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(54) Title: PROTEIN TYROSINE PHOSPHATASE INHIBITORS AND USES THEREOF

(57) Abstract: Provided are compounds, methods for modulating or inhibiting PTPN1/2 and pharmaceutical compositions comprising such compounds and methods of treatment using such compounds.

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PROTEIN TYROSINE PHOSPHATASE INHIBITORS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This international patent application claims the benefit of International Application No. PCT/CN2022/143991, filed December 30, 2022, which is incorporated herein by reference in its entirety.

BACKGROUND

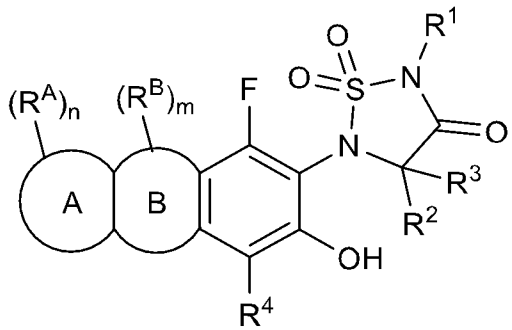
[0002] Protein-Tyrosine Phosphatase non-receptor type 1 (PTPN1) and Protein-Tyrosine Phosphatase non-receptor type 2 (PTPN2) are enzymes in humans encoded by the PTPN1 and PTPN2 gene, respectively. PTPN1 and PTPN2 are both members of the protein tyrosine phosphatase (PTP) family, and members of this family have a highly conserved catalytic motif, which is essential for the catalytic activity. PTPs can be signaling molecules that are able to regulate processes like cell growth, cell differentiation, the mitotic cycle, and oncogenic transformation.

[0003] There is a need for new cancer and metabolic disease therapies, specifically using PTPN1/2 inhibitors.

SUMMARY

[0004] Disclosed herein are compounds, or a pharmaceutically acceptable salt thereof, that are Protein Tyrosine Phosphatase non-receptor type 1 (PTPN1) and/or Protein Tyrosine Phosphatase non-receptor type 2 (PTPN2) inhibitors.

[0005] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I),

wherein:

Ring A is heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^A 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_6heteroalkylene(cycloalkyl), or C_1-

C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

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

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

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

Ring B is 5, 6 or 7 membered cycloalkyl or heterocycloalkyl;

each R^B 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12};

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

or two R^B on the same atom or adjacent atoms are taken together to form a cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12};

each R^{12} 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;

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

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^2 is hydrogen, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^3 is hydrogen, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^4 is hydrogen, halogen, -OH, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

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;

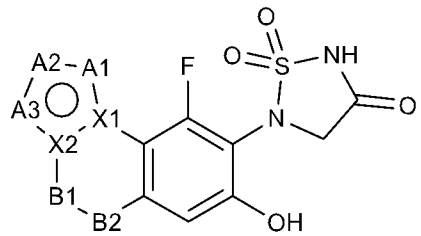
R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), 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;

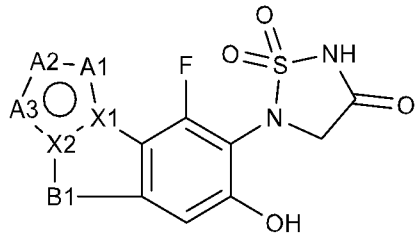
or two R on the same atom form an oxo.

[0006] In some embodiments, described herein is compound or a pharmaceutically acceptable salt thereof having a structure of Formula (Ia) as described herein,



Formula (Ia).

[0007] In some embodiments, described herein is a compound or a pharmaceutically acceptable salt thereof having a structure of Formula (Ib),



Formula (Ib).

[0008] In some embodiments, the compound is selected from Table 1.

[0009] In another aspect, described herein is a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0010] In another aspect, described herein is a method of modulating a protein tyrosine phosphatase enzyme, comprising administering to a subject in need of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure.

[0011] In another aspect, described herein is a method of inhibiting a protein tyrosine phosphatase enzyme, comprising administering to a subject in need of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure.

