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(54) Title: CBL-B INHIBITORS AND METHODS OF USES THEREOF

(57) Abstract: The disclosure provides for compounds and methods for modulating or inhibiting CBL-B.

CBL-B INHIBITORS AND METHODS OF USES THEREOF

CROSS-REFERENCE

[0001] This patent application claims the benefit of International Application No. PCT/CN2022/141595, filed December 23, 2022; International Application No. PCT/CN2023/073188, filed January 19, 2023; and International Application No. PCT/CN2023/095484, filed May 22, 2023; and which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Dysregulated signaling is a prominent feature in cellular transformation and tumorigenesis. The proto-oncogene Casitas B-lineage lymphoma (Cbl or c-Cbl), encodes an E3 ubiquitin ligase that downregulates PTK-directed cell signaling through ubiquitination, thereby targeting these kinases for lysosomal or proteasomal degradation. Cbl is a member of the Cbl family of proteins, so characterized based on a highly conserved N-terminal region that contains the structural components required for ubiquitin ligase activity. In simpler eukaryotic organisms, such as *Caenorhabditis elegans* and *Dictyostelium discoideum*, only one Cbl protein is present, but in mammals there are three, including Cbl, Cbl-b and Cbl-c.

[0003] The conserved N-terminus of Cbl family proteins contains a substrate tyrosine kinase-binding domain (TKBD), a linker helix region (LHR) and a RING domain. The TKBD confers specificity to Cbl's ligase activity based on the selective recruitment of phosphorylated substrates containing an (N/D)XpY(S/T)XXP, DpYR or RA(V/I)XNQpY(S/T) motif. The RING domain mediates the transfer of ubiquitin (Ub) from an E2 Ub-conjugating enzyme to the substrate. Within the LHR is a conserved tyrosine (Tyr371 in Cbl) that is crucial for regulating ligase activity. Phosphorylation of this tyrosine enhances ligase activity and is essential for ubiquitination of receptor PTKs. In addition to the highly conserved N-terminus, Cbl and Cbl-b also have extensive C-termini that confer adaptor-like functions to these proteins based on the ability to mediate multiple protein-protein interactions. These include a proline rich region that mediates interactions with SH3 domain-containing proteins and a tyrosine rich region that, upon phosphorylation, becomes a binding motif for other SH2 domain-containing proteins. Cbl and Cbl-b terminate with an ubiquitin-associated domain, which is crucial for homo- and heterodimerization of these two Cbl proteins.

[0004] Cbl-b is an important T cell immune response braker. In contrast to Cbl, which mainly regulates thymocyte development, Cbl-b mainly regulates peripheral T-cell activation through negative regulation of TCR (T-cell receptor) signal transduction pathways. Specifically, Cbl-b inhibits VAV1 activation upon TCR engagement and imposes a requirement for CD28 costimulation for proliferation and IL-2 production in naïve T cells. Cbl-b also ubiquitylates PIK3R1/p85, which inhibits its recruitment to CD28 and TCRζ, therefore suppressing the activation of PI3K, an important kinase involved in T cell activation and differentiation. Moreover, in activated T-cells, Cbl-b inhibits PLCG1 activation and calcium mobilization upon restimulation and thus promotes T cell anergy. Therefore, Cbl-b restricts unnecessary T cell overactivation under physiological condition. Indeed, Cbl-b KO mice had increased T

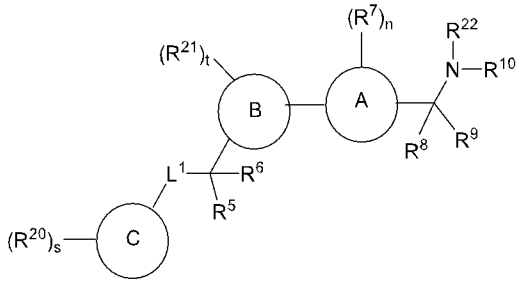
cell proliferation, spontaneous autoimmunity characterized by auto-antibody production, infiltration of activated T and B lymphocytes into multiple organs. On the other hand, in tumor microenvironment, T cells anergy, exhaustion and exclusion are widely present. Thus, to unleash T cell's full power through release of the Cbl-b brake as an immune-oncological anti-cancer therapy holds great promise.

[0005] There is a need for new cancer therapies, specifically using Cbl-b inhibitors.

SUMMARY

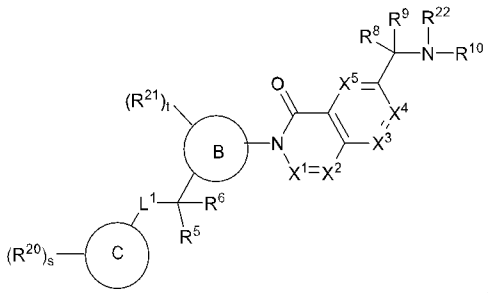
[0006] Disclosed herein are compounds, or a pharmaceutically acceptable salt or stereoisomer thereof, that are Cbl-b inhibitors.

[0007] Disclosed herein is a compound of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:

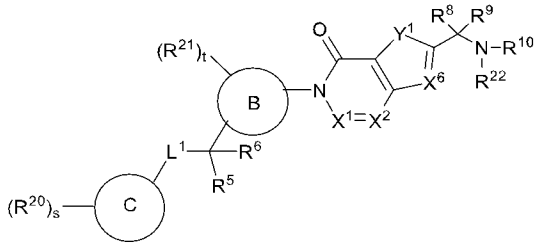


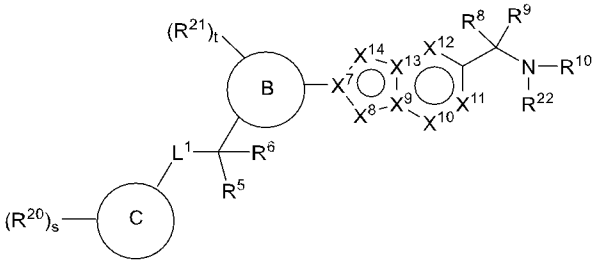
Formula (A) as described herein.

[0008] Also disclosed herein is a compound of Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt or stereoisomer thereof:



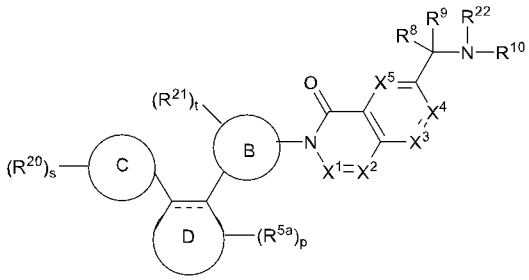
Formula (I),

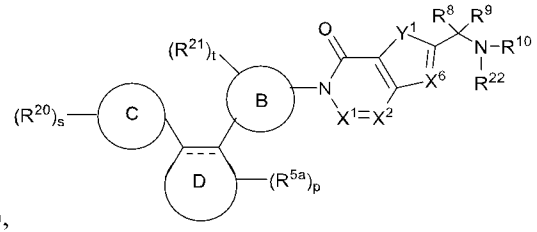




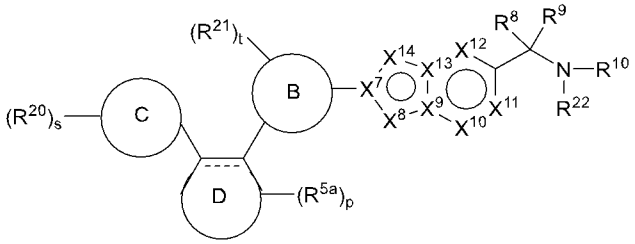
Formula (II), Formula (III), as described herein.

[0009] In some embodiments, the compound is of Formula (Ia), (IIa), or (IIIa):





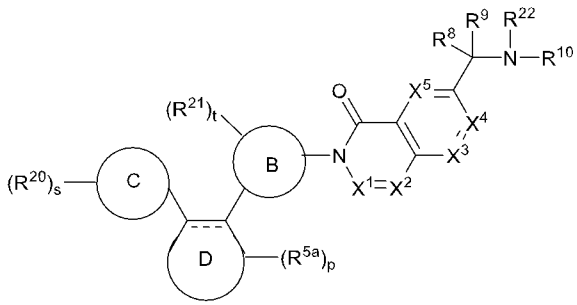
Formula (Ia),



Formula (IIa),

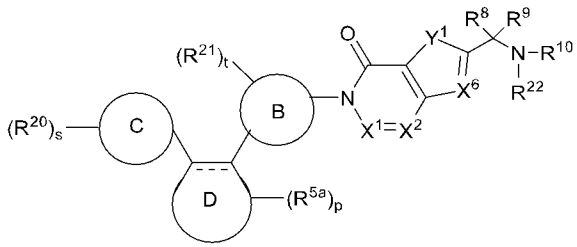
Formula (IIIa), as described herein.

[0010] In some embodiments the compound is of Formula (Ia), or a pharmaceutically acceptable salt or stereoisomer thereof:



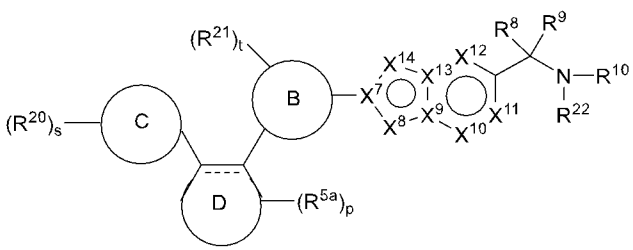
Formula (Ia) as described herein.

[0011] In some embodiments the compound is of Formula (IIa), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (IIa) as described herein.

[0012] In some embodiments the compound is of Formula (IIIa), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (IIIa) as described herein.

Also disclosed herein is a compound of Formula (IV), Formula (IVa), Formula (IVb), Formula (IVc), or a pharmaceutically acceptable salt or stereoisomer thereof, as described herein.

[0013] Also disclosed herein is a compound of Formula (V), Formula (Va), Formula (Vb), Formula (Vc), or a pharmaceutically acceptable salt or stereoisomer thereof, as further described herein. Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0014] Also disclosed herein is a method of treating a cancer, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[0015] Also disclosed herein is a method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[0016] In some embodiments, the cancer is a hematologic cancer. In some embodiments, the cancer is a lymphoma, a leukemia, or a myeloma. In some embodiments, the cancer is a non-hematologic cancer. In some embodiments, the cancer is a sarcoma, a carcinoma, or a melanoma. In some embodiments, the cancer is solid tumor cancer.

[0017] Also disclosed herein is a method of inhibiting abnormal cell proliferation, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[0018] Also disclosed herein is a method of modulating the immune response, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[0019] Also disclosed herein is a method of inhibiting Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[0020] Also disclosed herein is a method for treating a disease or condition associated with Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

INCORPORATION BY REFERENCE

[0021] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

Definitions

[0022] In the following description, certain specific details are set forth to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0023] Reference throughout this specification to "some embodiments" or "an embodiment" means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0024] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0025] "oxo" refers to =O.

[0026] "Carboxyl" refers to -COOH.

[0027] "Cyano" refers to -CN.

[0028] "Alkyl" refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" or "C_{1-6}alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_{1-10}alkyl. In some embodiments, the alkyl is a C_{1-6}alkyl. In some embodiments, the alkyl is a C_{1-5}alkyl. In some embodiments, the alkyl is a C_{1-4}alkyl. In some embodiments, the alkyl is a C_{1-3}alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In

some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0029] "Alkenyl" refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl ($-CH=CH_2$), 1-propenyl ($-CH_2CH=CH_2$), isopropenyl [$-C(CH_3)=CH_2$], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" or "C_{2-6}alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0030] "Alkynyl" refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" or "C_{2-6}alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0031] "Alkylene" refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0032] "Alkoxy" refers to a radical of the formula -Oalkyl where alkyl is as defined above. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0033] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0034] "Cycloalkyl" refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C_3-C_{15} fully saturated cycloalkyl or C_3-C_{15} cycloalkenyl), from three to ten carbon atoms (e.g., C_3-C_{10} fully saturated cycloalkyl or C_3-C_{10} cycloalkenyl), from three to eight carbon atoms (e.g., C_3-C_8 fully saturated cycloalkyl or C_3-C_8 cycloalkenyl), from three to six carbon atoms (e.g., C_3-C_6 fully saturated cycloalkyl or C_3-C_6 cycloalkenyl), from three to five carbon atoms (e.g., C_3-C_5 fully saturated cycloalkyl or C_3-C_5 cycloalkenyl), or three to four carbon atoms (e.g., C_3-C_4 fully saturated cycloalkyl or C_3-C_4 cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane,

bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0035] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0036] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0037] "Haloalkoxy" refers to a radical of the formula -Ohaloalkyl where haloalkyl is as defined above. In some embodiments, the haloalkoxy comprises 1 to 3 halogens. In some embodiments, the haloalkoxy comprises 1 to 3 fluoros. In some embodiments, the haloalkoxy is $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CF_3$, $-OCH_2CHF_2$, or $-OCH_2CH_2F$.

[0038] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0039] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0040] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_3$, or $-CH_2CH_2N(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some

embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0041] "Heterocycloalkyl" refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C_2-C_{15} fully saturated heterocycloalkyl or C_2-C_{15} heterocycloalkenyl), from two to ten carbon atoms (e.g., C_2-C_{10} fully saturated heterocycloalkyl or C_2-C_{10} heterocycloalkenyl), from two to eight carbon atoms (e.g., C_2-C_8 fully saturated heterocycloalkyl or C_2-C_8 heterocycloalkenyl), from two to seven carbon atoms (e.g., C_2-C_7 fully saturated heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to six carbon atoms (e.g., C_2-C_6 fully saturated heterocycloalkyl or C_2-C_6 heterocycloalkenyl), from two to five carbon atoms (e.g., C_2-C_5 fully saturated heterocycloalkyl or C_2-C_5 heterocycloalkenyl), or two to four carbon atoms (e.g., C_2-C_4 fully saturated heterocycloalkyl or C_2-C_4 heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the

heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0042] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl,

pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0043] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0044] The term "one or more" when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, four, or more substituents. In some embodiments, the subject group is optionally substituted with one, two, three or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

[0045] An "effective amount" or "therapeutically effective amount" refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

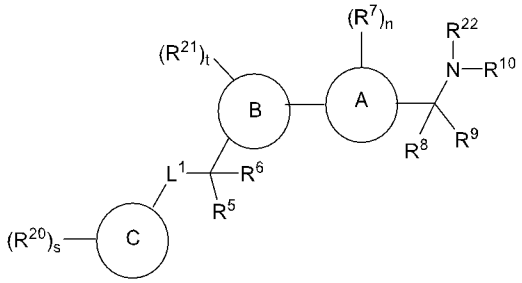
[0046] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

[0047] As used herein, a "disease or disorder associated with cbl-b" or, alternatively, "a cbl-b-mediated disease or disorder" means any disease or other deleterious condition in which cbl-b, or a mutant thereof, is known or suspected to play a role.

Compounds

[0048] Described herein are compounds, or a pharmaceutically acceptable salt or stereoisomer thereof, useful in the treatment of a disease or disorder associated with cbl-b.

[0049] Disclosed herein is a compound of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A),

wherein:

Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{20} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

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

L^1 is absent or -CR^3R^4-;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{21} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

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

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

R^{22} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl optionally substituted with one or more halogens), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a};

each R^{10a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

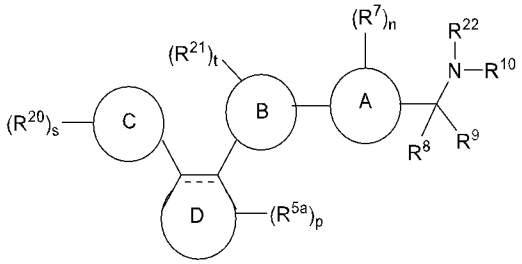
R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF_5, -SH, -$S(=O)C_1$-C_3alkyl, -$S(=O)_2C_1$-C_3alkyl, -$S(=O)_2NH_2$, -$S(=O)_2NHC_1$-C_3alkyl, -$S(=O)_2N(C_1$-C_3alkyl$)_2$, -$S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), -NH_2, -NHC_1-C_3alkyl, -$N(C_1$-C_3alkyl$)_2$, -$N=S(=O)(C_1$-C_3alkyl$)_2$, -$C(=O)C_1$-C_3alkyl, -C(=O)OH, -$C(=O)OC_1$-C_3alkyl, -$C(=O)NH_2$, -$C(=O)NHC_1$-C_3alkyl, -$C(=O)N(C_1$-C_3alkyl$)_2$, -$P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo.

[0050] In some embodiments of a compound of Formula (A), the compound of Formula (A) is of Formula (Aa)



Formula (Aa),

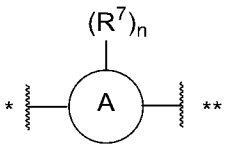
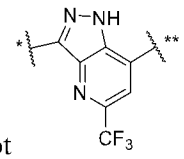
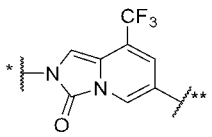
wherein:

$\equiv$ is a single bond or a double bond;

Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

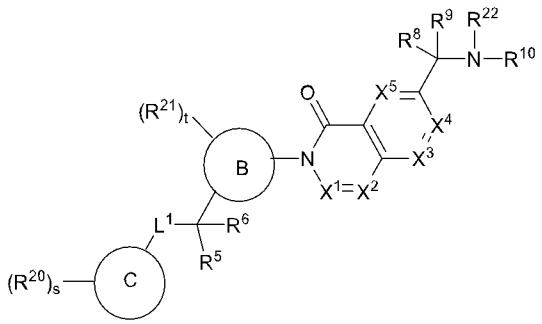
and

p is 0, 1, 2, 3, or 4.

[0051] In some embodiments of a compound of Formula (A) or (Aa), Ring A is C_{6-12} aryl, or 5-12 membered heteroaryl, provided that  is not  or 

wherein * represents the attachment point to the ring B and ** represents the attachment point to $-CR^8R^9-$.

[0052] Also disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (I),

wherein

X^1, X^2, X^3, X^4, and X^5 are independently N or $CR^{7'}$;

$R^{7'}$ is hydrogen or R^7;

Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{20} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

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

L^1 is absent or $-CR^3R^4-$;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{21} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

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

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-

C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

R^{22} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl optionally substituted with one or more halogens), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{10a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

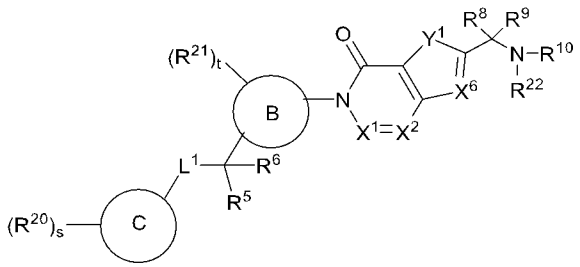
each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, $-P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo.

[0053] In some embodiments of a compound of Formula (I), each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl.

[0054] In some embodiments of a compound of Formula (I), each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[0055] Also disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (II),

wherein

X^1, X^2, and X^6 are independently N or $CR^{7'}$;

Y^1 is O, S, or $NR^{7''}$;

$R^{7'}$ is hydrogen or R^7;

$R^{7''}$ is hydrogen, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{20} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

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

L^1 is absent or $-CR^3R^4-$;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{21} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

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

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

R^{22} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl optionally substituted with one or more halogens), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{10a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF_5, -SH, -$S(=O)C_1$-C_3alkyl, -$S(=O)_2C_1$-C_3alkyl, -$S(=O)_2NH_2$, -$S(=O)_2NHC_1$-C_3alkyl, -$S(=O)_2N(C_1$-C_3alkyl$)_2$, -$S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), -NH_2, -NHC_1-C_3alkyl, -$N(C_1$-C_3alkyl$)_2$, -$N=S(=O)(C_1$-C_3alkyl$)_2$, -$C(=O)C_1$-C_3alkyl, -C(=O)OH, -$C(=O)OC_1$-C_3alkyl, -$C(=O)NH_2$, -$C(=O)NHC_1$-C_3alkyl, -$C(=O)N(C_1$-C_3alkyl$)_2$, -$P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

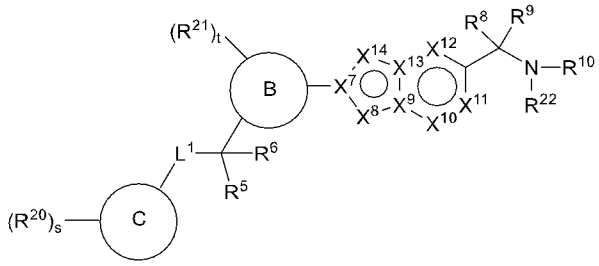
or two R on the same atom form an oxo.

[0056] In some embodiments of a compound of Formula (II), each R^{21} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl.

