $\mathbf{R^D}$ and $\mathbf{R^E}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl or a substituted or an unsubstituted C_3-C_6 cycloalkyl; and

$\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, or a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl; or alternatively

$\mathbf{R^B}$ and $\mathbf{R^C}$, together with the carbon atom that each of $\mathbf{R^B}$ and $\mathbf{R^C}$ is respectively connected thereto, form a substituted or an unsubstituted 5-membered heteroaryl, wherein:

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$, for each instance, are each independently a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl or a substituted or an unsubstituted 4- to 6-membered heterocyclyl.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are each independently –CH or –CF.

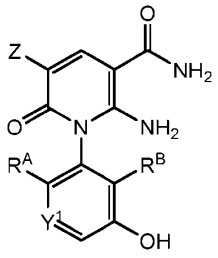
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, halogen, –CN, –OH, $-O\mathbf{R^{35}}$, $-S\mathbf{R^{36}}$, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6 alkynyl, a substituted or an unsubstituted C_1-C_6 alkoxy or a substituted or an unsubstituted C_3-C_6 cycloalkyl.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, F, Cl, Br, –CN, –OH or a substituted or an unsubstituted C_1-C_6 alkyl.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are each independently hydrogen, F, –CN, –OH, an unsubstituted C_1-C_4 alkyl or C_1-C_4 haloalkyl.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ are not all hydrogen.

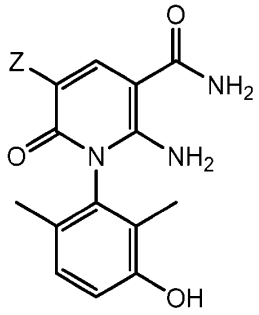
10. The compound of any one of claims 1, 2, and 4 to 9, wherein the compound is represented by the following Formula (II):



Formula (II)

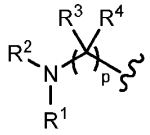
or a pharmaceutically acceptable salt thereof.

11. The compound of any one of 1, 2, and 4 to 10, wherein the compound is represented by the following Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein **Z** is  , a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_2-C_6 alkenyl, a substituted or an unsubstituted C_2-C_6

alkynyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted phenyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently hydrogen, a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_1-C_6 heteroalkyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl, wherein:

when a C_1-C_6 alkyl or a C_1-C_6 heteroalkyl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_1-C_6 alkyl or the C_1-C_6 heteroalkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy and C_3-C_6 cycloalkyl;

when a C_3-C_6 cycloalkyl, a 4- to 10-membered heterocyclyl, or a 5- to 10-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the C_3-C_6 cycloalkyl, the 4- to 10-membered heterocyclyl, or the 5- to 10-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy; or alternatively

$\mathbf{R^1}$ and $\mathbf{R^2}$, together with the nitrogen atom connected thereto, form a substituted or an unsubstituted 4- to 8-membered heterocyclyl or a substituted or an unsubstituted 5- to 8-membered heteroaryl, wherein:

when a 4- to 8-membered heterocyclyl or a 5- to 8-membered heteroaryl represented by $\mathbf{R^1}$ or $\mathbf{R^2}$ is substituted, the 4- to 8-membered heterocyclyl or the 5- to 8-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy.

14. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted C_1-C_6 alkyl, a substituted or an unsubstituted C_3-C_6 cycloalkyl, a substituted or an unsubstituted phenyl, a substituted or an unsubstituted 4- to 10-membered heterocyclyl or a substituted or an unsubstituted 5- to 10-membered heteroaryl.

15. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted C_1-C_6 alkyl, wherein:

when a C_1-C_6 alkyl represented by **Z** is substituted, the C_1-C_6 alkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkoxy, a C_3-C_6 cycloalkyl and a 4- to 8-membered heterocyclyl.

16. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted C_2-C_6 alkenyl, wherein:

when a C_2-C_6 alkenyl represented by **Z** is substituted, the C_2-C_6 alkenyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkoxy, a C_3-C_6 cycloalkyl and a 4- to 8-membered heterocyclyl.

17. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted C_2-C_6 alkynyl, wherein:

when a C_2-C_6 alkynyl represented by **Z** is substituted, the C_2-C_6 alkynyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkoxy, a C_3-C_6 cycloalkyl and a 4- to 8-membered heterocyclyl.

18. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted C_3-C_6 cycloalkyl; wherein:

when a C_3-C_6 cycloalkyl represented by **Z** is substituted, the C_3-C_6 cycloalkyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with C_1-C_4 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy and phenyl.

19. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted phenyl; wherein:

when a phenyl represented by **Z** is substituted, the phenyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy.

20. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl; wherein:

when a 4- to 10-membered heterocyclyl represented by **Z** is substituted, the 4- to 10-membered heterocyclyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with –OH, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy.

21. The compound of any one of claims 1 to 12 and 20, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted 4- to 10-membered heterocyclyl; wherein:

when a 4- to 10-membered heterocyclyl represented by **Z** is substituted, the 4- to 10-membered heterocyclyl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 alkoxy.

22. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **Z** is a substituted or an unsubstituted 5- to 10-membered heteroaryl; wherein:

when a 5- to 10-membered heteroaryl represented by **Z** is substituted, the 5- to 10-membered heteroaryl is substituted with one or more groups each independently selected from halogen, –CN, –OH, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with C_1-C_2 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 alkoxy and a 4- to 6-membered heterocyclyl.

23. The compound of any one of claims 1 to 4, wherein the compound is selected from any one of Compound Nos. 1-A to 61-C in Table 1, or a pharmaceutically acceptable salt thereof.

24. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein one or more hydrogen atoms of the compound is replaced by deuterium.

25. A pharmaceutical composition comprising the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or a combination thereof.

26. A method for ameliorating or treating a cancer in a subject, comprising administering to the subject an effective amount of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25.

27. A method for inhibiting replication of a malignant growth or tumor in a subject, comprising administering to the subject an effective amount of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25; wherein the malignant growth or tumor is due to a cancer.

28. Use of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25 for the manufacture of a medicament for ameliorating or treating a cancer.

29. Use of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25 for the manufacture of a medicament for inhibiting replication of a malignant growth or tumor, wherein the malignant growth or tumor is due to a cancer.

30. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25 for use in ameliorating or treating a cancer.

31. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 25 for use in inhibiting replication of a malignant growth or tumor, wherein the malignant growth or tumor is due to a cancer.

32. The method of claim 26 or 27, or the use of claim 28 or 29, or the compound of claim 30 or 31, wherein the cancer is selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter

cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.