[0012] In some embodiments, the protein tyrosine phosphatase enzyme is protein tyrosine phosphatase non-receptor type 1 (PTPN1), or protein tyrosine phosphatase nonreceptor type 2 (PTPN2).

[0013] In some embodiments, the subject has a disease or disorder.

[0014] In another aspect, described herein is a method of treating a disease or disorder, comprising administering to a subject in need of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure.

[0015] In some embodiments, the disease or disorder is associated with protein tyrosine phosphatase enzyme.

[0016] In some embodiments, the disease or disorder is cancer.

[0017] In some embodiments, the cancer is selected from bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, prostate cancer, marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

[0018] In some embodiments, the cancer is melanoma.

[0019] In some embodiments, the disease or disorder is a metabolic disease.

[0020] In some embodiments, the metabolic disease is selected from non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, metabolic syndrome, phenylketonuria, proliferative retinopathy, and Kearns-Sayre disease.

[0021] In some embodiments, the diabetes is Type I diabetes.

[0022] In some embodiments, the diabetes is Type II diabetes.

[0023] In some embodiments, the diabetes is gestational diabetes.

INCORPORATION BY REFERENCE

[0024] 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

[0025] 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.

[0026] 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.

[0027] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0028] "oxo" refers to =O.

[0029] "Carboxyl" refers to -COOH.

[0030] "Cyano" refers to -CN.

[0031] "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.

[0032] "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.

[0033] "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.

[0034] "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.

[0035] "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.

[0036] "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.

[0037] "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.

[0038] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0039] "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.

[0040] "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.

[0041] "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.

[0042] "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.

[0043] "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.

[0044] "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, benzodioxolyl, 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

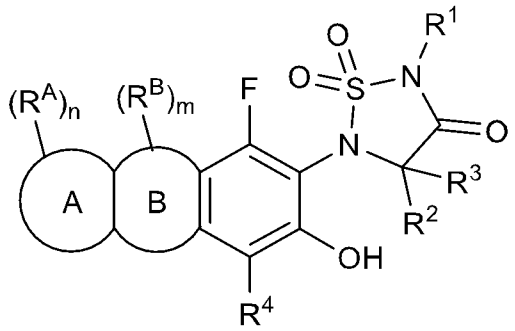
[0049] As used herein, the term "PTPN1/2" means Protein Tyrosine Phosphatase Nonreceptor (PTPN) type 1 (PTPN1) and/or type 2 (PTPN2).

[0050] As used herein, a "disease or disorder associated with PTPN1/2" or, alternatively, "a PTPN1/2-mediated disease or disorder" means any disease or other deleterious condition in which PTPN1/2, or a mutant thereof, is known or suspected to play a role.

Compounds

[0051] Described herein are compounds, or a pharmaceutically acceptable salt thereof useful in the treatment of a disease or disorder associated with PTPN1/2.

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



Formula (I)

wherein:

Ring A is heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^A 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

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

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, or heteroaryl; wherein

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

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

Ring B is 5, 6 or 7 membered cycloalkyl or heterocycloalkyl;

each R^B 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12};

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

or two R^B on the same atom or adjacent atoms are taken together to form a cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12};

each R^{12} 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;

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

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^2 is hydrogen, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^3 is hydrogen, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^4 is hydrogen, halogen, -OH, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

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

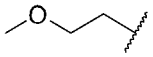
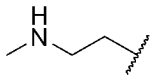
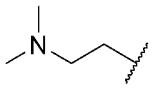
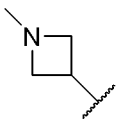
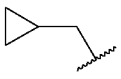
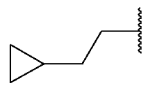
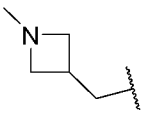
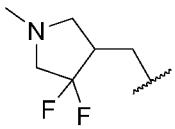
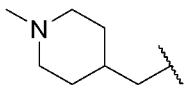
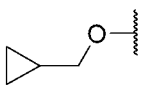
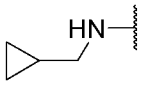
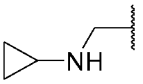
each R is independently halogen, -CN, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl$)_2$, $-S(=O)(=NC_1$-C_3alkyl$)(C_1$-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl$)_2$, $-N=S(=O)(C_1$-C_3alkyl$)_2$, $-C(=O)C_1$-C_3alkyl,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

or two R on the same atom form an oxo.