[0057] In some embodiments of a compound of Formula (II), each R^{21} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-

C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[0058] Also disclosed herein is a compound of Formula (III), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (III),

wherein

X^{10}, X^{11}, and X^{12} are independently N or $CR^{7'}$;

X^7 is N or C;

X^8 is O, S, N, or $NR^{7''}$ and X^{14} is N or CR^7; or X^{14} is O, S, N, or $NR^{7''}$ and X^8 is N or $CR^{7'}$;

X^9 and X^{13} are independently N or C, provided that X^9 and X^{13} are not both N;

$R^{7'}$ is hydrogen or R^7;

$R^{7''}$ is hydrogen, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{20} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

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

L^1 is absent or $-CR^3R^4$-;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

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

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

R^{22} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl optionally substituted with one or more halogens), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{10a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

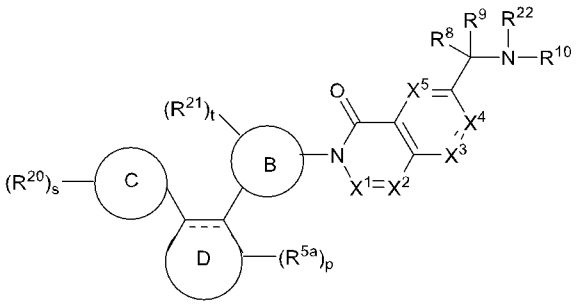
each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, $-P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo.

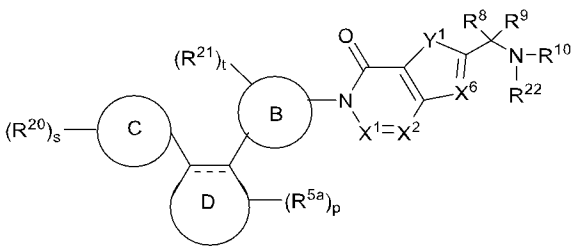
[0059] In some embodiments of a compound of Formula (III), each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl.

[0060] In some embodiments of a compound of Formula (III), each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

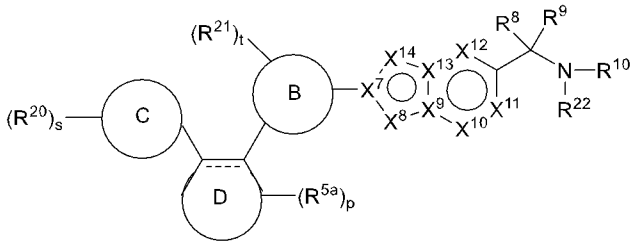
[0061] In some embodiments, the compound is of Formula (Ia), (IIa), or (IIIa):



Formula (Ia),



Formula (IIa),



Formula (IIIa),

wherein:

=== is a single bond or a double bond;

Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

and

p is 0, 1, 2, 3, or 4.

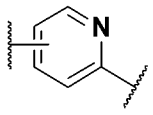
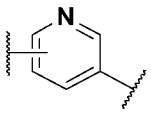
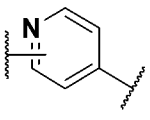
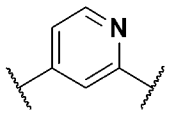
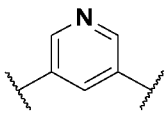
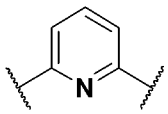
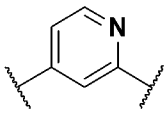
[0062] In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), Ring D is aryl or heteroaryl. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), Ring D is phenyl. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), Ring D is 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), Ring D is 6-membered heteroaryl.

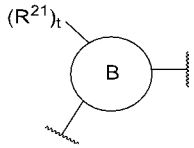
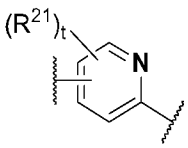
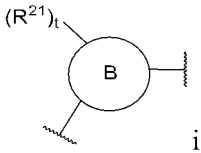
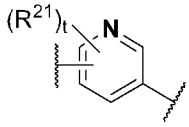
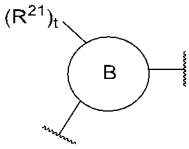
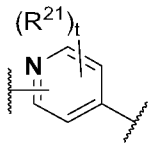
[0063] In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 0, 1, or 2. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 1 or 2. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 0 or 1. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 0. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 1. In some embodiments of a compound of Formula (Aa), (Ia), (IIa), or (IIIa), p is 2.

[0064] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring C is heteroaryl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring C is 5-membered heteroaryl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring C is imidazolyl or triazolyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring C is triazolyl.

[0065] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{20} is independently halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{20} is independently C_1-C_6alkyl.

[0066] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 0, 1, or 2. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 1 or 2. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 0 or 1. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 0. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 1. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each s is 2.

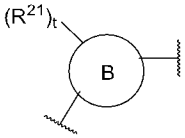
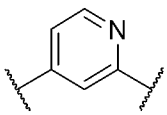
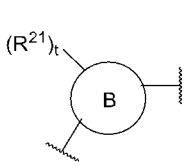
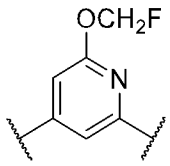
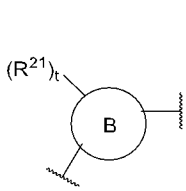
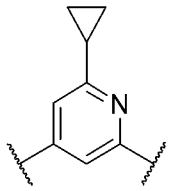
[0067] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is aryl or heteroaryl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is phenyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is 6-membered heteroaryl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is pyridinyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is  ,  ,  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is  ,  , or  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), Ring B is  .

[0068] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  .

[0069] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{21} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{21} is independently cycloalkyl optionally substituted with one or more halogens.

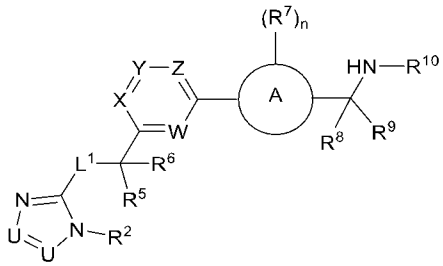
[0070] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{21} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), each R^{21} is independently cycloalkyl.

[0071] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 0, 1, or 2. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 1 or 2. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 0 or 1. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 0. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 1. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), t is 2.

[0072] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa),  is  .

[0073] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), R^{22} is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), or (IIIa), R^{22} is hydrogen.

[0074] Also disclosed herein is a compound of Formula (IV), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (IV),

wherein:

each U is independently -N- or -CR^1-;

each R^1 is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl;

R^2 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl;

L^1 is absent or -CR^3R^4-;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

X is -N- or -CR^X-;

R^X is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

Y is -N- or -CR^Y-;

R^Y is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl

optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

Z is -N- or -CR^Z-;

R^Z is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

W is -N- or -CR^W-;

R^W is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

or R^X and R^Y are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each optionally substituted with one or more R;

or R^Y and R^Z are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each optionally substituted with one or more R;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

each R^{10a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -

$C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

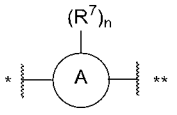
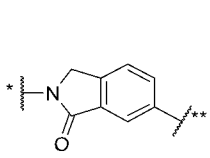
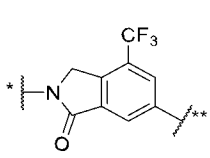
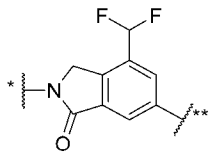
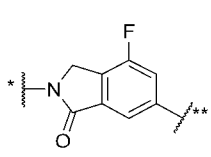
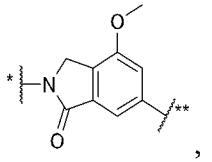
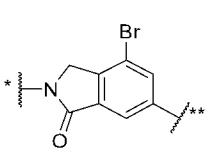
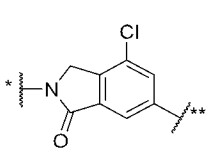
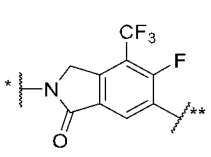
each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

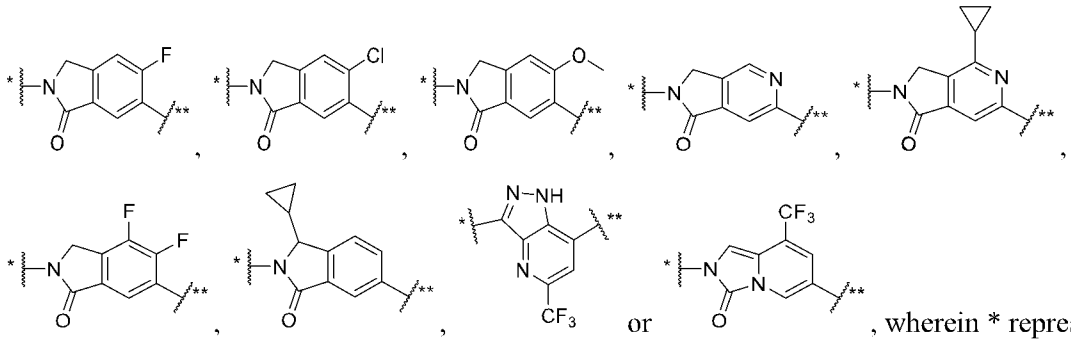
R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, $-P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo;

provided that  is not  ,  ,  ,  ,  ,  ,  ,  .



or , wherein * represents the attachment point to the ring containing X, Y, Z and W and ** represents the attachment point to -CR^8R^9-.

[0075] In some embodiments of a compound of Formula (IV), R^Y is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl.

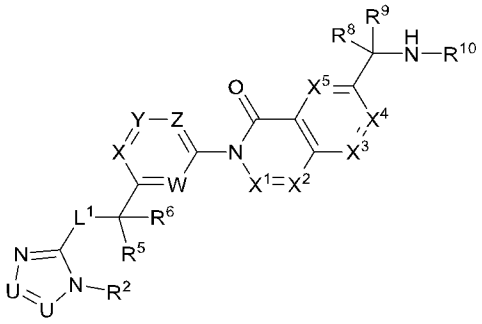
[0076] In some embodiments of a compound of Formula (IV), R^Y is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[0077] In some embodiments of a compound of Formula (A), (Aa), or (IV), Ring A is aryl or heteroaryl. In some embodiments of a compound of Formula (A), (Aa), or (IV), Ring A is heteroaryl. In some embodiments of a compound of Formula (A), (Aa), or (IV), Ring A is a 6-6 fused ring. In some embodiments of a compound of Formula (A), (Aa), or (IV), Ring A is a 6-5 or 5-6 fused ring containing 3 or more heteroatoms selected from N, O, and S.

[0078] In some embodiments of a compound of Formula (A), (Aa), or (IV), wherein Ring A is a 6-6 fused ring containing 1-4 ring nitrogen atoms. In some embodiments of a compound of Formula (A), (Aa), or (IV), wherein Ring A is a 6-6 fused ring containing 2 ring nitrogen atoms. In some embodiments of a compound of Formula (A), (Aa), or (IV), wherein Ring A is a 6-6 fused ring containing 3 ring nitrogen atoms.

[0079] In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 0, 1, 2, 3, or 4. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 1, 2, or 3. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 1 or 2. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 1. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 2. In some embodiments of a compound of Formula (A), (Aa), or (IV), n is 3.

[0080] In some embodiments of a compound of Formula (IV), the compound of Formula (IV) is of Formula (IVa):



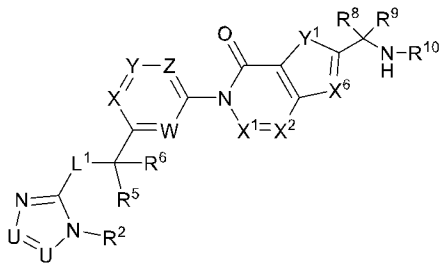
Formula (IVa),

wherein

X^1, X^2, X^3, X^4, and X^5 are independently N or $CR^{7'}$; and

$R^{7'}$ is hydrogen or R^7.

[0081] In some embodiments of a compound of Formula (IV), the compound of Formula (IV) is of Formula (IVb):



Formula (IVb),

wherein:

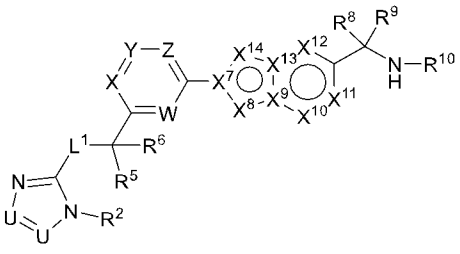
X^1, X^2, and X^6 are independently N or $CR^{7'}$;

Y^1 is O, S, or $NR^{7''}$;

$R^{7'}$ is hydrogen or R^7; and

$R^{7''}$ is hydrogen, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl.

[0082] In some embodiments of a compound of Formula (IV), the compound of Formula (IV) is of Formula (IVc):



Formula (IVc),

X^7 is N or C;

X^8 is O, S, N, or $NR^{7''}$ and X^{14} is N or $CR^{7'}$; or X^{14} is O, S, N, or $NR^{7''}$ and X^8 is N or $CR^{7'}$;

X^9 and X^{13} are independently N or C, provided that X^9 and X^{13} are not both N;

X^{10}, X^{11}, and X^{12} are independently N or $CR^{7'}$;

$R^{7'}$ is hydrogen or R^7; and

$R^{7''}$ is hydrogen, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl.

[0083] In some embodiments of a compound of Formula (I), (Ia), (II), (IIa), (IVa), or (IVb), X^1 is $CR^{7'}$. In some embodiments of a compound of Formula (I), (Ia), (II), (IIa), (IVa), or (IVb), X^1 is N.

[0084] In some embodiments of a compound of Formula (I), (Ia), (II), (IIa), (IVa), or (IVb), X^2 is $CR^{7'}$. In some embodiments of a compound of Formula (I), (Ia), (II), (IIa), (IVa), or (IVb), X^2 is N.

[0085] In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^3 is $CR^{7'}$. In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^3 is N.

[0086] In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^4 is $CR^{7'}$. In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^4 is N.

[0087] In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^5 is $CR^{7'}$. In some embodiments of a compound of Formula (I), (Ia), or (IVa), X^5 is N.

[0088] In some embodiments of a compound of Formula (II), (IIa), or (IVb), X^6 is $CR^{7'}$. In some embodiments of a compound of Formula (II), (IIa), or (IVb), X^6 is N.

[0089] In some embodiments of a compound of Formula (II), (IIa), or (IVb), Y^1 is O. In some embodiments of a compound of Formula (II), (IIa), or (IVb), Y^1 is S. In some embodiments of a compound of Formula (II), (IIa), or (IVb), Y^1 is $NR^{7''}$.

[0090] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^7 is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^7 is C.

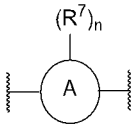
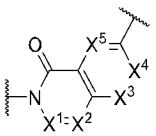
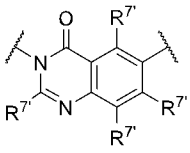
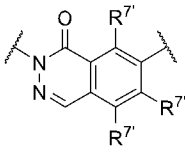
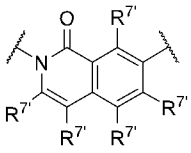
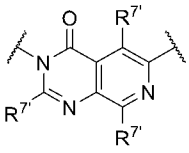
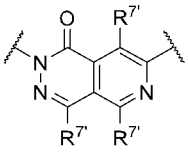
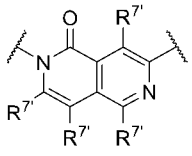
[0091] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^9 is N and X^{13} is C. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^9 is C and X^{13} is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^9 is C and X^{13} is C.

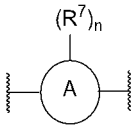
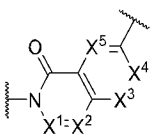
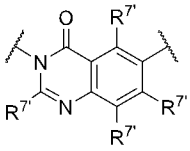
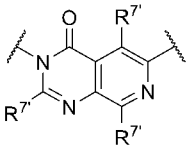
[0092] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{10} is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{10} is $CR^{7'}$.

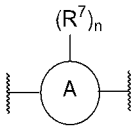
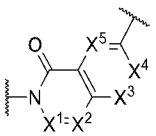
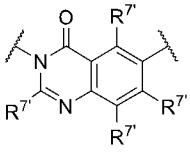
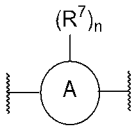
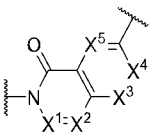
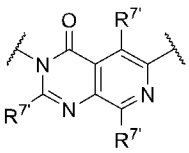
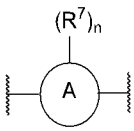
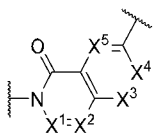
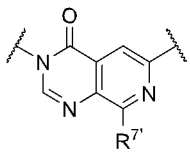
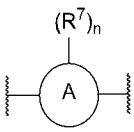
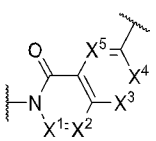
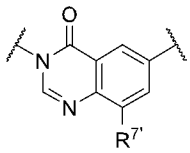
[0093] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{11} is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{11} is $CR^{7'}$.

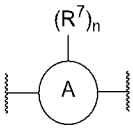
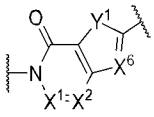
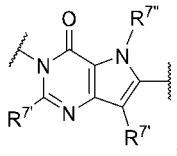
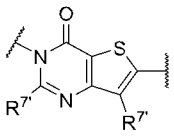
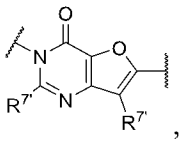
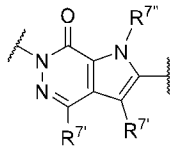
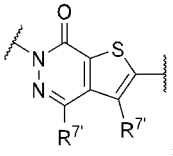
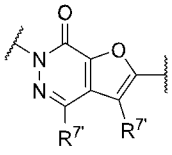
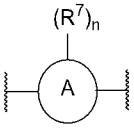
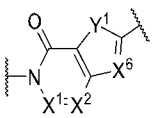
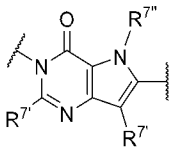
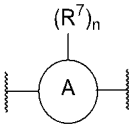
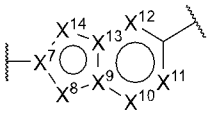
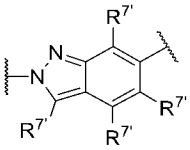
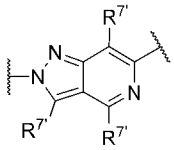
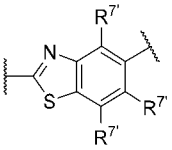
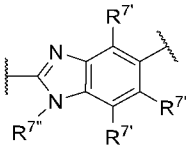
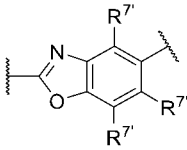
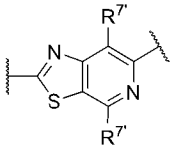
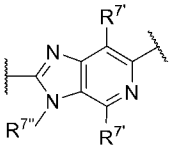
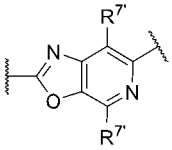
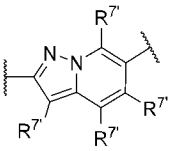
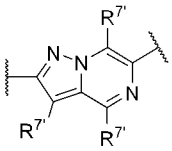
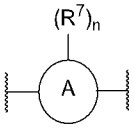
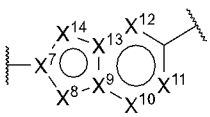
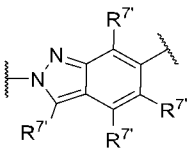
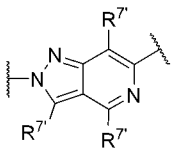
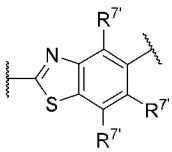
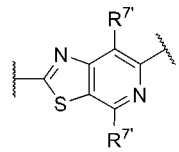
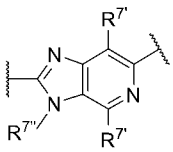
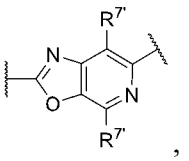
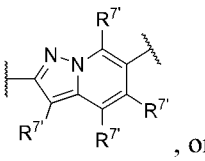
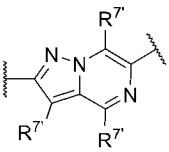
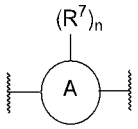
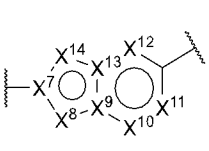
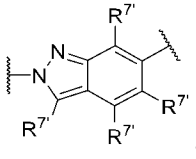
[0094] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{12} is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{12} is $CR^{7'}$.

[0095] In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^8 is O, S, N, or $NR^{7''}$ and X^{14} is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^8 is O, S, N, or $NR^{7''}$ and X^{14} is CR^7. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{14} is O, S, N, or $NR^{7''}$ and X^8 is N. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{14} is O, S, N, or $NR^{7''}$ and X^8 is CR^7. In some embodiments of a compound of Formula (III), (IIIa), or (IVc), X^{14} is N and X^8 is CR^7.

[0096] In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  ,  ,  ,  ,  , or  .