[0053] In some embodiments of Formula (I), Ring A is a heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, Ring A is a heteroaryl. In some embodiments, Ring A is a cycloalkyl. In some embodiments, Ring A is a heterocycloalkyl. In some embodiments, Ring A is a 5 or 6 membered heteroaryl, 5 or 6 membered cycloalkyl, or a 5 or 6 membered heterocycloalkyl. In some embodiments, Ring A is a 5 or 6 membered heteroaryl. In some embodiments, Ring A is a 5 or 6 membered cycloalkyl. In some embodiments, Ring A is a 5 or 6 membered heterocycloalkyl. In some embodiments, Ring A is a 5 membered heteroaryl. In some embodiments, Ring A is a 6 membered heteroaryl. In some embodiments, Ring A is a 5 membered cycloalkyl. In some embodiments, Ring A is a 6 membered cycloalkyl. In some embodiments, Ring A is a 5 membered heterocycloalkyl. In some embodiments, Ring A is a 6 membered heterocycloalkyl. In some embodiments, ring A is fused with ring B.

[0054] In some embodiments of Formula (I), Ring A is pyridine, pyrimidine, or pyrazine. In some embodiments, Ring A is pyridine. In some embodiments, Ring A is pyrimidine. In some embodiments, Ring A is pyrazine. In some embodiments, Ring A is pyrrole, pyrazole, imidazole, triazole, oxazole, or thiazole. In some embodiments, Ring A is pyrrole. In some embodiments, Ring A is pyrazole. In some embodiments, Ring A is imidazole. In some embodiments, Ring A is triazole. In some embodiments, Ring A is oxazole. In some embodiments, Ring A is thiazole.

[0055] In some embodiments of Formula (I), Ring B is a 5, 6, or 7 membered cycloalkyl or heterocycloalkyl. In some embodiments, Ring B is a 5 or 6 membered cycloalkyl. In some embodiments, Ring B is a 5 or 6 membered heterocycloalkyl. In some embodiments, Ring B is a 5 membered cycloalkyl. In some embodiments, Ring B is a 6 membered cycloalkyl. In some embodiments, Ring B is a 7 membered cycloalkyl. In some embodiments, Ring B is a 5 membered heterocycloalkyl. In some embodiments, Ring B is a 6 membered heterocycloalkyl. In some embodiments, Ring B is a 6 membered heterocycloalkyl containing 1 to 2 ring nitrogen atoms. In some embodiments, Ring B is a 7 membered heterocycloalkyl.

[0056] In some embodiments of Formula (I), each R^A 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11} (e.g., 1, 2, 3, 4 or 5 R^{11}). In some embodiments, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl). In some embodiments, R^A is halogen (e.g., F). In some embodiments, R^A is C_1-C_6alkyl. In some embodiments, R^A is methyl or isopropyl. In some embodiments, R^A is methyl. In some embodiments, R^A is isopropyl. In some embodiments, R^A is C_1-C_6haloalkyl. In some embodiments, R^A is -$CH_2CH_2CF_3$. In some embodiments, R^A is C_1-C_6hydroxyalkyl. In some embodiments, R^A is C_1-C_6aminoalkyl. In some embodiments, R^A is C_1-C_6heteroalkyl. In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is heterocycloalkyl. In some embodiments, R^A is  . In some embodiments, R^A is C_1-C_6alkylene(cycloalkyl). In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is C_1-C_6alkylene(heterocycloalkyl). In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is C_1-C_6heteroalkylene(cycloalkyl). In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is  . In some embodiments, R^A is C_1-

C_6heteroalkylene(heterocycloalkyl). In some embodiments, two R^A on the same atom are taken together to form an oxo.