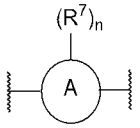
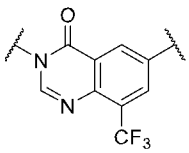
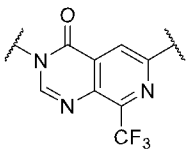
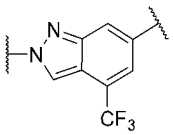
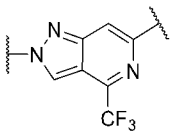
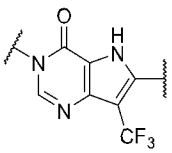
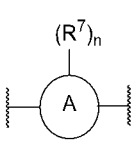
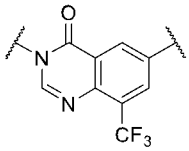
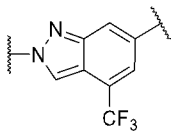
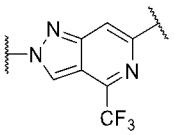
[0097] In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  or  .

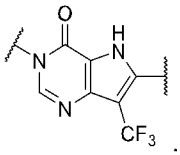
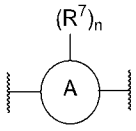
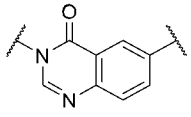
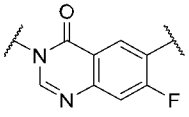
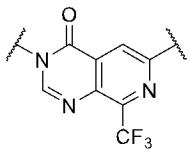
[0098] In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (Ia), (IV), or (IVa),  or  is  .

[0099] In some embodiments of a compound of Formula (A), (Aa), (II), (IIa), (IV), or (IVb),  or  is  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (A), (Aa), (II), (IIa), (IV), or (IVb),  or  is  . In some embodiments of a compound of Formula (A), (Aa), (III), (IIIa), (IV), or (IVc),  or  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or . In some embodiments of a compound of Formula (A), (Aa), (III), (IIIa), (IV), or (IVc),  or  is  ,  ,  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (A), (Aa), (III), (IIIa), (IV), or (IVc),  or  is  .

[00100] In some embodiments of a compound of Formula (IIa), (IIIa), (IVb), or (IVc), $R^{7'}$ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl. In some embodiments of a compound of Formula (IIa), (IIIa), (IVb), or (IVc), $R^{7'}$ is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IIa), (IIIa), (IVb), or (IVc), $R^{7'}$ is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IIa), (IIIa), (IVb), or (IVc), $R^{7'}$ is hydrogen. In some embodiments of a compound of Formula (IIa), (IIIa), (IVb), or (IVc), $R^{7'}$ is C_1-C_6alkyl.

[00101] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl; wherein each alkyl and cycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl,or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently halogen or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^7 is independently C_1-C_6haloalkyl.

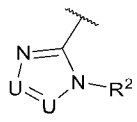
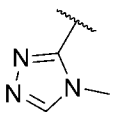
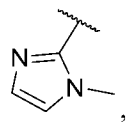
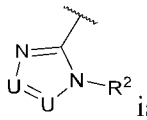
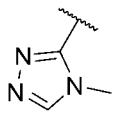
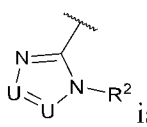
[00102] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc),  is  ,  ,  ,  , or  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc),  is  ,  ,  , or

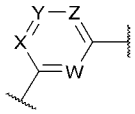
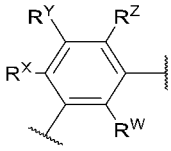
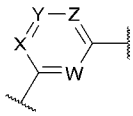
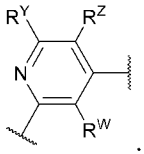
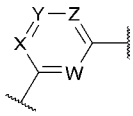
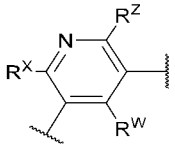
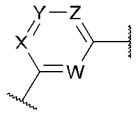
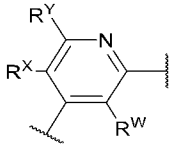

. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), or (IVa),  is  ,  , or  .

[00103] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each U is independently -CR^1-. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), one U is -N- and the other U is -CR^1-.

[00104] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each R^1 is independently hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each R^1 is independently hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each R^1 is independently hydrogen or halogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each R^1 is independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), each R^1 is independently hydrogen.

[00105] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^2 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^2 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^2 is hydrogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^2 is C_1-C_6alkyl.

[00106] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  ,  , or  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  .

[00107] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), X is -CR^X-. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), X is -N-.

[00108] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^X is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^X is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^X is hydrogen or halogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^X is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^X is hydrogen.

[00109] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), Y is -CR^Y-. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), Y is -N-.

[00110] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[00111] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_1-C_6haloalkoxy.

[00112] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is -OR^a. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is C_1-C_6haloalkoxy. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is C_1-C_3haloalkoxy. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is -OCH_2F.

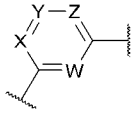
[00113] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl optionally substituted with one or more halogens, or

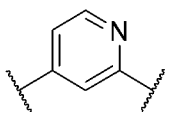
heterocycloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, halogen, C_1-C_6alkyl, or cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen, C_1-C_6alkyl, or cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen or cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen or cycloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is hydrogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Y is cycloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), Z is -CR^Z-. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), Z is -N-.

[00114] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Z is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Z is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Z is hydrogen or halogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Z is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^Z is hydrogen.

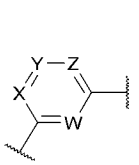
[00115] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), W is -CR^W-. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), W is -N-.

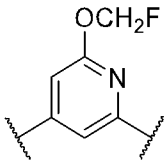
[00116] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^W is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^W is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^W is hydrogen or halogen. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^W is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), R^W is hydrogen.

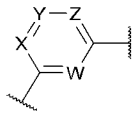
[00117] In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), 

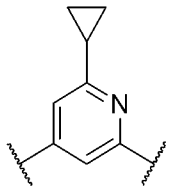
is 

. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc),



is 

. In some embodiments of a compound of Formula (IV), (IVa), (IVb), or (IVc), 

is 

.

[00118] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), L^1 is $-CR^3R^4-$. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), L^1 is absent.

[00119] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^3 and R^4 are each independently hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^3 and R^4 are each independently hydrogen.

[00120] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^5 and R^6 are each independently hydrogen, halogen, or C_1-C_6alkyl.

[00121] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a}.

[00122] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^5 and R^6 are taken together to form a cycloalkyl optionally substituted with one or more R^{5a}.

[00123] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), or (IVb), or (IVc), R^5 and R^6 are taken together to form a heterocycloalkyl optionally substituted with one or more R^{5a}.

[00124] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a}.

[00125] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl optionally substituted with one or more R^{5a}.

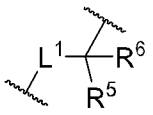
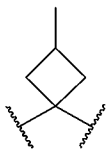
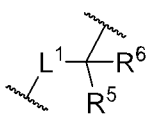
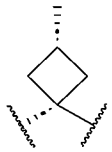
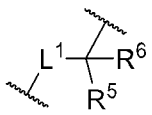
[00126] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form a phenyl optionally substituted with one or more R^{5a}.

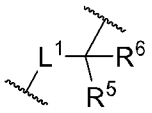
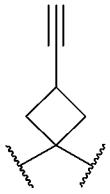
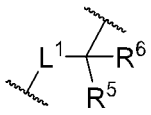
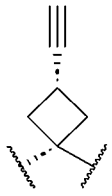
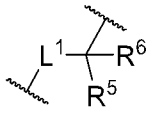
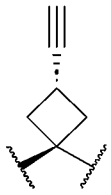
[00127] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form a heteroaryl optionally substituted with one or more R^{5a}.

[00128] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form a 5- or 6-membered heteroaryl optionally substituted with one or more R^{5a}.

[00129] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc), L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form a 6-membered heteroaryl optionally substituted with one or more R^{5a}.

[00130] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen, C_1-C_6alkyl, C_2-C_6alkynyl, or cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_2-C_6alkynyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen or C_2-C_6alkynyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently C_2-C_6alkynyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), (IVb), or (IVc), each R^{5a} is independently halogen.

[00131] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  .

[00132] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (IV), (IVa), (IVb), or (IVc),  is  .

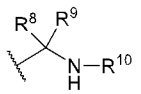
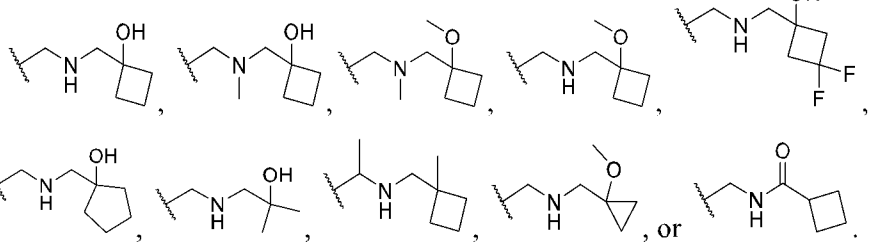
[00133] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), each R^8 and R^9 are each independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), each R^8 and R^9 are each hydrogen.

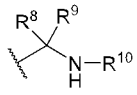
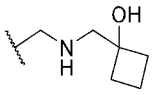
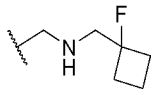
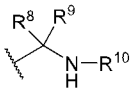
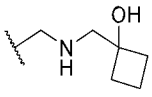
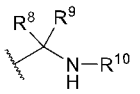
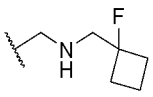
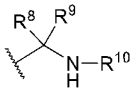
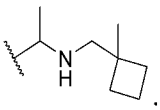
[00134] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), R^{10} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, cycloalkyl optionally substituted with one or more halogens, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl); wherein the alkyl, alkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{10a}. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), R^{10} is C_1-C_6hydroxyalkyl or C_1-C_6alkylene(cycloalkyl); wherein the alkyl, alkylene, and cycloalkyl is independently optionally substituted with one or more R^{10a}. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), R^{10} is C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), R^{10} is C_1-C_6alkylene(cycloalkyl); wherein the alkylene and cycloalkyl optionally substituted with one or more R^{10a}. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), each R^{10a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, or C_1-C_6haloalkyl.

[00135] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), each R^{10a} is -OH.

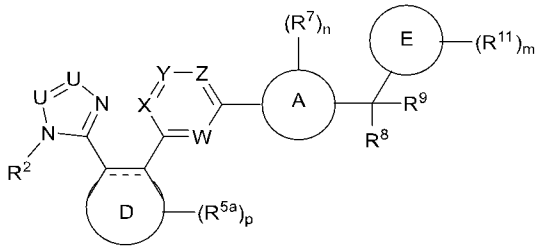
[00136] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb), R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a}. In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),

R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a}.

[00137] In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),  is  , , or .

In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),  is  or  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),  is  . In some embodiments of a compound of Formula (A), (Aa), (I), (II), (III), (Ia), (IIa), (IIIa), (IV), (IVa), or (IVb),  is  .

[00138] Also disclosed herein is a compound of Formula (V), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (V),

wherein:

each U is independently -N- or $-CR^1-$;

each R^1 is independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

R^2 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

≡ is a single bond or a double bond;

Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{5a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

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

X is -N- or -CR^X-;

R^X is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

Y is -N- or -CR^Y-;

R^Y is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

Z is -N- or -CR^Z-;

R^Z is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

W is -N- or -CR^W-;

R^W is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^8 and R^9 are taken together to form an oxo;

Ring E is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{11} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{11} on the same atom are taken together to form an oxo;

m is 0, 1, 2, 3, 4, 5, or 6;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

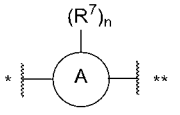
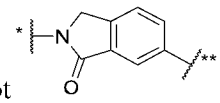
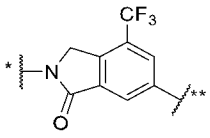
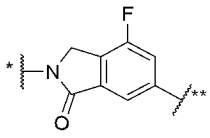
each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, $-P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo;

provided that  is not  ,  ,  , wherein * represents the attachment point to the ring containing X, Y, Z and W and ** represents the attachment point to $-CR^8R^9-$.

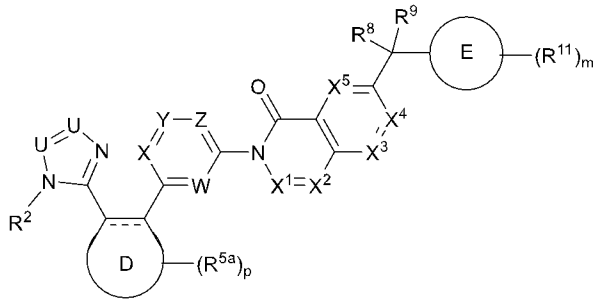
[00139] In some embodiments of a compound of Formula (V), R^Y is hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl.

[00140] In some embodiments of a compound of Formula (V), R^Y is hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[00141] In some embodiments of a compound of Formula (V), Ring A is aryl or heteroaryl. In some embodiments of a compound of Formula (V), Ring A is heteroaryl. In some embodiments of a compound of Formula (V), Ring A is a 6-6 fused ring. In some embodiments of a compound of Formula (V), Ring A is a 6-5 or 5-6 fused ring containing 3 or more heteroatoms selected from N, O, and S.

[00142] In some embodiments of a compound of Formula (V), n is 0, 1, 2, 3, or 4. In some embodiments of a compound of Formula (V), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (V), n is 1, 2, or 3. In some embodiments of a compound of Formula (V), n is 1 or 2. In some embodiments of a compound of Formula (V), n is 1. In some embodiments of a compound of Formula (V), n is 2. In some embodiments of a compound of Formula (V), n is 3.

[00143] In some embodiments of a compound of Formula (V), the compound of Formula (V) is of Formula (Va):



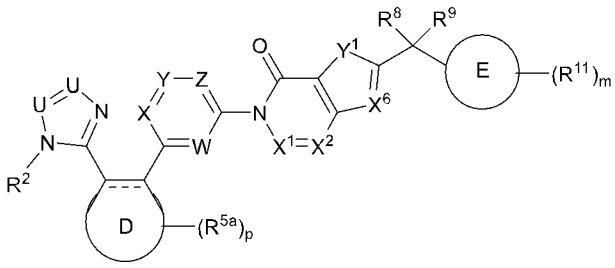
Formula (Va)

wherein

X^1, X^2, X^3, X^4, and X^5 are independently N or $CR^{7'}$; and

$R^{7'}$ is hydrogen or R^7.

[00144] In some embodiments of a compound of Formula (V), the compound of Formula (V) is of Formula (Vb):



Formula (Vb)

wherein:

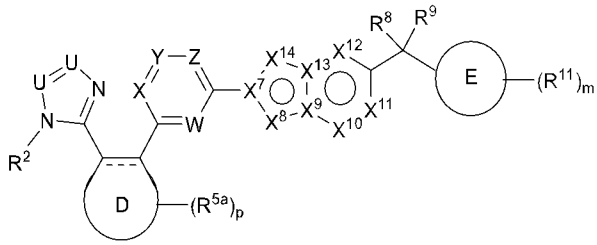
X^1, X^2, and X^6 are independently N or $CR^{7'}$;

Y^1 is O, S, or $NR^{7''}$;

$R^{7'}$ is hydrogen or R^7; and

$R^{7''}$ is hydrogen, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl.

[00145] In some embodiments of a compound of Formula (V), the compound of Formula (V) is of Formula (Vc):



Formula (Vc)

X^7 is N or C;

X^8 is O, S, N, or $NR^{7''}$ and X^{14} is N or $CR^{7'}$; or X^{14} is O, S, N, or $NR^{7''}$ and X^8 is N or $CR^{7'}$;

X^9 and X^{13} are independently N or C, provided that X^9 and X^{13} are not both N;

X^{10}, X^{11}, and X^{12} are independently N or $CR^{7'}$;

$R^{7'}$ is hydrogen or R^7; and

$R^{7''}$ is hydrogen, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl.

[00146] In some embodiments of a compound of Formula (Va) or (Vb), X^1 is $CR^{7'}$. In some embodiments of a compound of Formula (Va) or (Vb), X^1 is N.

[00147] In some embodiments of a compound of Formula (Va) or (Vb), X^2 is $CR^{7'}$. In some embodiments of a compound of Formula (Va) or (Vb), X^2 is N.

[00148] In some embodiments of a compound of Formula (Va), X^3 is $CR^{7'}$. In some embodiments of a compound of Formula (Va), X^3 is N.

[00149] In some embodiments of a compound of Formula (Va), X^4 is $CR^{7'}$. In some embodiments of a compound of Formula (Va), X^4 is N.

[00150] In some embodiments of a compound of Formula (Va), X^5 is $CR^{7'}$. In some embodiments of a compound of Formula (Va), X^5 is N.

[00151] In some embodiments of a compound of Formula (Vb), X^6 is $CR^{7'}$. In some embodiments of a compound of Formula (Vb), X^6 is N.

[00152] In some embodiments of a compound of Formula (Vb), Y^1 is O. In some embodiments of a compound of Formula (Vb), Y^1 is S. In some embodiments of a compound of Formula (II), (IIa), or (IVb), Y^1 is $NR^{7''}$.

[00153] In some embodiments of a compound of Formula (Vc), X^7 is N. In some embodiments of a compound of Formula (Vc), X^7 is C.

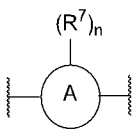
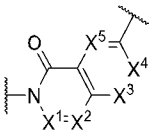
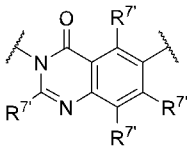
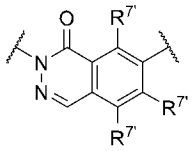
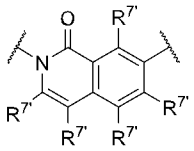
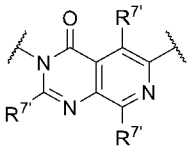
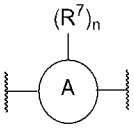
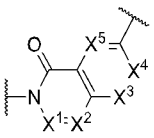
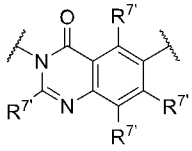
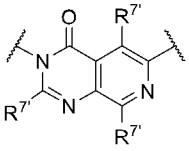
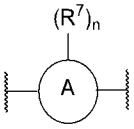
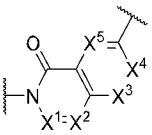
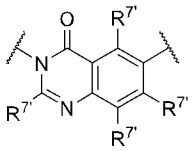
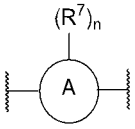
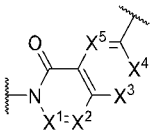
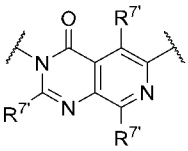
[00154] In some embodiments of a compound of Formula (Vc), X^9 is N and X^{13} is C. In some embodiments of a compound of Formula (Vc), X^9 is C and X^{13} is N. In some embodiments of a compound of Formula (Vc), X^9 is C and X^{13} is C.

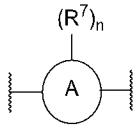
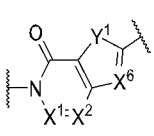
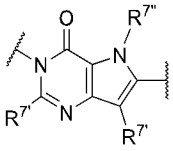
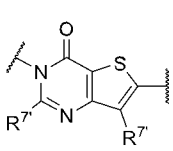
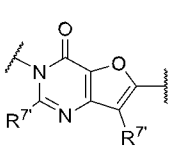
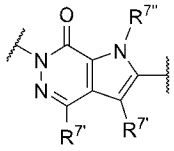
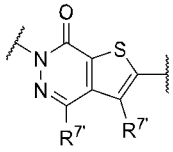
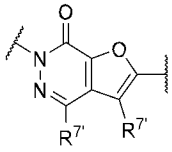
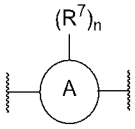
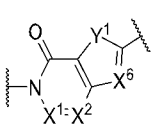
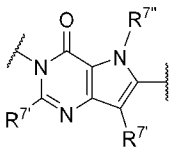
[00155] In some embodiments of a compound of Formula (Vc), X^{10} is N. In some embodiments of a compound of Formula (Vc), X^{10} is $CR^{7'}$.

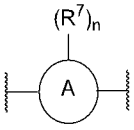
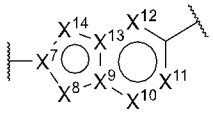
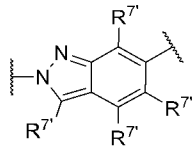
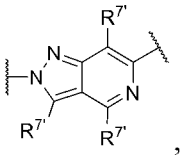
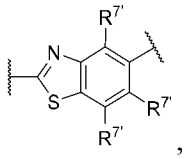
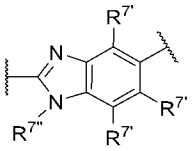
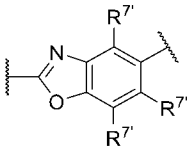
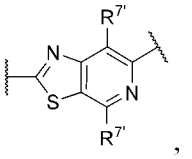
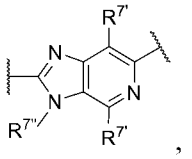
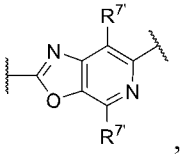
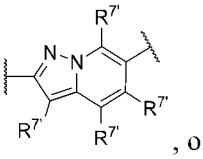
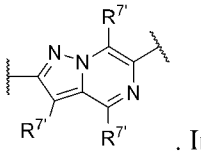
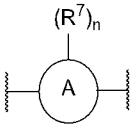
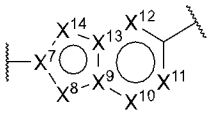
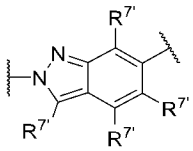
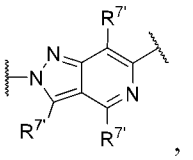
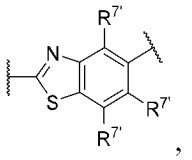
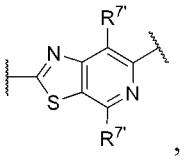
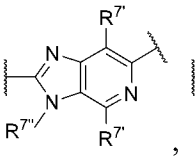
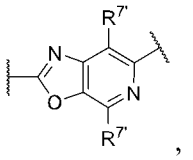
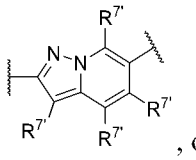
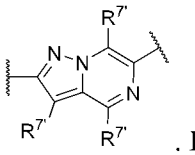
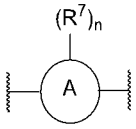
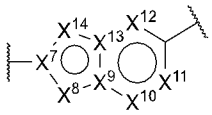
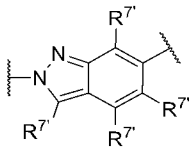
[00156] In some embodiments of a compound of Formula (Vc), X^{11} is N. In some embodiments of a compound of Formula (Vc), X^{11} is $CR^{7'}$.

[00157] In some embodiments of a compound of Formula (Vc), X^{12} is N. In some embodiments of a compound of Formula (Vc), X^{12} is $CR^{7'}$.

[00158] In some embodiments of a compound of Formula (Vc), X^8 is O, S, N, or $NR^{7''}$ and X^{14} is N. In some embodiments of a compound of Formula (Vc), X^8 is O, S, N, or $NR^{7''}$ and X^{14} is CR^7. In some embodiments of a compound of Formula (Vc), X^{14} is O, S, N, or $NR^{7''}$ and X^8 is N. In some embodiments of a compound of Formula (Vc), X^{14} is O, S, N, or $NR^{7''}$ and X^8 is CR^7. In some embodiments of a compound of Formula (Vc), X^{14} is N and X^8 is CR^7.

[00159] In some embodiments of a compound of Formula (V) or (Va),  or  is  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (V) or (Va),  or  is  or  . In some embodiments of a compound of Formula (V) or (Va),  or  is  . In some embodiments of a compound of Formula (V) or (Va),  or  is  .

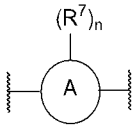
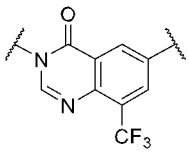
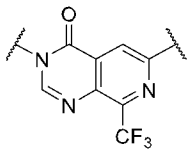
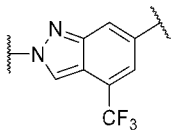
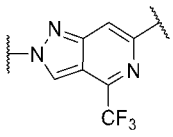
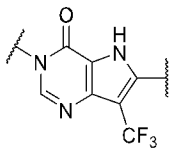
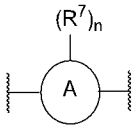
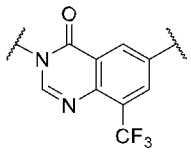
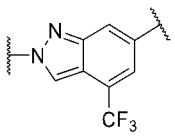
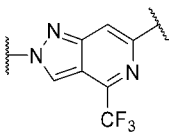
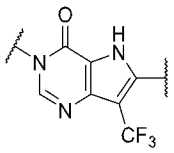
[00160] In some embodiments of a compound of Formula (V) or (Vb),  or  is  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (V) or (Vb),  or  is  .

[00161] In some embodiments of a compound of Formula (V) or (Vc),  or  is  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (V) or (Vc),  or  is  ,  ,  ,  ,  ,  ,  , or  . In some embodiments of a compound of Formula (V) or (Vc),  or  is  .

[00162] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl; wherein each alkyl and cycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl,or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently halogen or C_1-C_6haloalkyl. In some

embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^7 is independently C_1-C_6haloalkyl.

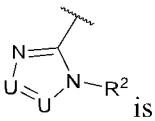
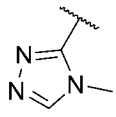
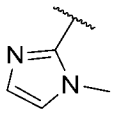
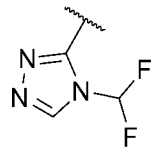
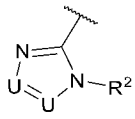
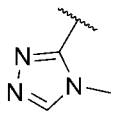
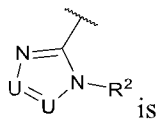
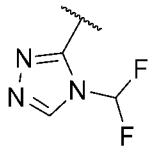
[00163] In some embodiments of a compound of Formula (Vb) or (Vc), $R^{7''}$ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl. In some embodiments of a compound of Formula (Vb) or (Vc), $R^{7''}$ is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (Vb) or (Vc), $R^{7''}$ is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (Vb) or (Vc), $R^{7''}$ is hydrogen. In some embodiments of a compound of Formula (Vb) or (Vc), $R^{7''}$ is C_1-C_6alkyl.

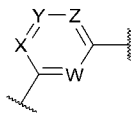
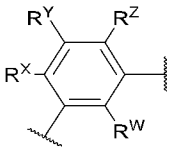
[00164] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  ,  ,  ,  , or  . In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  ,  ,  , or  .

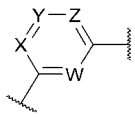
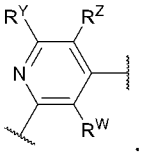
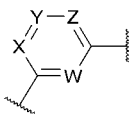
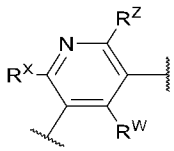
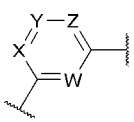
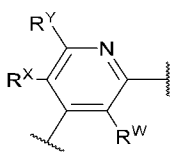
[00165] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each U is independently -CR^1-. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), one U is -N- and the other U is -CR^1-.

[00166] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^1 is independently hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^1 is independently hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^1 is independently hydrogen or halogen. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^1 is independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^1 is independently hydrogen.

[00167] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^2 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^2 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^2 is hydrogen. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^2 is C_1-C_6alkyl.

[00168] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  ,  , or  . In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  . In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  .

In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  .

In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  . In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  . In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc),  is  .

[00169] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), X is -CR^X-. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), X is -N-.

[00170] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^X is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^X is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^X is hydrogen or halogen. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^X is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^X is hydrogen.

[00171] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Y is -CR^Y-. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Y is -N-.

[00172] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens.

[00173] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl.

[00174] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, or C_1-C_6haloalkoxy.

[00175] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is $-OR^a$. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is C_1-C_6haloalkoxy. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is C_1-C_3haloalkoxy. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is $-OCH_2F$.

[00176] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl optionally substituted with one or more halogens.

[00177] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, halogen, C_1-C_6alkyl, or cycloalkyl optionally substituted with one or more halogens.

[00178] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen, C_1-C_6alkyl, or cycloalkyl optionally substituted with one or more halogens.

[00179] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen or cycloalkyl optionally substituted with one or more halogens.

[00180] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen or cycloalkyl.

[00181] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is hydrogen.

[00182] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is cycloalkyl optionally substituted with one or more halogens.

[00183] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Y is cycloalkyl.

[00184] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Z is $-CR^Z-$. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Z is -N-.

[00185] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Z is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Z is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Z is hydrogen or halogen. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Z is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^Z is hydrogen.

[00186] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), W is $-CR^W-$. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), W is -N-.

[00187] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^W is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va),

(Vb), or (Vc), R^W is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^W is hydrogen or halogen. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^W is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), R^W is hydrogen.

[00188] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring D is aryl or heteroaryl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring D is phenyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring D is 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring D is 6-membered heteroaryl.

[00189] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{5a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkynyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{5a} is independently halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_2-C_6alkynyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{5a} is independently halogen or C_2-C_6alkynyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{5a} is independently halogen.

[00190] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 0, 1, or 2. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 1 or 2. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 0 or 1. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 0. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 1. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), p is 2.

[00191] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^8 and R^9 are each independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^8 and R^9 are each hydrogen.

[00192] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring E is 3-or 6-membered heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring E is 3-membered heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring E is 4-membered heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring E is 5-membered heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), Ring E is 6-membered heterocycloalkyl.

[00193] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{11} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl). In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{11} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{11} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{11} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, or C_1-

C_6haloalkyl. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), each R^{11} is independently C_1-C_6alkyl.

[00194] In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 0, 1, or 2. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 1 or 2. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 0 or 1. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 0. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 1. In some embodiments of a compound of Formula (V), (Va), (Vb), or (Vc), m is 2.

[00195] In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl), wherein each alkyl, alkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl or C_1-C_6haloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C_1-C_6alkyl.

[00196] In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl), wherein each alkyl, alkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound disclosed herein, each R^b is hydrogen. In some embodiments of a compound disclosed herein, each R^b is independently C_1-C_6alkyl.

[00197] In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl), wherein each alkyl, alkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each hydrogen. In some embodiments of a compound disclosed herein, R^c and R^d are each independently C_1-C_6alkyl.

[00198] In some embodiments of a compound disclosed herein, R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R.

[00199] In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, $-NH_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, or C_3-C_6cycloalkyl optionally substituted with one or more halogens. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, $-NH_2$, C_1-C_3alkyl, or C_1-C_3haloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, $-NH_2$, or C_1-C_3alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen or C_1-C_3alkyl.

[00200] In some embodiments of a compound disclosed herein, one or more of R, R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{10a}, R^{11}, R^{21}, R^{22}, R^X, R^Y, R^Z, R^W, R^a, R^b, R^c, and R^d groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[00201] In some embodiments of a compound disclosed herein, one or more ^{1}H are replaced with one or more deuteriums in one or more of the following groups R, R^{1}, R^{2}, R^{3}, R^{4}, R^{5}, R^{5a}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10}, R^{10a}, R^{11}, R^{21}, R^{22}, R^{X}, R^{Y}, R^{Z}, R^{W}, R^{a}, R^{b}, R^{c}, and R^{d}.

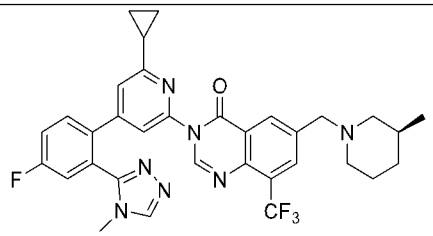
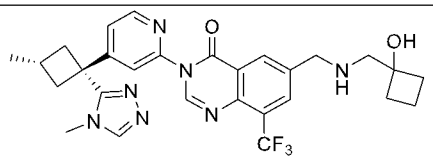
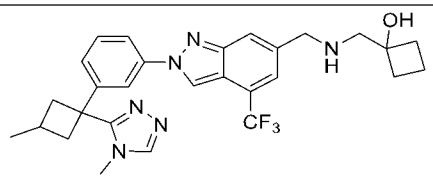
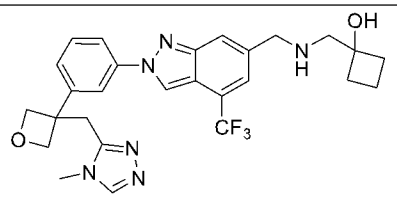
[00202] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R, R^{1}, R^{2}, R^{3}, R^{4}, R^{5}, R^{5a}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10}, R^{10a}, R^{11}, R^{21}, R^{22}, R^{X}, R^{Y}, R^{Z}, R^{W}, R^{a}, R^{b}, R^{c}, and R^{d} is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

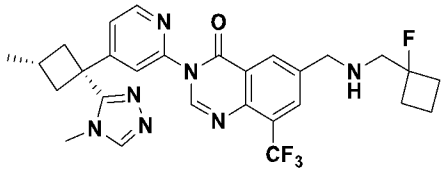
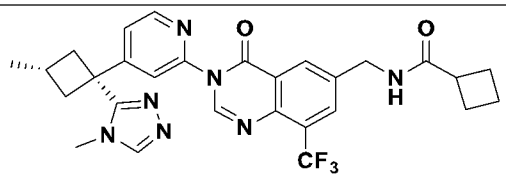
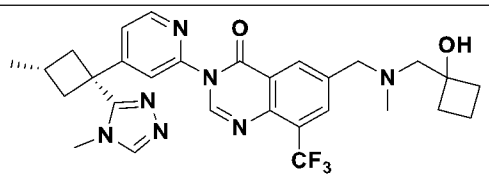
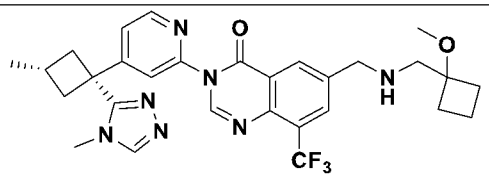
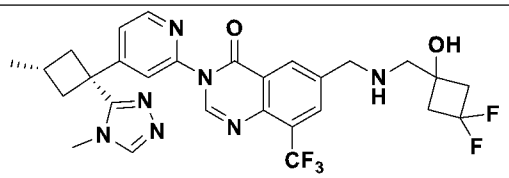
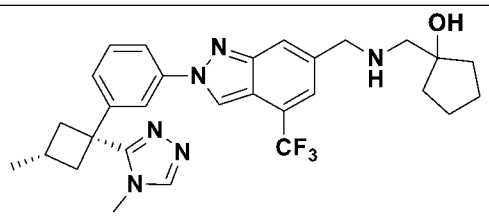
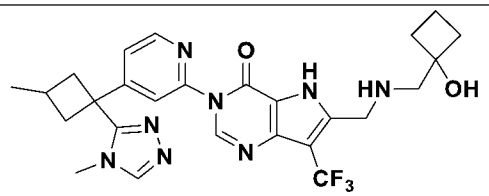
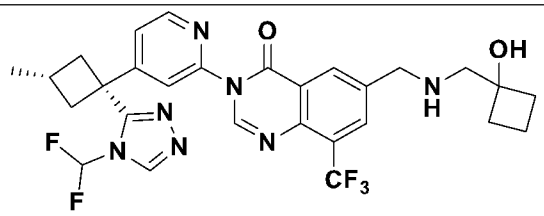
[00203] In some embodiments of a compound disclosed herein, one or more ^{1}H of Ring A, Ring B, Ring C, Ring D, or Ring E are replaced with one or more deuteriums.

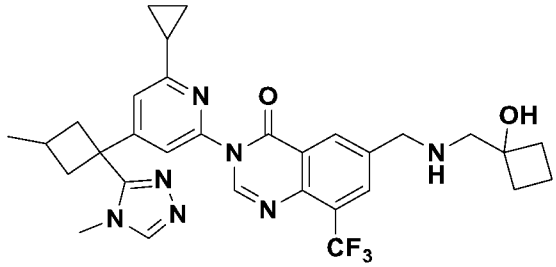
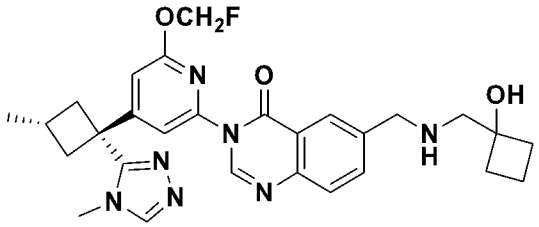
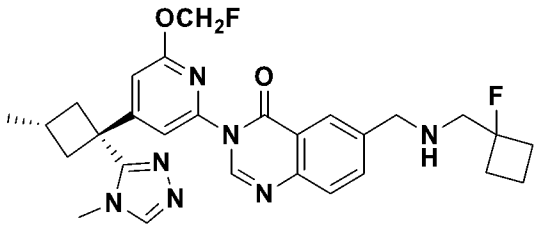
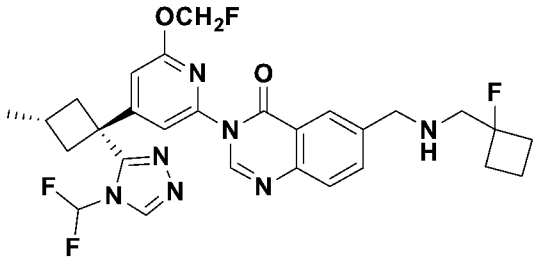
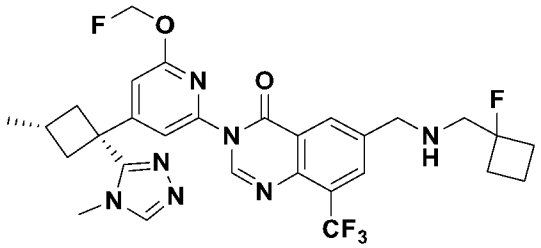
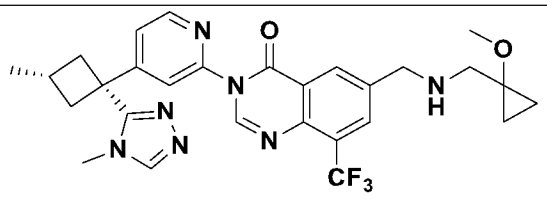
[00204] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

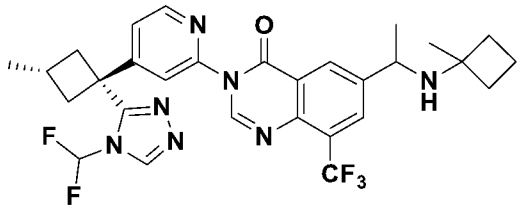
[00205] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, is one of the compounds in Table 1.

TABLE 1

Ex.	Structure
1	
2**	
3*	
4	

Ex.	Structure
5**	
6**	
7**	
8**	
9**	
10**	
11*	
12**	

Ex.	Structure
13*	
14**	
15**	
16**	
17**	
18**	

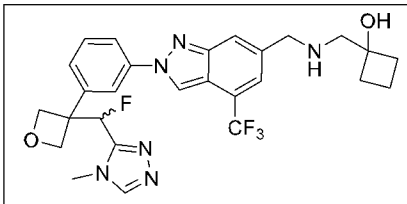
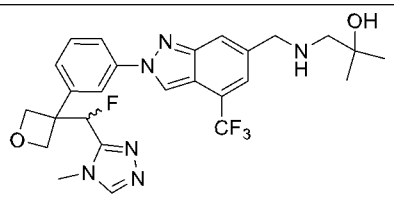
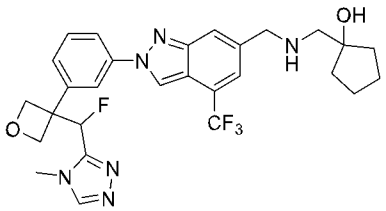
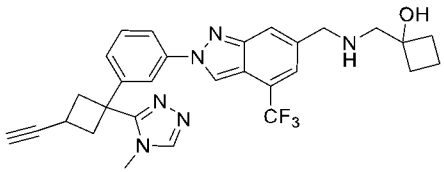
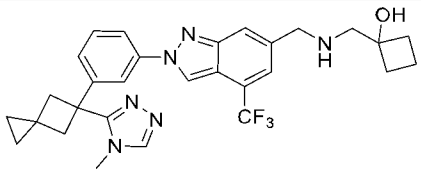
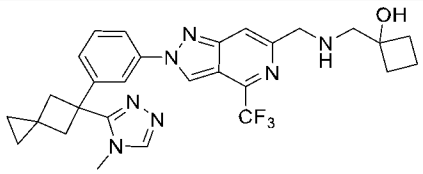
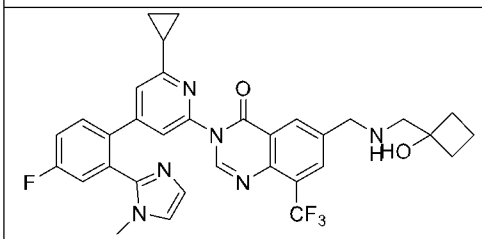
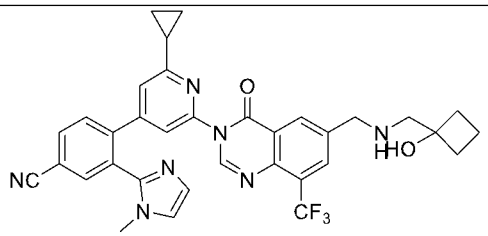
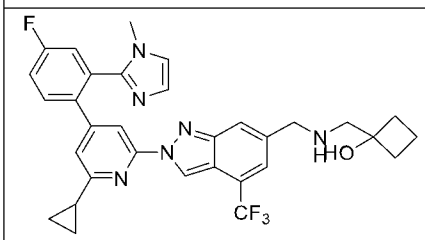
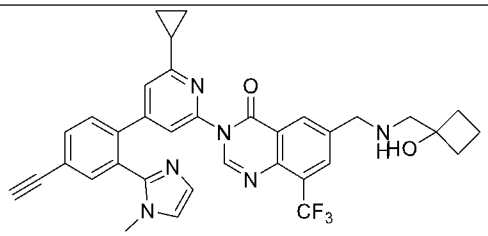
Ex.	Structure
19**	

* trans and cis isomers were not separated.