[0057] In some embodiments of Formula (I), each R^B 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12} (e.g., 1, 2, 3, 4 or 5 R^{12}). In some embodiments, each R^B is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, or -$OC(=O)NR^cR^d$. In some embodiments, R^B is halogen (e.g., F). In some embodiments, R^B is C_1-C_6alkyl. In some embodiments, R^B is methyl. In some embodiments, R^B is C_1-C_6haloalkyl. In some embodiments, R^B is C_1-C_6hydroxyalkyl. In some embodiments, R^B is C_1-C_6aminoalkyl. In some embodiments, R^B is C_1-C_6heteroalkyl. In some embodiments, R^B is C_2-C_6alkenyl. In some embodiments, R^B is C_2-C_6alkynyl. In some embodiments, R^B is amino. In some embodiments, two R^B on the same atom are taken together to form an oxo. In some embodiments, two R^B on the same atom or adjacent atoms are taken together to form a cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}. In some embodiments, two R^B on the same atom are taken together to form a cycloalkyl. In some embodiments, two R^B on the same atom are taken together to form a cyclopropyl. In some embodiments, two R^B on the same atom are taken together to form a heterocycloalkyl.

[0058] In some embodiments of Formula (I), R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6alkyl. In some embodiments, R^1 is C_1-C_6haloalkyl. In some embodiments, R^1 is C_2-C_6alkenyl. In some embodiments, R^1 is C_2-C_6alkynyl.

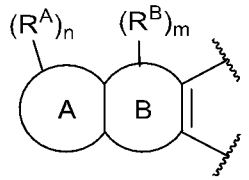
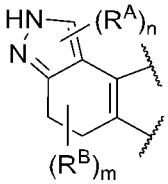
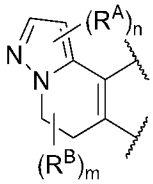
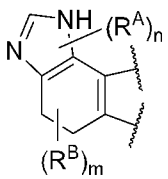
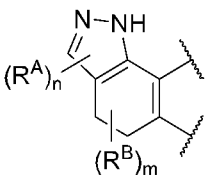
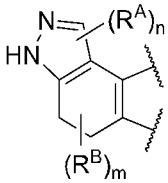
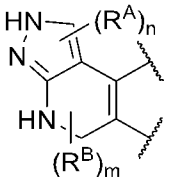
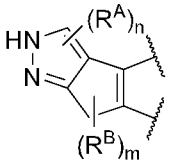
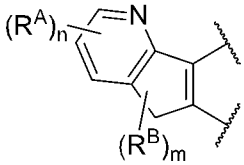
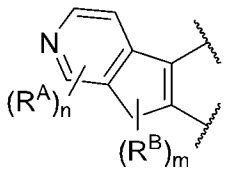
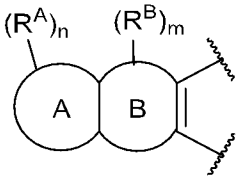
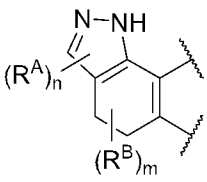
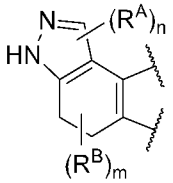
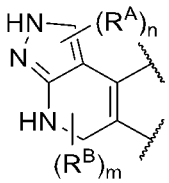
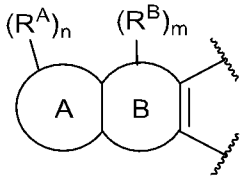
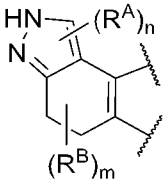
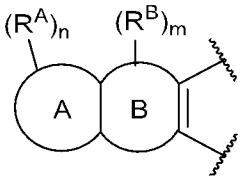
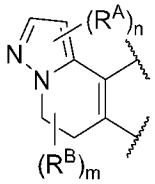
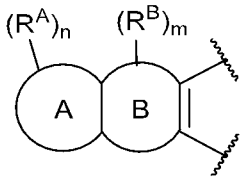
[0059] In some embodiments of Formula (I), R^2 is hydrogen, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl. In some embodiments, R^2 is hydrogen or C_1-C_3alkyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is -CN. In some embodiments, R^2 is -NO_2. In some embodiments, R^2 is C_1-C_6alkyl. In some embodiments, R^2 is C_1-C_6haloalkyl. In some embodiments, R^2 is C_1-C_6hydroxyalkyl. In some embodiments, R^2 is C_1-C_6aminoalkyl. In some embodiments, R^2 is C_1-C_6heteroalkyl. In some embodiments, R^2 is C_1-C_6alkoxy. In some embodiments, R^2 is C_1-C_6haloalkoxy. In some embodiments, R^2 is C_2-C_6alkenyl. In some embodiments, R^2 is C_2-C_6alkynyl.