** trans and cis isomers were separated and the absolute stereochemistry of cyclobutyl group was determined.

[00206] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, is one of the compounds in Table 2 or Table 3.

TABLE 2

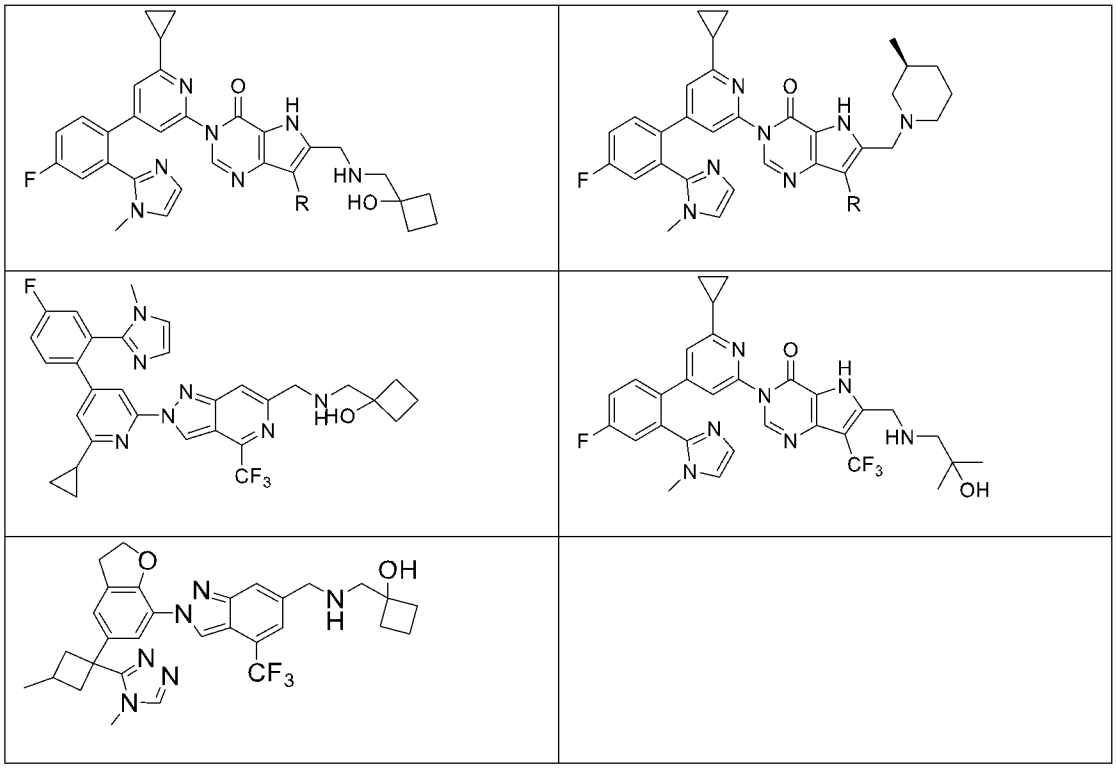
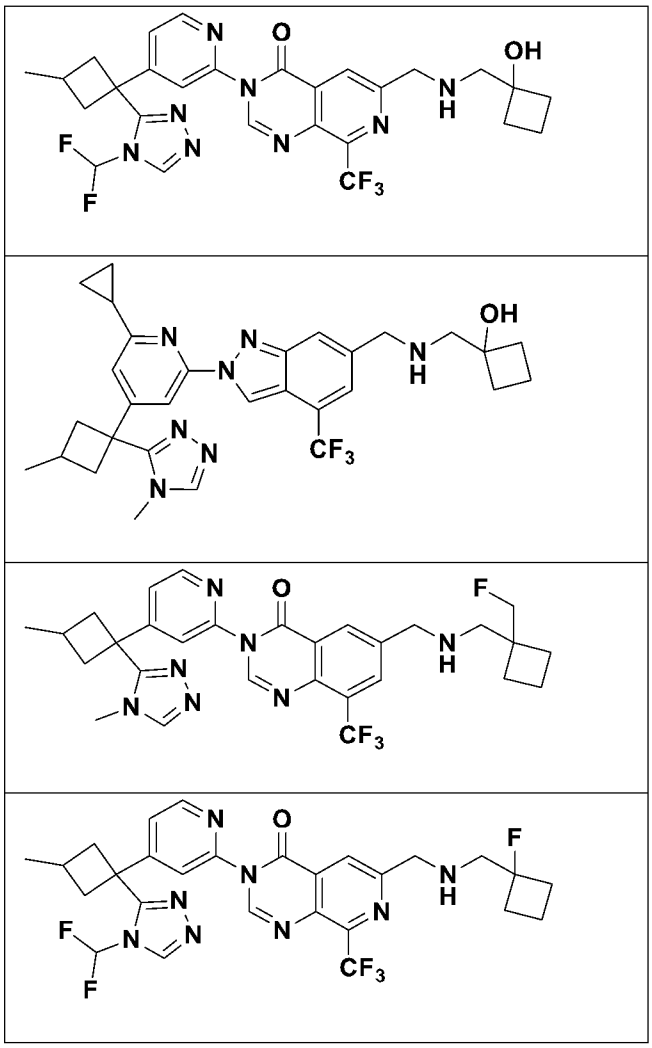


TABLE 3a



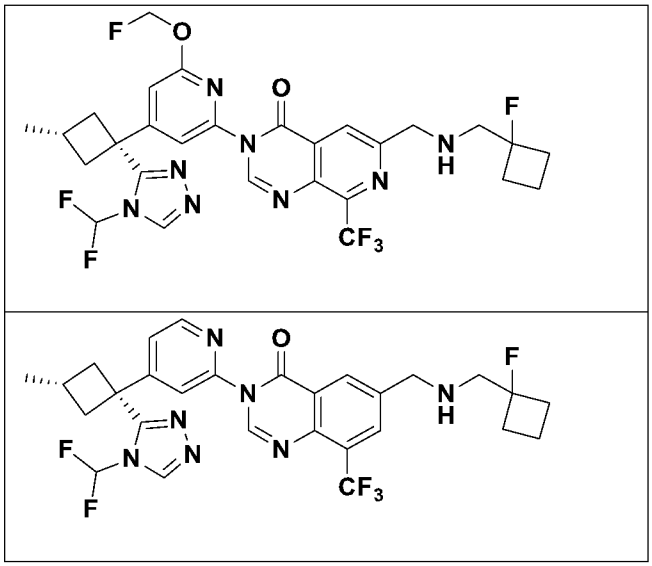
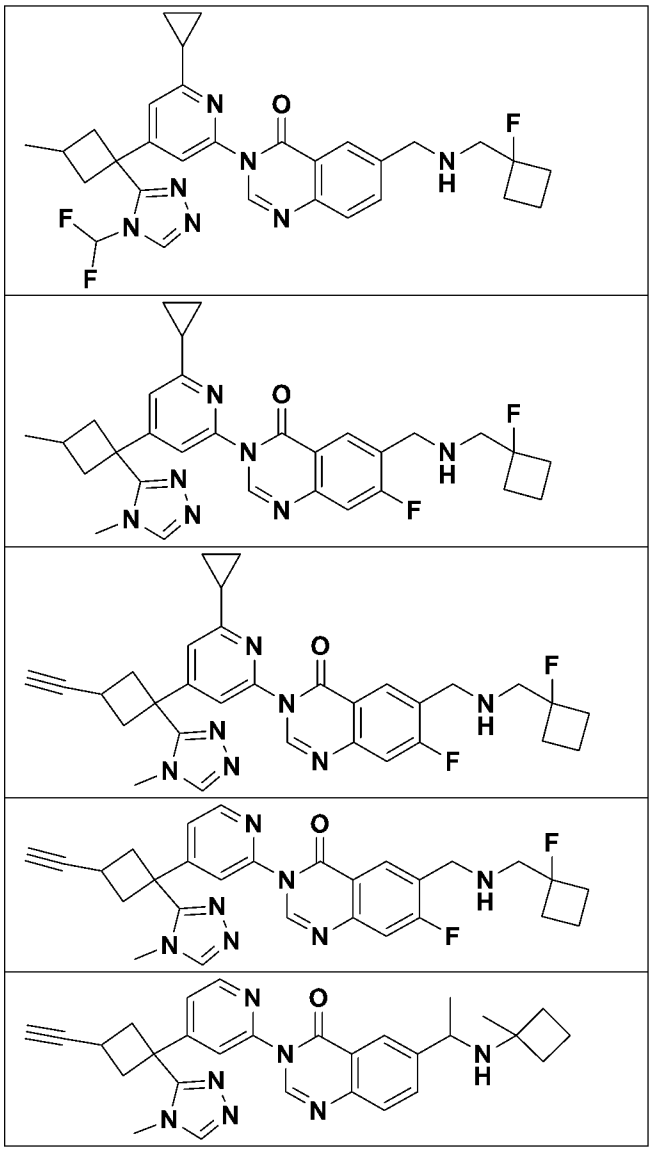
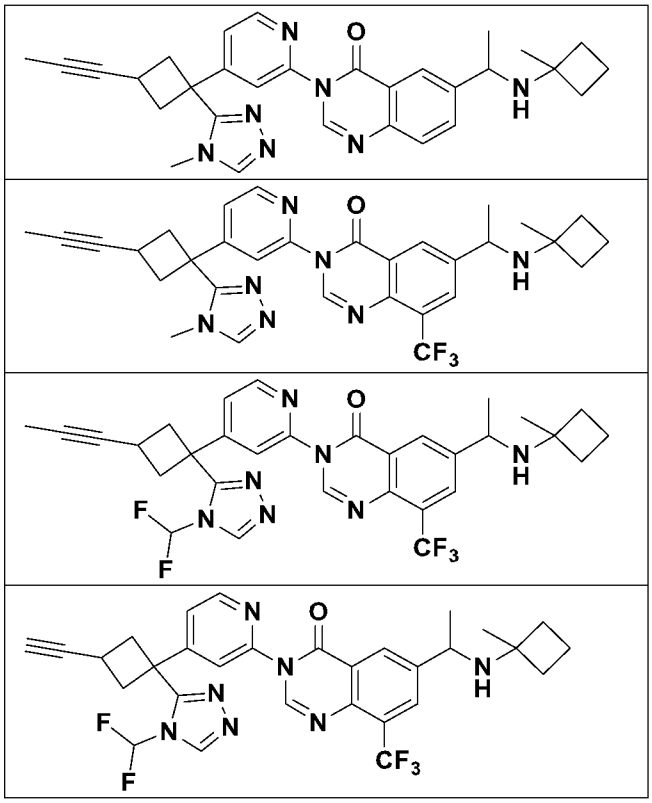


TABLE 3b





Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00207] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Isotopically enriched compounds

[00208] Unless otherwise stated, compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H (protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford some therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism.

[00209] For example, the compounds described herein may be artificially enriched in one or more particular isotopes. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes that are not predominantly found in nature. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes selected from deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In some embodiments, the compounds described herein are artificially enriched in one or more isotopes selected from ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{131}I, and ^{125}I. In some embodiments, the abundance of the enriched isotopes is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[00210] In some embodiments, the compound is deuterated in at least one position. In some embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms.

[00211] The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997, and the following synthetic methods. For example, deuterium substituted compounds may be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

Pharmaceutically acceptable salts

[00212] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00213] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to

form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00214] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[00215] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, and their pharmaceutically acceptable acid addition salts.

[00216] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative

examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[00217] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Tautomers

[00218] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Method of Treatment

[00219] Disclosed herein are methods of modulating the activity of an immune cell (e.g., a T-cell, a B-cell, or a NK-cell) such as by contacting the immune cell with an effective amount of a Cbl-b inhibitor described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a composition thereof. Also disclosed herein is a method of modulating activity of an immune cell, the method comprising contacting the immune cell with an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00220] Also disclosed herein is a method of treating a cancer, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00221] Also disclosed herein is a method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00222] Also disclosed herein is a method of inhibiting abnormal cell proliferation, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00223] Also disclosed herein is a method of modulating the immune response, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00224] Also disclosed herein is a method of inhibiting Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00225] Also disclosed herein is a method for treating a disease or condition associated with Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

[00226] In some embodiments, the disease or condition associated with Cbl-b activity is cancer.

[00227] In some embodiments, the cancer is a hematologic cancer. In some embodiments, the cancer is a lymphoma, a leukemia, or a myeloma. In some embodiments, the cancer is a non-hematologic cancer. In some embodiments, the cancer is a sarcoma, a carcinoma, or a melanoma. In some embodiments, the cancer is solid tumor cancer.

[00228] Hematologic cancers include, but are not limited to, one or more leukemias such as B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including, but not limited to, chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm (BPDCN), Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, and "preleukemia," which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells.

[00229] Non-hematologic cancers include but are not limited to, a neuroblastoma, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer (e.g., NSCLC), pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, uterine cancer, adrenal cancer, and head and neck cancer.

Dosing

[00230] In certain embodiments, the compositions containing the compound(s) described herein are administered for therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00231] In various embodiments, the dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

Routes of Administration

[00232] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

Pharmaceutical Compositions/Formulations

[00233] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

[00234] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

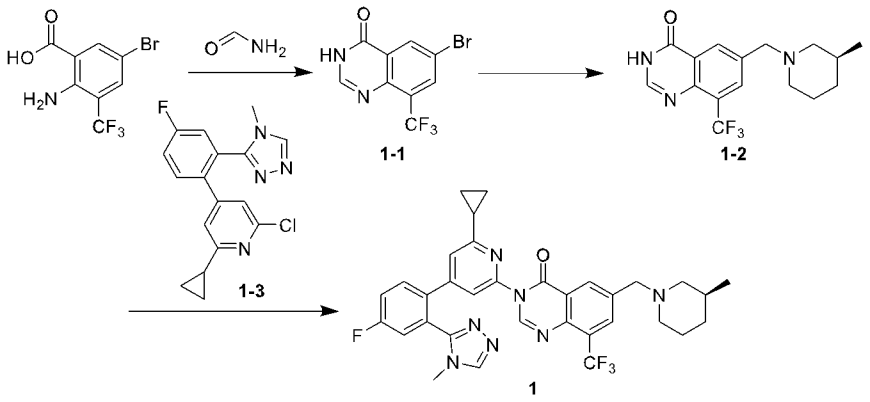
EXAMPLES

[00235] The following examples are offered to illustrate, but not to limit the claimed invention. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[00236] The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art

would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein.

Example 1: Preparation of (*S*)-3-(6-cyclopropyl-4-(4-fluoro-2-(4-methyl-4*H*-1,2,4-triazol-3-yl)phenyl)pyridin-2-yl)-6-((3-methylpiperidin-1-yl)methyl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Step 1: Preparation of Compound 1-1

[00237] A mixture of 2-amino-5-bromo-3-(trifluoromethyl)benzoic acid (1 g, 3.521 mmol) in formamide (10 mL) was stirred at 110 °Covernight in sealed tube. Upon completion, the mixture was partitioned between EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to afford **Compound 1-1** (250 mg). LCMS: 292.9 $[M+H]^+$.

Step 2: Preparation of Compound 1-2

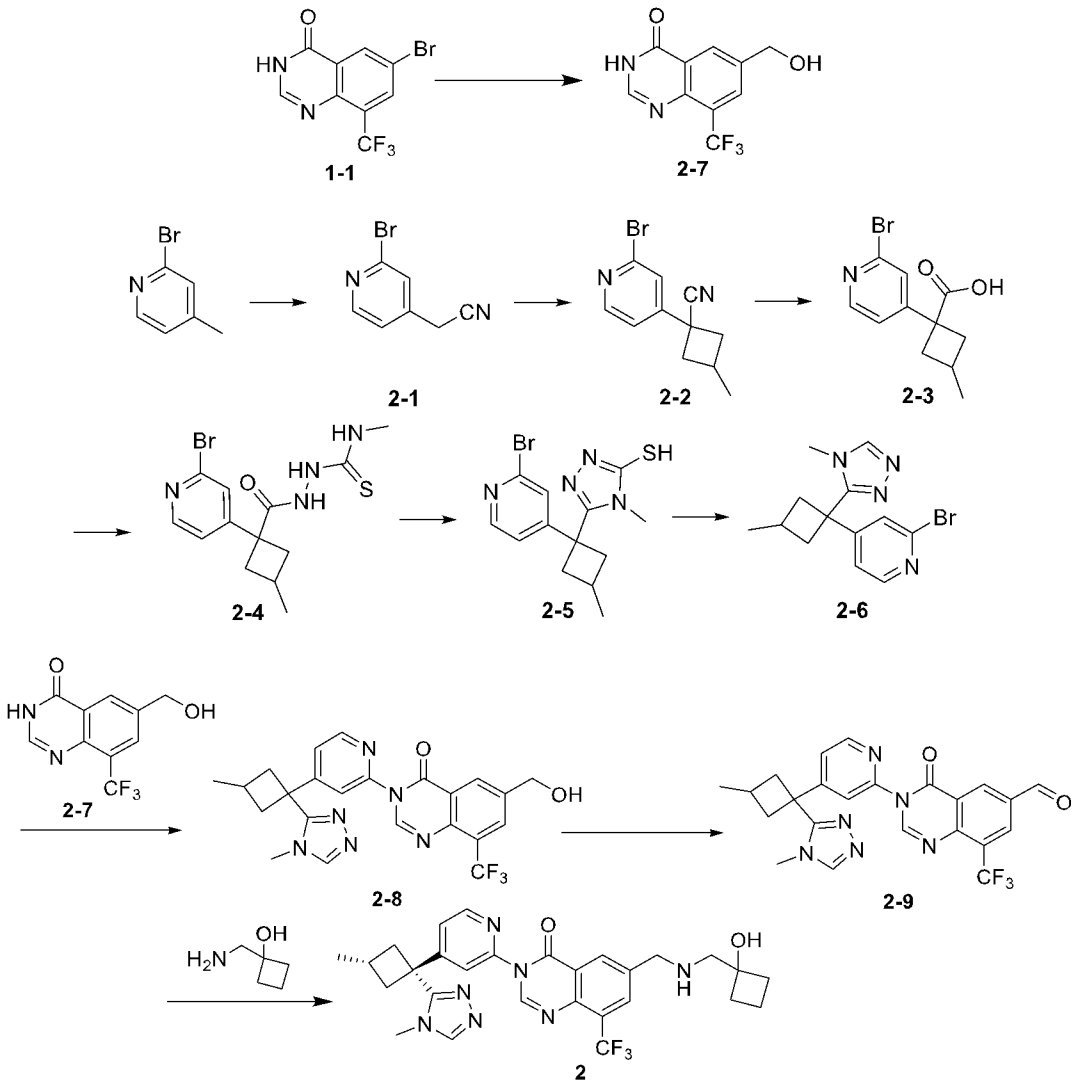
[00238] To a solution of **Compound 1-1** (250 mg, 0.853 mmol) in dioxane (5 mL) and H_2O (1.5 mL) was added Ruphos Pd G_4 (145.10 mg, 0.171 mmol), Cs_2CO_3 (555.93 mg, 1.706 mmol) and potassium (S)-trifluoro((3-methylpiperidin-1-yl)methyl)borate (560.76 mg, 2.559 mmol). The resulting mixture was stirred at 90 °C for 16 hrs under N_2. Upon completion, the mixture was diluted with H_2O (20 mL) and then extracted with EtOAc (40 mL ×3). The combined organic layers was washed with brine (50 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford **Compound 1-2** (100 mg). LCMS: 326.0 $[M+H]^+$.

Step 3: Preparation of (*S*)-3-(6-cyclopropyl-4-(4-fluoro-2-(4-methyl-4*H*-1,2,4-triazol-3-yl)phenyl)pyridin-2-yl)-6-((3-methylpiperidin-1-yl)methyl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one

[00239] To a solution of **Compound 1-3** (40 mg, 0.122 mmol, synthesized according to the standard procedure in WO2022217276) and **Compound 1-2** (43.5 mg, 0.134 mmol) in dioxane (1.5 mL) were added CuI (7.0 mg, 0.036 mmol), DMEDA (8.6 mg, 0.097 mmol) and K_2CO_3 (45.4 mg, 0.328 mmol) at room temperature. The mixture was stirred at 110 °C for 5 hrs under N_2. Upon completion, the reaction

mixture was cooled to room temperature and then partitioned between water (3 mL) and EtOAc (6 mL). The organic phase was separated, washed with water (2 mL ×3), and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford the title compound. LCMS: 618.1 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d_4) δ 8.59 - 8.43 (m, 3H), 8.20 (s, 1H), 7.83 - 7.76 (m, 1H), 7.56 - 7.45 (m, 2H), 7.37 (s, 1H), 7.16 (s, 1H), 3.70 (s, 2H), 3.35 (s, 3H), 2.87 - 2.78 (m, 2H), 2.15 - 1.97 (m, 3H), 1.74 - 1.64 (m, 4H), 1.06 - 0.99 (m, 4H), 0.91 - 0.84 (m, 4H).

Example 2: Preparation of 6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-3-(4-((*1s,3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Step 1: Preparation of Compound 2-7

[00240] To a solution of **Compound 1-1** (300 mg, 1.024 mmol) in dioxane (5 mL) was added (Tributylstannyl)methanol (986.3 mg, 3.072 mmol) and XPhos Pd G_2 (80.6 mg, 0.102 mmol). The mixture was stirred at 80 °C for 12 hrs under N_2. The solvent was concentrated to give a residue, which was purified by flash silica gel chromatography to afford **Compound 2-7** (182 mg) as a white solid. LCMS: 245.1 $[M+H]^+$;

Step 2: Preparation of Compound 2-1

[00241] A solution of 2-bromo-4-methylpyridine (20 g, 116 mmol) in 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (40.5 g, 232 mmol) was stirred at 110 ℃ for 15 hours. After being cooled to room temperature, the reaction mixture was concentrated to afford a residue, to which was added water (20 mL) and aminomethanesulfonic acid (2.5 g, 22.106 mmol). The resulting mixture was stirred at room temperature for 1 hour. Then the mixture was filtered, suspended in water, and extracted with DCM (100 mL ×2). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford **Compound 2-1** (18.0 g). LCMS: 198.0 $[M+H]^+$;

Step 3: Preparation of Compound 2-2

[00242] To a solution of **Compound 2-1** (9.00 g, 45.7 mmol) and 1,3-dibromo-2-methylpropane (9.90 g, 45.7 mmol) in N,N-Dimethylformamide (6 mL) was added sodium hydride (2.20 g, 91.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. Upon completion, the reaction was quenched by addition of the saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (300mL × 2). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue, which was purified by silica gel chromatography to give **Compound 2-2** (7.40 g). LCMS: 252.0 $[M+H]^+$;

Step 4: Preparation of Compound 2-3

[00243] A solution of **Compound 2-2** (7.40 g, 29.5 mmol) and sodium hydroxide (3.5 g, 88.4 mmol) in ethanol (68 mL) and H_2O (13 mL) was stirred at 80 °C for 16 hours. The pH was adjusted to 5 by addition of 1 M HCl at 0 °C. The aqueous layer was extracted with EtOAc (400 mL ×3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **Compound 2-3** (6 g). LCMS: 271.9 $[M+H]^+$;

Step 5: Preparation of Compound 2-4

[00244] To a solution of **Compound 2-3** (5.8 g, 21.5 mmol), DIPEA (14.2 mL, 85.9 mmol) and N-methylhydrazinecarbothioamide (2.50 g, 23.6 mmol) in DMF (50 mL) was added T_3P (10.2 g, 32.2 mmol) at 0 °C. The mixture was stirred at room temperature for 16 hrs. Upon completion, the mixture was concentrated under reduced pressure to afford a residue, which was purified by silica gel chromatography to afford **Compound 2-4** (3.80 g). LCMS: 358.6 $[M+H]^+$;

Step 6: Preparation of Compound 2-5

[00245] A mixture of **Compound 2-4** (3.00 g, 53.2 mmol) and KOH (3.80 g, 10.6 mmol) in H_2O (20 mL) was stirred at 25 °C for 16 hrs. The pH was adjusted to 5 by addition of 1 M HCl at 0 °C. The aqueous layer was extracted with EtOAc (150 mL ×3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **Compound 2-5** (1.40 g). LCMS: 339.0 $[M+H]^+$;

[00246] Step 7: Preparation of Compound 2-6

To a solution of **Compound 2-5** (3.50 g, 10.3 mmol) in dichloromethane (20 mL) and acetic acid (2.06 mL, 36.104 mmol) was added hydrogen peroxide (1.80 g, 51.6 mmol) at 0 ℃. The mixture was stirred at 25 ℃ for 1 hrs. The reaction was quenched with 20% $Na_2S_2O_3$ aqueous solution (10 mL) and the mixture was adjusted to pH = 7 with saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with

DCM (200 mL ×3), the combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by silica gel chromatography to afford **Compound 2-6** (1.20 g). LCMS: 308.9 $[M+H]^+$;

Step 8: Preparation of Compound 2-8

[00247] To a solution of **Compound 2-7** (182 mg, 0.745 mmol) and **Compound 2-6** (343.4 mg, 1.118 mmol) in dioxane (3 mL) was added CuI (71.0 mg, 0.373 mmol), K_2CO_3 (206.0 mg, 1.491 mmol) and DMEDA (65.7 mg, 0.745 mmol). The mixture was stirred at 100 °C for 12 hrs under N_2. After concentrated, the residue was purified by prep-HPLC to afford **Compound 2-8** (301 mg). LCMS: 471.5 $[M+H]^+$;

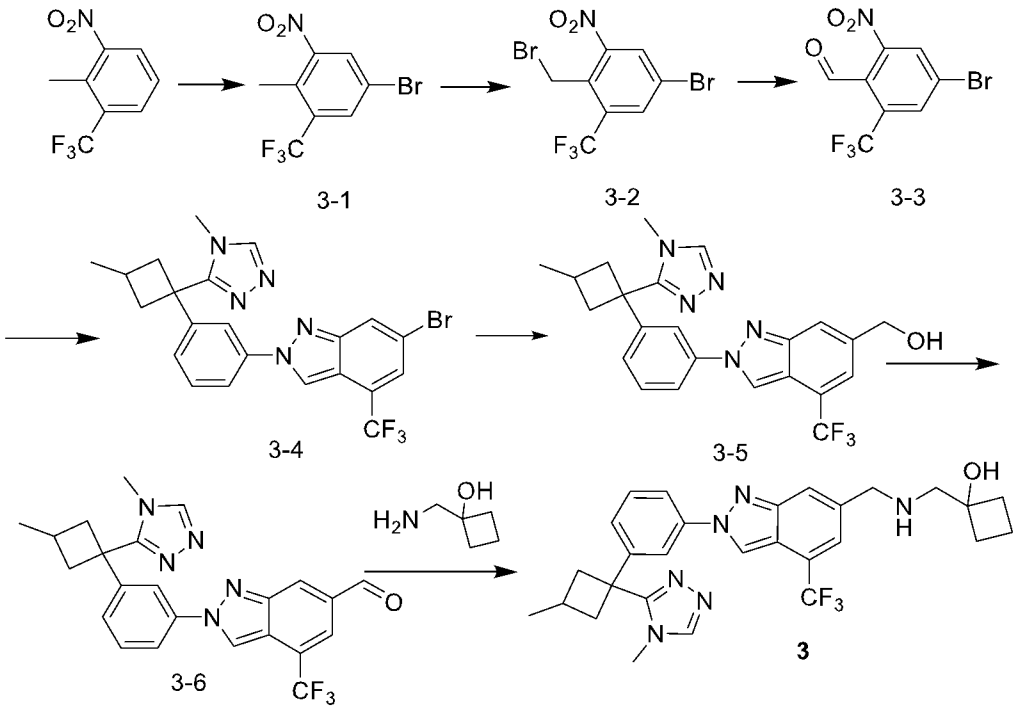
Step 9: Preparation of Compound 2-9

[00248] To a solution of **Compound 2-8** (100 mg, 0.213 mmol) in DCM (3 mL) was added DMP (135.2 mg, 0.319 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h under N_2. The mixture was filtered and the cake was washed with DCM (5 mL ×2), the filtrate was concentrated to afford the crude **Compound 2-9** (90 mg). The crude product was used directly to the next step without further purification. LCMS: 469.1 $[M+H]^+$;

Step 10: Preparation of 6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-3-(4-((*1s,3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one

[00249] To a solution of **Compound 2-9** (100 mg, 0.213 mmol) and 1-(aminomethyl)cyclobutan-1-ol (32.2 mg, 0.319 mmol) in DCE (3 mL) was added AcOH (1 drop), the mixture was stirred at 25 °C for 30 min, then $NaBH(OAc)_3$ (225.2 mg, 1.063 mmol) was added. The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was partitioned between DCM (10 mL) and $NaHCO_3$ (aq. sat. 10 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford the title compound (29.85 mg). LCMS: 554.8 $[M+H]^+$; **^{1}H NMR:** (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 8.66 - 8.53 (m, 3H), 8.18 (s, 1H), 7.65 - 7.60 (m, 1H), 7.56 - 7.51 (m, 1H), 4.45 (s, 2H), 3.44 (s, 3H), 3.31 (s, 2H), 2.96 - 2.89 (m, 2H), 2.76 - 2.70 (m, 3H), 2.18 - 2.06 (m, 4H), 1.81 - 1.72 (m, 1H), 1.61 - 1.51 (m, 1H), 1.21 - 1.13 (m, 3H).

Example 3: Preparation of 1-((((2-(3-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)phenyl)-4-(trifluoromethyl)-2*H*-indazol-6-yl)methyl)amino)methyl)cyclobutan-1-ol



Step 1: Preparation of Compound 3-1

[00250] To a solution of 2-methyl-1-nitro-3-(trifluoromethyl)benzene (15 g, 73.121 mmol) in concentrated H_2SO_4 (150 mL) was added 1,3-dibromo-4,4-dimethyl-2-oxotetrahydro-1*H*-imidazol-5-one (12.54 g, 43.872 mmol) at 0 °C. Then the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into ice water (200 mL). After 10 min, the mixture was extracted with ethyl acetate (300 mL ×3). The combined organic layers were washed with saturated $NaHCO_3$ (aq.), filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 3-1** (12 g). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H), 2.51 (d, J = 1.4 Hz, 3H).

Step 2: Preparation of Compound 3-2

[00251] To a solution of **Compound 3-1** (1.00 g, 3.521 mmol) and benzoic peroxyanhydride (0.09 g, 0.352 mmol) in tetrachloromethane (30 mL) was added NBS (0.66 g, 3.697 mmol). The mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to afford **Compound 3-2** (789 mg). LCMS: 383.9 $[M+Na]^+$.

Step 3: Preparation of Compound 3-3

[00252] To a mixture of **Compound 3-2** (1 g, 2.755 mmol) and 4Å molecular sieves (200 mg) in MeCN (10 mL) was added 4-methyl-1,4-oxazinane 4-oxide (0.68 g, 5.841 mmol) at room temperature and the resulting mixture was stirred for 1.5 h under N_2. The mixture was diluted with ethyl acetate and filtered. The filtrate was washed with H_2O, 1N HCl. The organic layer was washed with brine 70 mL, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 3-3** (1.4 g).

Step 4: Preparation of Compound 3-4

[00253] To a solution of **Compound 3-3** (30.0 mg, 0.101 mmol) in propan-2-ol (6 mL) was added 3-(3-methyl-1-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)aniline (26.83 mg, 0.111 mmol), and the mixture was stirred at 80 °C for 4 h. Then tributylphosphane (93.95 mg, 0.464 mmol) was added and the resulting mixture was stirred at 80 °C for 16 h. The mixture was cooled to room temperature and diluted with EtOAc (10 mL). The organics was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography to afford **Compound 3-4**. LCMS: 490.0 $[M+1]^+$.

Step 5: Preparation of Compound 3-5

[00254] To a solution of **Compound 3-4** (288 mg, 0.587 mmol) in dioxane (5 mL) was added (tributylstannyl)methanol (565.79 mg, 1.762 mmol) and XPhos Pd G_2 (3.21 mg, 0.004 mmol). The mixture was stirred at 80 °C for 5 hrs. Then the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography to afford **Compound 3-5** (145 mg). LCMS: 442.2 $[M+H]^+$;

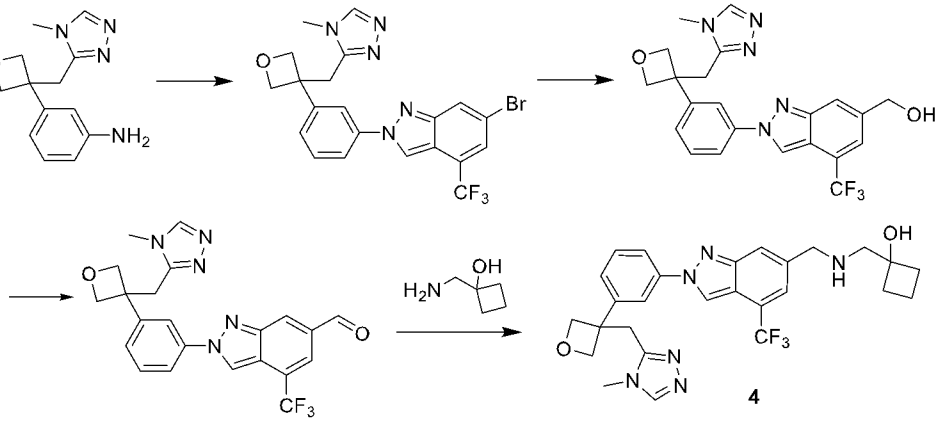
Step 6: Preparation of Compound 3-6

[00255] To a solution of **Compound 3-5** (50 mg, 0.113 mmol) in DCM (2 mL) was added 1,1-diacetoxy-3-oxo-1,3-dihydrobenzo[*d*][1,2]iodoxole-1-yl acetate (72.06 mg, 0.170 mmol). The mixture was stirred at 20 °C for 1 hrs. The reaction was diluted with DCM (20 mL), washed with saturated Na_2SO_3(10 M), saturated aqueous $NaHCO_3$(10 mL) and brine (10 mL), and then concentrated to give **Compound 3-6** (50 mg), which was used to next step without further purification. LCMS: 440.2 $[M+H]^+$

Step 7: Preparation of 1-((((2-(3-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)phenyl)-4-(trifluoromethyl)-2*H*-indazol-6-yl)methyl)amino)methyl)cyclobutan-1-ol

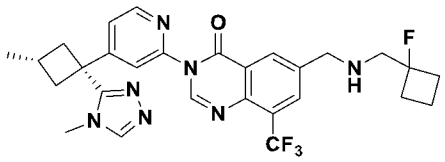
[00256] According to the procedure of **Step 10** in **Example 2**, the title compound (8.71 mg) was synthesized with **Compound 3-6** (100 mg, 0.228 mmol) as the substrate. LCMS: 525.3 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.55 - 8.42 (m, 1H), 8.11 - 7.80 (m, 3H), 7.79 - 7.68 (m, 1H), 7.58 - 7.44 (m, 2H), 7.43 - 7.31 (m, 1H), 4.18 (s, 2H), 3.30 - 3.19 (m, 4H), 3.03 - 2.88 (m, 4H), 2.78 - 2.66 (m, 2H), 2.17 - 2.03 (m, 4H), 1.81 - 1.70 (m, 1H), 1.58 - 1.43 (m, 1H), 1.21 - 1.11 (m, 3H).

Example 4: Preparation of 1-((((2-(3-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)phenyl)-4-(trifluoromethyl)-2*H*-indazol-6-yl)methyl)amino)methyl)cyclobutan-1-ol



[00257] According to the procedure of **Example 3**, the title compound (formate form) was synthesized with 3-(3-((4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)oxetan-3-yl)aniline as the starting material. LCMS: 527.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.23 - 8.19 (m, 2H), 8.04 (d, J = 8.7 Hz, 1H), 7.93 (s, 1H), 7.90 - 7.84 (m, 1H), 7.62 (s, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 4.98 (s, 4H), 3.93 (s, 2H), 3.59 (s, 2H), 3.00 (s, 3H), 2.56 (s, 2H), 2.08 - 1.55 (m, 6H).

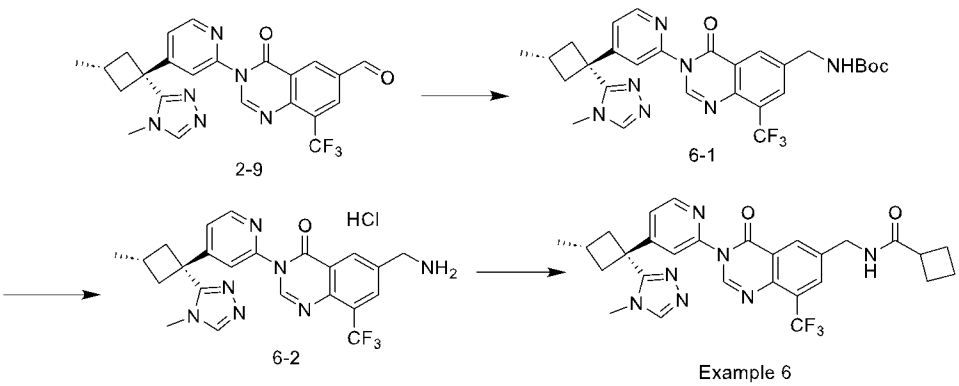
Example 5: Preparation of 6-((((1-fluorocyclobutyl)methyl)amino)methyl)-3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Example 5

[00258] The title compound was synthesized according to **Example 2**. LCMS: 556.3 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 8.57 (d, J = 5.3 Hz, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 8.04 (s, 1H), 7.93 (s, 1H), 7.32 (s, 1H), 4.05 (s, 2H), 3.33 (s, 3H), 2.99 – 2.62 (m, 7H), 2.44 – 2.10 (m, 4H), 1.96 – 1.75 (m, 1H), 1.51 – 1.39 (m, 2H), 1.17 (d, J = 6.1 Hz, 3H).

Example 6: Preparation of N-((3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-4-oxo-8-(trifluoromethyl)-3,4-dihydroquinazolin-6-yl)methyl)cyclobutanecarboxamide



Example 6

Step 1: Preparation of Compound 6-1

[00259] To a solution of **Compound 2-9** (62 mg, 0.132 mmol) and NH_2Boc (46.5 mg, 0.397 mmol) in ACN (2 mL) was added Et_3SiH (153.9 mg, 1.324 mmol) and TFA (45.3 mg, 0.397 mmol). The mixture was stirred at 25 °C for overnight. The reaction mixture was concentrated under reduced pressure to give a crude **Compound 6-1**, which was used directly for the next step without purification. LCMS: 570.2 $[M+H]^+$;

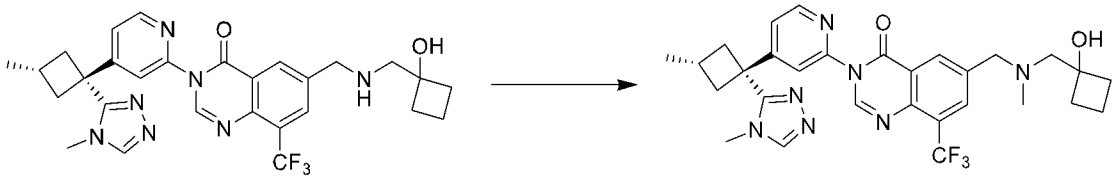
Step 2: Preparation of Compound 6-2

[00260] To a solution of **Compound 6-1** (80 mg, 0.140 mmol) in DCM (1 mL) was added TFA (160.1 mg, 1.404 mmol). The mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to give a crude **Compound 6-2**, which was used directly for the next step without purification. LCMS: 470.3 $[M+H]^+$;

Step 3: Preparation of N-((3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-4-oxo-8-(trifluoromethyl)-3,4-dihydroquinazolin-6-yl)methyl)cyclobutanecarboxamide

[00261] To a solution of cyclobutanecarboxylic acid (29.8 mg, 0.298 mmol) and DIEA (0.06 mL, 0.373 mmol) in DMF (2 mL) were added HATU (85.0 mg, 0.224 mmol) and **Compound 6-2** (70 mg, 0.149 mmol), the mixture was stirred at 25 °C overnight. The reaction mixture was partitioned between EtOAc (10 mL) and H_2O (5 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford the title compound. LCMS: 552.4 $[M+H]^+$;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.64 (d, J = 5.3 Hz, 1H), 8.43 – 8.38 (m, 2H), 8.33 (s, 1H), 8.13 (s, 1H), 7.82 (s, 1H), 7.47 (d, J = 5.3 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.26 (s, 3H), 3.10 (p, J = 8.5 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.69 – 2.54 (m, 3H), 2.19 – 2.02 (m, 4H), 1.91 (h, J = 8.8 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.09 (d, J = 5.3 Hz, 3H).

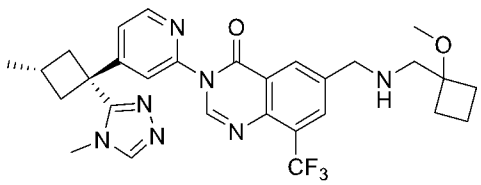
Example 7: Preparation of 6-((((1-hydroxycyclobutyl)methyl)(methyl)amino)methyl)-3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Example 2 Example 7

[00262] The title compound was synthesized according to **Step 10** in **Example 2**. LCMS: 568.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.63 (d, J = 5.3 Hz, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 8.25 (s, 1H), 7.84 (s, 1H), 7.46 (dd, J = 5.3, 1.6 Hz, 1H), 4.93 (s, 1H), 3.82 (s, 2H), 3.25 (s, 3H), 2.90 – 2.85 (m, 2H), 2.72 – 2.31 (m, 5H), 2.27 (s, 3H), 2.05 – 1.99 (m, 2H), 1.95 – 1.87 (m, 2H), 1.61 (d, J = 10.6 Hz, 1H), 1.39 – 1.26 (m, 1H), 1.09 (d, J = 5.4 Hz, 3H).

Example 8: Preparation of 6-((((1-methoxycyclobutyl)methyl)amino)methyl)-3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one

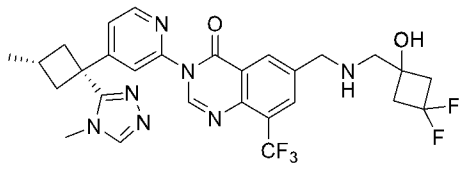


Example 8

[00263] The title compound was synthesized according to **Example 2**. LCMS: 568.3 $[M+H]^+$; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.75 (s, 1H), 8.57 (d, J = 5.3 Hz, 1H), 8.52 (s, 1H), 8.26 (s, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.37 – 7.30 (m, 1H), 4.25 – 4.17 (m, 1H), 4.12 (s, 2H), 3.34 (s, 3H), 3.17 (s, 3H), 2.96

– 2.88 (m, 2H), 2.86 (s, 2H), 2.81 – 2.65 (m, 3H), 2.27 – 2.15 (m, 2H), 1.98 – 1.89 (m, 2H), 1.80 – 1.69 (m, 1H), 1.61 – 1.48 (m, 1H), 1.17 (d, J = 6.0 Hz, 3H).

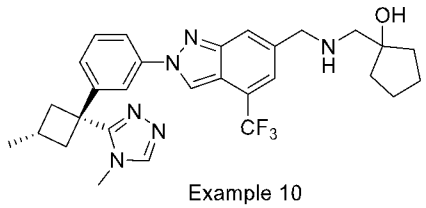
Example 9: Preparation of 6-((((3,3-difluoro-1-hydroxycyclobutyl)methyl)amino)methyl)-3-(4-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Example 9

[00264] The title compound was synthesized according to **Example 2**. LCMS: 590.3 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 8.57 (d, J = 5.2 Hz, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 8.05 (s, 1H), 7.90 (s, 1H), 7.38 – 7.32 (m, 1H), 4.09 (s, 2H), 3.34 (s, 3H), 2.99 – 2.89 (m, 4H), 2.82 – 2.61 (m, 7H), 2.18 – 1.58 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H).

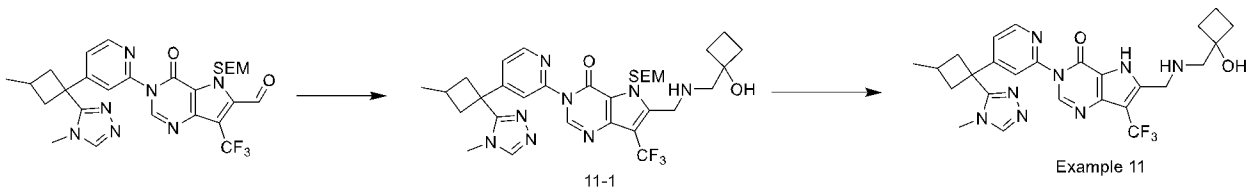
Example 10: Preparation of 1-((((2-(3-((*1s*,*3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)phenyl)-4-(trifluoromethyl)-2*H*-indazol-6-yl)methyl)amino)methyl)cyclopentan-1-ol



Example 10

[00265] The title compound was synthesized according to **Example 2**. LCMS: 539.4 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 8.05 – 7.98 (m, 2H), 7.96 (s, 1H), 7.83 – 7.67 (m, 1H), 7.62 – 7.47 (m, 2H), 7.47 – 7.32 (m, 1H), 4.12 (s, 2H), 3.25 (s, 3H), 3.02 – 2.91 (m, 2H), 2.88 (s, 2H), 2.79 – 2.71 (m, 2H), 1.86 – 1.72 (m, 4H), 1.69 – 1.48 (m, 5H), 1.18 (d, J = 5.3 Hz, 3H).

Example 11: Preparation of 6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-3-(4-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-7-(trifluoromethyl)-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one



11-1

Example 11

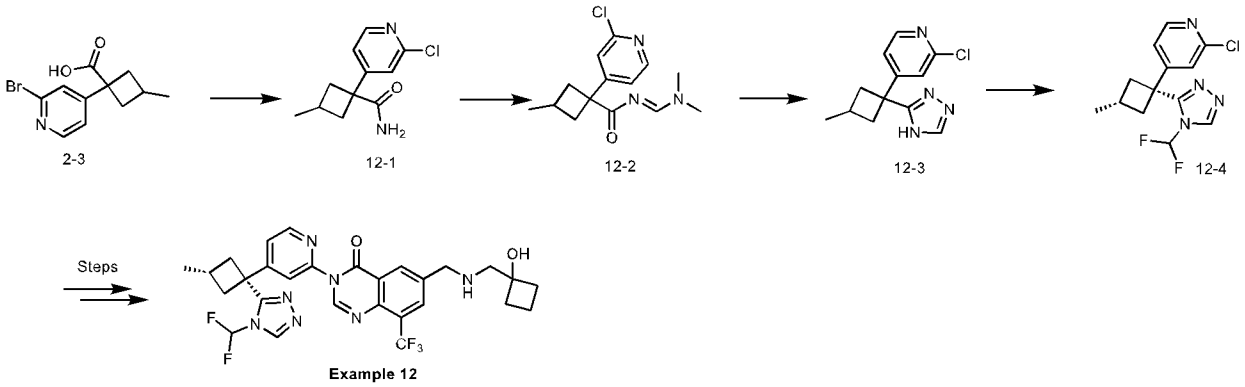
Step 1: Preparation of Compound 11-1

[00266] The title compound was synthesized according to **Step 10** in **Example 2** with 3-(4-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-4-oxo-7-(trifluoromethyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-6-carbaldehyde as the starting material. LCMS: 673.4 $[M+H]^+$;

Step 2: Preparation of 6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-3-(4-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-7-(trifluoromethyl)-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one

[00267] To a solution of **Compound 11-1** (158 mg, 0.235 mmol) in DCM (1.5 mL) was added TFA (6 mL, 0.705 mmol) at room temperature. After addition, the mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford the title compound. LCMS: 543.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 5.3 Hz, 1H), 8.42 – 8.32 (m, 2H), 7.74 (s, 1H), 7.45 (dd, J = 5.3, 1.6 Hz, 1H), 5.04 (s, 1H), 3.98 (s, 2H), 3.26 (s, 3H), 2.91 – 2.85 (m, 2H), 2.66 – 2.56 (m, 4H), 2.05 – 1.82 (m, 5H), 1.65 – 1.55 (m, 1H), 1.46 – 1.35 (m, 1H), 1.08 (d, J = 5.4 Hz, 3H).

Example 12: Preparation of 3-(4-((*1s*,*3s*)-1-(4-(difluoromethyl)-4*H*-1,2,4-triazol-3-yl)-3-methylcyclobutyl)pyridin-2-yl)-6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Step 1: Preparation of Compound 12-1

[00268] A solution **2-3** (8.50 g, 31.5 mmol) in $SOCl_2$ (35 mL) was stirred at 80 °C for 1 hr. Then the mixture was concentrated to give a residue. A solution of the above residue in DCM (35 mL) was added to NH_3/MeOH (7 N, 35 mL) dropwise. The mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by flash silica gel column chromatography to afford **Compound 12-1** (5.0 g, 70.7 %). LCMS: 225.0 $[M+H]^+$.

Step 2: Preparation of Compound 12-2

[00269] A solution of **Compound 12-1** (5.0 g, 22.3 mmol) in DMF-DMA (20 mL) was stirred at 100 °C for 12 hrs. After being cooled to room temperature, the mixture was concentrated under reduced pressure to give the crude **Compound 12-2** (5.0 g, crude), which was used to the next step without further purification. LCMS: 280.2 $[M+H]^+$.

Step 3: Preparation of Compound 12-3

[00270] To a solution of **Compound 12-2** (5.0 g, crude) in HOAc (14 mL) was added hydrazine hydrate (14 mL). The mixture was stirred at 80 °C for 4 hrs. After being cooled to room temperature, the reaction mixture was concentrated to give a residue, which was diluted with water (200 mL) and extracted with EtOAc (300 mL ×3). The combined organic layers were washed with brine (100 mL), dried over

anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by reversed-phase HPLC to afford **Compound 12-3** (4 g, 72.3%). LCMS: 249.0 $[M+H]^+$;

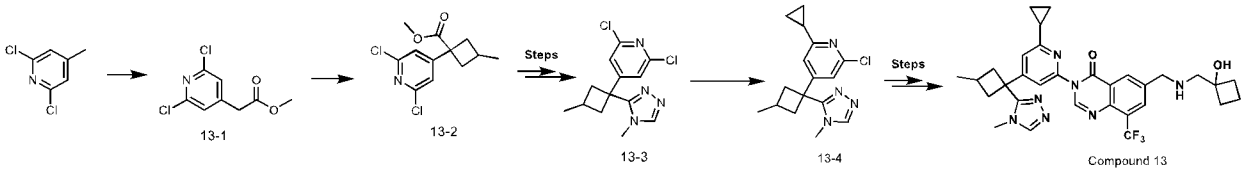
Step 4: Preparation of Compound 12-4

[00271] To a solution of **Compound 12-3** (2.00 g, 8.07 mmol) in DMF (20 mL) was added sodium 2-chloro-2,2-difluoroacetate (2.50 g, 16.1 mmol) and K_2CO_3 (2.20 g, 16.1 mmol). The mixture was stirred at 140 °C for 5 hrs. After being cooled to room temperature, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL ×3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the residue, which was purified by reversed-phase HPLC to afford **Compound 12-4** (0.15 g, 5.0 %). LCMS: 299.0 $[M+H]^+$.

Step 5: Preparation of Compound 12

[00272] The title compound was synthesized according to the previous steps with **Compound 12-4** as the starting material. LCMS: 590.2 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 8.60 (d, J = 5.3 Hz, 1H), 8.53 (s, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 7.95 (s, 1H), 7.31 (d, J = 5.1 Hz, 1H), 6.74 (t, J = 60.4 Hz, 1H), 4.11 (s, 2H), 2.97 – 2.84 (m, 4H), 2.80 (t, J = 10.1 Hz, 2H), 2.74 – 2.64 (m, 1H), 2.15 – 1.98 (m, 4H), 1.82 – 1.71 (m, 1H), 1.58 – 1.46 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H).

Example 13: Preparation of 3-(6-cyclopropyl-4-(3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-6-((((1-hydroxycyclobutyl)methyl)amino)methyl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one



Step 1: Preparation of 13-1

[00273] To a stirred solution of 2,6-dichloro-4-methylpyridin*e* (63 g, 388.889 mmol) in anhydrous THF (500 mL) was slowly added LDA (388.89 mL, 777.778 mmol) at -78 ℃ under N_2. The mixture stirred at -78 ℃ for 0.5 h. A solution of methyl methoxymethanoate (81.94 mL, 972.222 mmol) in dry THF (130 mL) was added dropwise. The solution was stirred at 0 ℃ for 1 h. The reaction was quenched with aq. NH_4Cl (500 mL). The resulting mixture was extracted with EtOAc (200 mL ×3). The combined organic phase was washed with aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. After filtration, the organic layer was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford **Int 13-1**. LCMS: 220.1 $[M+H]^+$.

Step 2: Preparation of 13-2

[00274] To a solution of **13-1** (50.0 g, 231.364 mmol) in DMF (510 mL) was added NaH (20.4 g, 509 mmol) in batches at 0 °C. The mixture was stirred at 0 °C for 30 mins. Then the solution was stirred at 25 °C for 2 hrs. Upon completion, the mixture was poured into ammonium chloride aqueous solution (700 mL). Then the mixture was extracted with Ethyl acetate (300 mL ×3). The combined organic phase was

washed with brine (100 mL), dried over anhydrous Na2SO4, filtered, concentrated in vacuo, and purified by column chromatography to afford **13-2**. LCMS: 274.1 $[M+H]^+$.

Step 3: Preparation of 13-3

[00275] With **13-2** as the substrate, **13-3** was synthesized according to the previous steps. LCMS: 297.1 $[M+H]^+$.

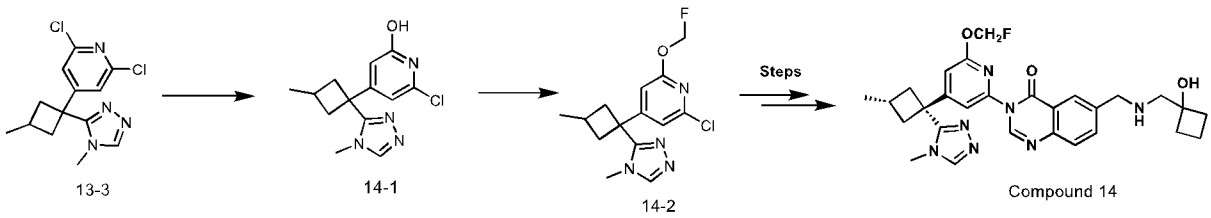
Step 4: Preparation of 13-4

[00276] To a solution of **Compound 13-3** (200 mg, 0.673 mmol) and cyclopropylboronic acid (60.7 mg, 0.707 mmol) in toluene (2 mL) was added K_3PO_4 (428.6 mg, 2.02 mmol), PCy_3 (24.5 mg, 0.088 mmol) and $Pd(OAc)_2$ (19.6 mg, 0.088 mmol) at room temperature. After addition, the mixture was stirred at 110 °C for 4 hrs under N_2. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 13-4** (crude), which was used to next step without further purification. LCMS: 303.2 $[M+H]^+$;

Step 5: Preparation of Compound 13

[00277] With **13-4** as the substrate, the title compound was synthesized according to the previous steps. LCMS: 594.3 $[M+H]^+$.

Example 14: Preparation of 3-(6-(fluoromethoxy)-4-((*1s*,*3s*)-3-methyl-1-(4-methyl-*4H*-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-yl)-6-((((1-hydroxycyclobutyl)methyl)amino)methyl)quinazolin-4(*3H*)-one



Step 1: Preparation of Compound 14-1

[00278] To a solution of **13-3** (400 mg, 1.346 mmol) in DMSO (6 mL) was added K_2CO_3 (558.0 mg, 4.038 mmol) and N-hydroxyacetamide (303.2 mg, 4.038 mmol). The mixture was stirred at 80 °C for 18 hrs. The mixture was purified by reverse phase prep-HPLC to afford **Compound 14-1**. LCMS: 279.2 $[M+H]^+$.

Step 2: Preparation of Compound 14-2

[00279] To a solution of **Compound 14-1** (250 mg, 0.897 mmol) in DMF (3 mL) was added Cs_2CO_3 (292.2 mg, 0.897 mmol). The mixture was stirred at 0 °C for 10 min and then fluoromethyl 4-methylbenzenesulfonate (366.3 mg, 1.794 mmol) was added. The resulting mixture was heated to 80 °C for 2 hrs under N_2. The mixture was purified by reverse phase prep-HPLC to afford **Compound 14-2**. LCMS: 311.2 $[M+H]^+$.

Step 3: Preparation of Compound 14

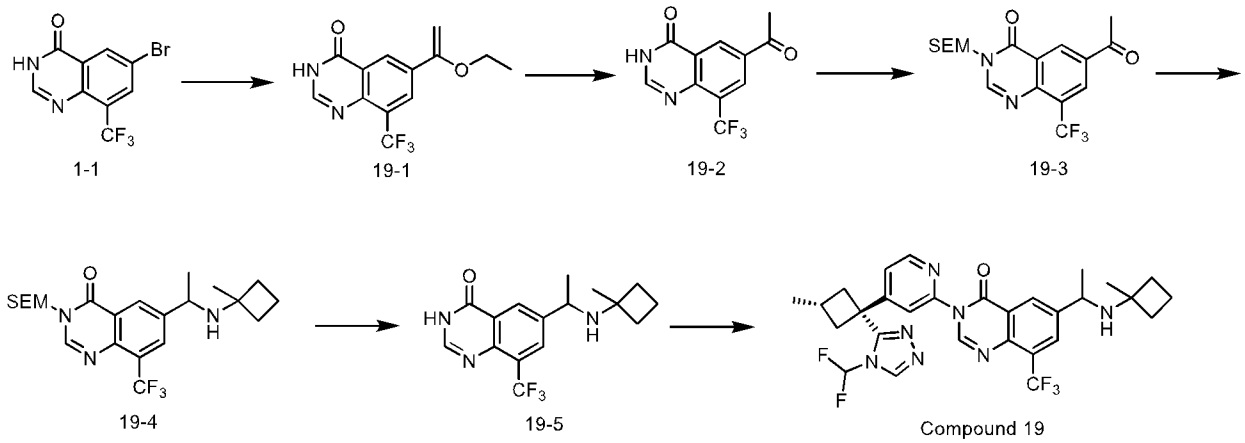
[00280] With **14-2** as the substrate, the title compound was synthesized according to the previous steps. LCMS: 534.4 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.76 – 7.60 (m, 2H), 6.91 (s, 1H), 6.03 (d, J = 51.8 Hz, 2H), 4.13 (s, 2H), 3.38 (s,

3H), 3.07 – 2.87 (m, 4H), 2.81 – 2.66 (m, 3H), 2.19 – 2.07 (m, 4H), 1.83 – 1.74 (m, 1H), 1.61 – 1.48 (m, 1H), 1.17 (d, J = 4.1 Hz, 3H).

[00281] The following compounds were synthesized according to a similar procedure with the corresponding substrates.

Example	LCMS	^{1}H NMR
15	536.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 7.87 (dd, J = 8.3, 1.8 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.05 (s, 1H), 6.12 (d, J = 52.2 Hz, 2H), 3.91 (s, 2H), 3.28 (s, 3H), 2.93 – 2.86 (m, 2H), 2.77 – 2.69 (m, 2H), 2.59 (d, J = 6.6 Hz, 3H), 2.16 (q, J = 8.0, 7.4 Hz, 4H), 1.78 – 1.67 (m, 1H), 1.40 (q, J = 8.8 Hz, 1H), 1.08 (d, J = 5.1 Hz, 3H).
16	572.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.57 (s, 1H), 8.20 (s, 1H), 7.88 (dd, J = 8.3, 1.6 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.48 (t, J = 58.6 Hz, 1H), 7.08 (s, 1H), 6.13 (d, J = 52.2 Hz, 2H), 3.93 (s, 2H), 2.97 – 2.83 (m, 2H), 2.83 – 2.69 (m, 2H), 2.69 – 2.55 (m, 3H), 2.24 – 2.03 (m, 4H), 1.81 – 1.66 (m, 1H), 1.49 – 1.33 (m, 1H), 1.09 (d, J = 5.1 Hz, 3H).
17	604.2 $[M+H]^+$	^{1}H NMR (400 MHz, Chloroform-d) δ 8.80 – 8.70 (m, 1H), 8.59 – 8.24 (m, 2H), 8.20 – 7.99 (m, 1H), 7.69 – 7.46 (m, 1H), 6.95 – 6.75 (m, 1H), 6.02 (dd, J = 51.7, 4.0 Hz, 2H), 4.18 (s, 2H), 3.53 – 3.30 (m, 3H), 3.29 – 2.86 (m, 4H), 2.79 – 2.60 (m, 3H), 2.35 – 2.22 (m, 4H), 1.92 – 1.70 (m, 1H), 1.66 – 1.35 (m, 1H), 1.21 – 1.09 (m, 3H).
18	554.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.64 (d, J = 5.3 Hz, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 8.29 (s, 1H), 8.14 (s, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.48 (dd, J = 5.3, 1.7 Hz, 1H), 4.04 (s, 2H), 3.25 (s, 3H), 3.18 (s, 3H), 2.95 – 2.81 (m, 2H), 2.75 (s, 2H), 2.68 – 2.57 (m, 3H), 1.14 – 1.01 (m, 3H), 0.74 – 0.60 (m, 2H), 0.56 – 0.44 (m, 2H).

Example 19: Preparation of 3-(4-((*1s*,*3s*)-1-(4-(difluoromethyl)-*4H*-1,2,4-triazol-3-yl)-3-methylcyclobutyl)pyridin-2-yl)-6-(1-((1-methylcyclobutyl)amino)ethyl)-8-(trifluoromethyl)quinazolin-4(*3H*)-one



Step 1: Preparation of Compound 19-1

[00282] To a solution of **Compound 1-1** (1.00 g, 3.41 mmol) in 1,4-dioxane (30 mL) were added 1-Ethoxyvinyltri-n-butyltin (2.50 g, 6.8 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.17 mmol) at room temperature. The resulting mixture was stirred at 110°C for 3 hrs under nitrogen atmosphere. The mixture was quenched by the addition of Potassium fluoride solution (5 mL) and extracted with EtOAc (50 mL ×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **Compound 19-1** (900 mg, 92.8%). The crude product was used into the next step without further purification. LCMS: 285.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1H), 8.27 (d, J = 3.3 Hz, 1H), 5.09 (d, J = 3.2 Hz, 1H), 4.52 (d, J = 3.0 Hz, 1H), 4.01 – 3.94 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H).

Step 2: Preparation of Compound 19-2

[00283] To a solution of **Compound 19-1** (900 mg, 3.16 mmol) in THF (10 mL) was added 3M HCl (28.46 mL, 56.92 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase chromatography (Isolera-Biotage Column: Agela C^{18} 80 g; Mobile Phase A: 0.1% TFA, Mobile Phase B: ACN; Flow rate: 40 mL/min; Gradient: 0% B to 50% B in 60 min; Detector: UV 254 nm) to afford **Compound 19-2** (650 mg, 80.1%). LCMS: 257.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 12.88 (s, 1H), 8.87 (s, 1H), 8.53 (s, 1H), 8.39 (d, J = 3.7 Hz, 1H), 2.73 (s, 3H).

Step 3: Preparation of Compound 19-3

[00284] To a solution of **Compound 19-2** (500 mg, 1.95 mmol) in DMF (5 mL) was added Cs_2CO_3 (1.91 g, 5.85 mmol) and SEMCl (488 mg, 2.92 mmol) at 0°C. The resulting mixture was stirred at room temperature for 3 hrs. The mixture was quenched with H_2O (20 mL), extracted with EtOAc (30 mL ×3). The combined organic layers were washed brine (20 mL ×2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue purified by flash silica gel chromatography (ISCO@; 25 g SepaFlash@ Silica Flash Column, Eluent of 0-20% EtOAc/PE @ 30 mL/min). (Plate1: PE/ EtOAc =5/1) to afford **Compound 19-3** (200 mg, 26.5%). LCMS: 387.1 $[M+H]^+$;

Step 4: Preparation of Compound 19-4

[00285] To a solution of **Compound 19-3** (110 mg, 0.28 mmol) in Titanium tetraisopropanolate (1 mL) was added 1-methylcyclobutan-1-amine (36.4 mg, 0.43 mmol) at room temperature. The reaction solution was stirred at 100°C for overnight. Then THF (1 mL) and $NaBH_4$ (64.6 mg, 1.71 mmol) were added at room temperature. The resulting mixture was stirred at room temperature for 4 hrs. The reaction mixture was diluted with EtOAc (8 mL), quenched by addition of water (1 mL) and MeOH (2 mL) at 10°C. The suspension was filtered, a filter cake was washed with EtOAc (8 mL ×3), the filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue purified by flash silica gel chromatography to afford **Compound 19-4** (80 mg, 61.7%). LCMS: 456.2 $[M+H]^+$;

Step 5: Preparation of Compound 19-5

[00286] To a solution of **Compound 19-4** (80 mg, 0.17 mmol) in 1,4-dioxane (1 mL) was added HCl (in 1,4-dioxane, 4M, 1 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The mixture was quenched by the addition of $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL ×3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase chromatography to afford **Compound 19-5**. LCMS: 326.3 $[M+H]^+$;

Step 6: Preparation of Compound 19

With **19-5** as the substrate, the title compound was synthesized according to the previous step. LCMS: 629.4 $[M+H+MeCN]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.67 – 8.60 (m, 2H), 8.51 (s, 1H), 8.34 (s, 1H), 7.86 (s, 1H), 7.60 – 7.28 (m, 2H), 4.21 – 4.06 (m, 1H), 2.94 – 2.78 (m, 3H), 2.65 – 2.59 (m, 3H), 1.83 – 1.71 (m, 2H), 1.62 – 1.50 (m, 2H), 1.46 – 1.39 (m, 1H), 1.35 – 1.20 (m, 4H), 1.14 – 1.03 (m, 6H).

Example A: assay

[00287] An HTRF based binding assay was applied to assess the affinity of candidate compounds to Cbl-b protein. CBL-B (GST-Tag) was purchased from BPS (Cat# 80415). A fluorescence labeled Cbl-b binding probe was made in-house. Anti GST-Tb cryptate monoclonal antibody was from Cisbio (61GSTTLB). In brief, compounds were diluted and transferred to opti-384F black plate (PE, 6007279) by echo. 1x Assay Buffer (HEPES pH 7.5 50 mM, NaCl 50 mM, $MgCl_2$ 5 mM, TCEP 1 mM, Tween-20 0.01%), 2x Protein mix (10 nM), and 2x Probe mix (120 nM) were prepared. 10 μL 2x Protein mix (or 1x Assay buffer, as no protein control) was added to assay plate. After 30 min incubation 25℃, 10 μl 2x Probe mix was added for another 2 h incubation at 25℃. Data were collected by Envision reading using Ex340/Em495/520.

[00288] The results are found in Table 4.

TABLE 4

Ex.	Binding activity
1	A
2	A
3	A
4	A
5	A
6	D
7	C
8	B
9	B
10	A
11	C
12	A
13	A
14	A
15	A

Ex.	Binding activity
16	A
17	A
18	C
19	A

0 < A ≤ 20 nM; 20 nM < B ≤ 50 nM; 50 nM < C ≤ 500 nM; 500 nM < D ≤ 1000 nM ; E > 1000 nM

NT: not tested

Example B: CYP inhibition Assay

[00289] Pooled human liver microsomes supplied by Corning (Cat No. 452117) were used. CYP isoform and substrate specific probe reactions were employed as per reported methods. The methods were standardized and validated. phenacetin O-deethylation for CYP1A2, diclofenac 4-hydroxylation for CYP2C9, S-mephenytoin 4-hydroxylation for CYP2C19, dextromethorphan Odemethylation for CYP2D6, midazolam 1′-hydroxylation for CYP3A4. In general, the typical incubation systems consisted of 100 mM potassium phosphate buffer (pH 7.4), 33 mM MgCl2, 10 mM NADPH, HLM (0.253 mg/mL). Substrates, compounds/positive controls, HLM, and NADPH solutions were added to corresponding wells, mixed, and incubated for 10 minutes for all CYPs at 37 water bath. Reaction was terminated by adding 400 μl cold stop solution (200 ng/ml Tolbutamide and Labetalol in CAN). Samples were centrifuged at 4000 rpm for 20 minutes to precipitate protein. 200 μl supernatant was transferred to 100 μl HPLC water and shaken for 10 minutes. Samples were analyzed by LC/MS/MS. XL fit was used to plot the percent of vehicle control versus the test compound concentrations, and for non-linear regression analysis of the data. IC50 values were reported as ">50 μM" when % inhibition at the highest concentration (50 μM) was less than 50%.

[00290] The results are found in Table 5.

Example C: Human and Mouse CL Determination

[00291] Microsomes (final concentration 0.5 mg/mL), 100 mM phosphate buffer pH 7.4, and compound (final concentration 1 μM) were added to the assay plate and allowed to preincubate for 10 min at 37 ℃. The reaction was initiated by the addition of NADPH (final concentration 1 mM), and the plate was constantly shaken at 37 ℃. After 0, 5-, 15-, 30-, 45-, and 60-min aliquots were taken, and the reaction was quenched using cold acetonitrile. The samples were shaken for 10 min, then centrifuged at 4000 rpm for 20 min at 4 ℃ and analyzed by LC-MS/MS. The *in vitro* intrinsic clearance was calculated from the rate of compound disappearance.

[00292] The results are found in Table 5.

TABLE 5

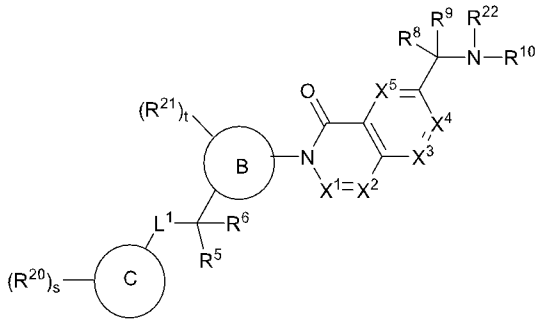
Example	**2**	**3**
CYP inhibition (μM) (1A2/2C9/2C19/2D6/3A4)	>50/>50/>50/>50/>50	9.2/12.7/26.3/18.9/5.9
LMMS (Human/Mouse, mL/min/Kg)	11.5/55.6	14.9/75.7

[00293] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (I),

wherein

X^1, X^2, X^3, X^4, and X^5 are independently N or $CR^{7'}$;

$R^{7'}$ is hydrogen or R^7;Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{20} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

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

L^1 is absent or $-CR^3R^4-$;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, -

$NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{21} is independently halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

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

each R^7 is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

R^{22} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl optionally substituted with one or more halogens), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is $-CR^3R^4-$, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or R^{10} and R^{22} are taken together to form a heterocycloalkyl optionally substituted with one or more R^{10a}, provided that L^1 is $-CR^3R^4-$, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{10a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

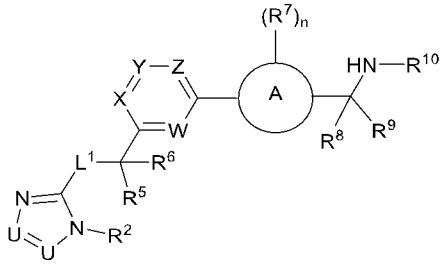
R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl$)_2$, $-P(=O)(C_1$-C_3alkyl$)_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo.

2. A compound of Formula (IV), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (IV),

wherein:

each U is independently -N- or -CR^1-;

each R^1 is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl;

R^2 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogen, or heterocycloalkyl;

L^1 is absent or -CR^3R^4-;

R^3 and R^4 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^3 and R^4 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

or R^3 and R^4 are taken together to form an oxo;

R^5 and R^6 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{5a};

or R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a};

or L^1 is -CR^3R^4-, R^4 and R^6 are defined as above, and R^5 and R^3 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a};

each R^{5a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein

each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^{5a} on the same atom are taken together to form an oxo;

X is -N- or -CR^X-;

R^X is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

Y is -N- or -CR^Y-;

R^Y is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6haloalkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl optionally substituted with one or more halogens;

Z is -N- or -CR^Z-;

R^Z is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

W is -N- or -CR^W-;

R^W is hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl;

or R^X and R^Y are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each optionally substituted with one or more R;

or R^Y and R^Z are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each optionally substituted with one or more R;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^7 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SF_5, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$N=S(=O)(R^b)_2$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or two R^7 on the same atom are taken together to form an oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^8 and R^9 are each independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl,

cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^8 and R^9 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R;

R^{10} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{10a};

each R^{10a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF_5, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^b)R^b, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -N=S(=O)$(R^b)_2$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -P(=O)$(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

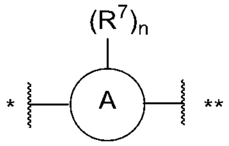
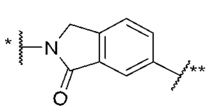
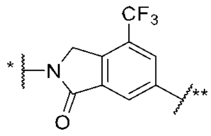
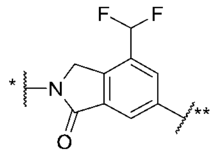
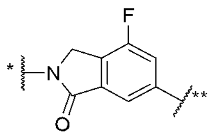
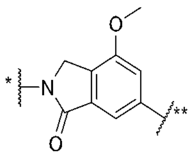
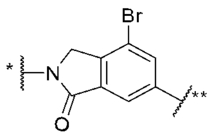
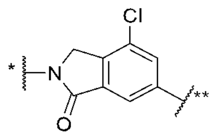
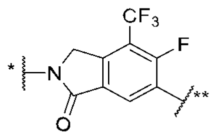
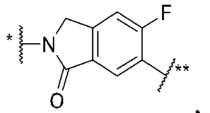
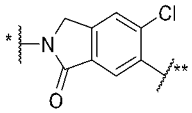
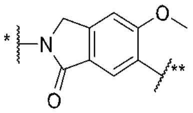
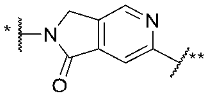
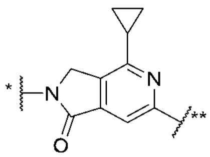
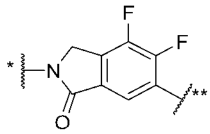
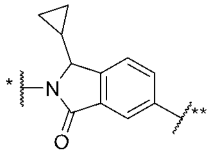
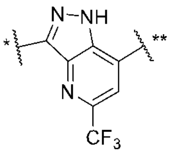
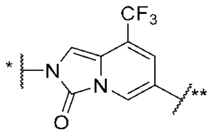
R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl), wherein each alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF_5, -SH, -S(=O)C_1-C_3alkyl, -$S(=O)_2C_1$-C_3alkyl, -$S(=O)_2NH_2$, -$S(=O)_2NHC_1$-C_3alkyl, -$S(=O)_2N(C_1$-C_3alkyl$)_2$, -S(=O)(=NC_1-C_3alkyl)(C_1-C_3alkyl), -NH_2, -NHC_1-C_3alkyl, -$N(C_1$-C_3alkyl$)_2$, -N=S(=O)$(C_1$-C_3alkyl$)_2$, -C(=O)C_1-C_3alkyl, -C(=O)OH, -C(=O)OC_1-C_3alkyl, -$C(=O)NH_2$, -C(=O)NHC_1-C_3alkyl, -$C(=O)N(C_1$-C_3alkyl$)_2$, -P(=O)$(C_1$-C_3alkyl$)_2$,

C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, or C_3-C_6cycloalkyl optionally substituted with one or more halogens;

or two R on the same atom form an oxo;

provided that  is not  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  , wherein * represents the attachment point to the ring containing X, Y, Z and W and ** represents the attachment point to -CR^8R^9-.

3. The compound of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is aryl or heteroaryl.

4. The compound of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 6-6 fused ring.

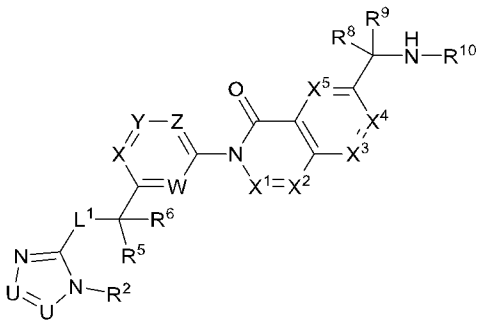
5. The compound of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 6-5 or 5-6 fused ring containing 3 or more heteroatoms selected from N, O, and S.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^7 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, or cycloalkyl optionally substituted with one or more halogens; or two R^7 on the same atom are taken together to form an oxo.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^7 is independently halogen, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl; or two R^7 on the same atom are taken together to form an oxo.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^7 is independently C_1-C_6haloalkyl; or two R^7 on the same atom are taken together to form an oxo.

9. The compound of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound of Formula (IV) is of Formula (IVa):



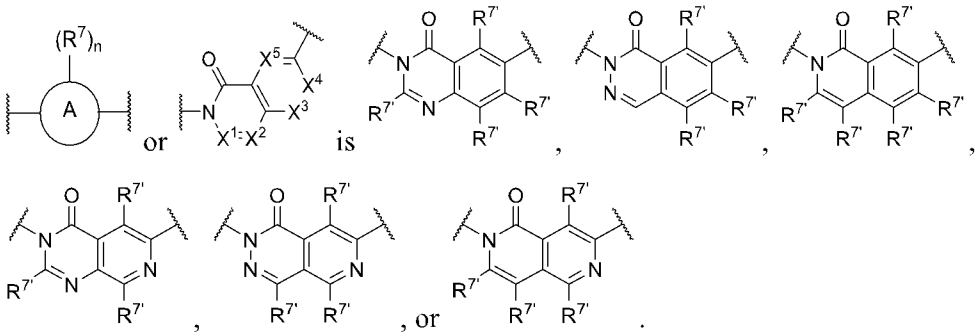
Formula (IVa),

wherein

X^1, X^2, X^3, X^4, and X^5 are independently N or $CR^{7'}$; and

$R^{7'}$ is hydrogen or R^7.

10. The compound of claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



11. The compound of any one of claims 2-9, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one U is -N- and the other U is $-CR^1-$.

12. The compound of any one of claims 2-11, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^1 is independently hydrogen.

13. The compound of any one of claims 2-12, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^2 is C_1-C_6alkyl.

14. The compound of any one of claims 2-13, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^X is hydrogen.

15. The compound of any one of claims 2-14, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^Y is hydrogen or cycloalkyl optionally substituted with one or more halogens.

16. The compound of any one of claims 2-15, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^Z is hydrogen.

17. The compound of any one of claims 2-16, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^W is hydrogen.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein L^1 is $-CR^3R^4-$.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^3 and R^4 are each independently hydrogen, halogen, or C_1-C_6alkyl.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^3 and R^4 are each independently hydrogen.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein L^1 is absent.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 and R^6 are each independently hydrogen, halogen, or C_1-C_6alkyl.

23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 and R^6 are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{5a}.

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 and R^6 are taken together to form a cycloalkyl optionally substituted with one or more R^{5a}.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 and R^6 are taken together to form a heterocycloalkyl optionally substituted with one or more R^{5a}.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form an aryl or heteroaryl; each optionally substituted with one or more R^{5a}.

27. The compound of any one of claims 26, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein L^1 is -CR^3R^4-, R^4 and R^6 are taken together to form a bond, and R^5 and R^3 are taken together to form a phenyl optionally substituted with one or more R^{5a}.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{5a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkynyl, cycloalkyl optionally substituted with one or more halogens, or heterocycloalkyl.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{5a} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_2-C_6alkynyl.

30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{5a} is independently halogen or C_2-C_6alkynyl.

31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^8 and R^9 are each independently hydrogen or C_1-C_6alkyl.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{10} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, cycloalkyl optionally substituted with one or more halogens, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl); wherein the alkyl, alkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{10a}.

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{10} is C_1-C_6hydroxyalkyl or C_1-C_6alkylene(cycloalkyl); wherein the alkyl, alkylene, and cycloalkyl is independently optionally substituted with one or more R^{10a}.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{10} is C_1-C_6hydroxyalkyl.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{10} is C_1-C_6alkylene(cycloalkyl); wherein the alkylene and cycloalkyl optionally substituted with one or more R^{10a}.

36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{10a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, or C_1-C_6haloalkyl.

37. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{10a} is -OH.

38. A compound, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound in table 1 or table 2.

39. A pharmaceutical composition comprising a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient.

40. A method of treating a cancer, the method comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

41. A method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

42. A method of inhibiting abnormal cell proliferation, the method comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

43. A method of inhibiting Cbl-b activity, the method comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

44. A method for treating a disease or condition associated with Cbl-b activity, the method comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/141007

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/14(2006.01)i; C07D403/14(2006.01)i; C07D403/10(2006.01)i; C07D405/14(2006.01)i; C07D471/04(2006.01)i; A61K31/513(2006.01)i; A61P35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, CNTXT, REGISTRY(STN), CAPLUS(STN), CNKI, BAIDU: INSILICO MEDICINE IP LIMITED, CBL, Casitas B, lineage lymphoma, cell proliferation, cancer?, tumour, tumor?, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2023072273 A1 (SIMCERE ZAIMING PHARMACEUTICAL CO., LTD.) 04 May 2023 (2023-05-04) pages 89-91, claims 1, 23-26	2-8, 11-44
Y	WO 2021021761 A1 (NURIX THERAPEUTICS, INC.) 04 February 2021 (2021-02-04) claims 1, 69-73, page 80	2-8,11-44
Y	WO 2022221704 A1 (HOTSPOT THERAPEUTICS, INC.) 20 October 2022 (2022-10-20) claims 1, 21-28; pages 34-94	2-8, 11-44
A	WO 2022169997 A1 (GENENTECH,INC.) 11 August 2022 (2022-08-11) claims 1-10, pages 120-165 table 1	1-44
A	WO 2020264398 A1 (NURIX THERAPEUTICS,INC.) 30 December 2020 (2020-12-30) claims 1, 32-36; pages 46-50 table 1	1-44
A	WO 2020236654 A1 (NURIX THERAPEUTICS,INC.) 26 November 2020 (2020-11-26) claims 1, 35-39; pages 53-57 table 1	1-44

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2024	**29 March 2024**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/141007

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **40-44**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 40-44 relates to methods for the treatment of human body by therapy as defined in PCT Rules 39.1(IV). This report has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2023/141007

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2023072273 A1	04 May 2023	None	
WO 2021021761 A1	04 February 2021	US 2022387395 A1	08 December 2022
		AU 2020320195 A1	10 March 2022
		EP 4003965 A1	01 June 2022
		CA 3148769 A1	04 February 2021
		MX 2022001199 A	22 February 2022
		JP 2022542323 A	30 September 2022
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		EP 4323358 A1	21 February 2024
		BR 112023021068 A2	23 January 2024
		AU 2022256514 A1	19 October 2023
		TW 202309023 A	01 March 2023
		IL 307732 A	01 December 2023
WO 2022169997 A1	11 August 2022	None	
WO 2020264398 A1	30 December 2020	US 2023150991 A1	18 May 2023
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		US 2021053961 A1	25 February 2021
		US 11401267 B2	02 August 2022
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		BR 112021026241 A2	07 June 2022
WO 2020236654 A1	26 November 2020	AU 2020278592 A1	02 December 2021
		MX 2021013751 A	26 January 2022
		US 2023212186 A1	06 July 2023
		JP 2022532247 A	13 July 2022
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		US 2021053986 A1	25 February 2021
		US 11530229 B2	20 December 2022