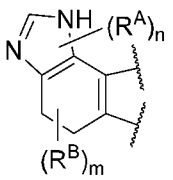
[0060] In some embodiments of Formula (I), R^3 is hydrogen, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl. In some embodiments, R^3 is hydrogen or C_1-C_3alkyl. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is -CN. In some embodiments, R^3 is -NO_2. In some embodiments, R^3 is C_1-C_6alkyl. In some embodiments, R^3 is C_1-C_6haloalkyl. In some embodiments, R^3 is C_1-

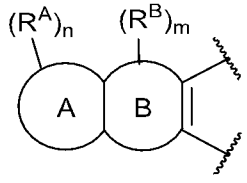
C_6hydroxyalkyl. In some embodiments, R^3 is C_1-C_6aminoalkyl. In some embodiments, R^3 is C_1-C_6heteroalkyl. In some embodiments, R^3 is C_1-C_6alkoxy. In some embodiments, R^3 is C_1-C_6haloalkoxy. In some embodiments, R^3 is C_2-C_6alkenyl. In some embodiments, R^3 is C_2-C_6alkynyl.

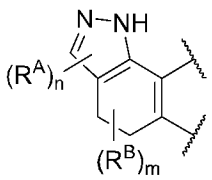
[0061] In some embodiments of Formula (I), R^4 is hydrogen, halogen, -OH, -CN, -NO_2, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl. In some embodiments, R^4 is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -OH. In some embodiments, R^4 is -CN. In some embodiments, R^4 is -NO_2. In some embodiments, R^4 is C_1-C_6alkyl. In some embodiments, R^4 is C_1-C_6haloalkyl. In some embodiments, R^4 is C_1-C_6hydroxyalkyl. In some embodiments, R^4 is C_1-C_6aminoalkyl. In some embodiments, R^4 is C_1-C_6heteroalkyl. In some embodiments, R^4 is C_1-C_6alkoxy. In some embodiments, R^4 is C_1-C_6haloalkoxy. In some embodiments, R^4 is C_2-C_6alkenyl. In some embodiments, R^4 is C_2-C_6alkynyl.

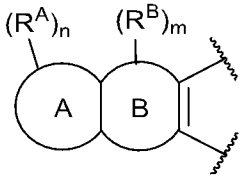
[0062] In some embodiments, the hydrogen is deuterium.

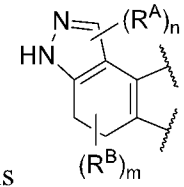
[0063] In some embodiments of Formula (I),  is  ,  ,  ,  ,  ,  ,  ,  ,  , or  is  ,  , or  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, 

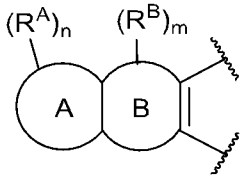


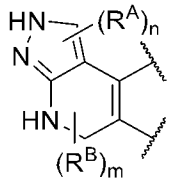
is . In some embodiments, 

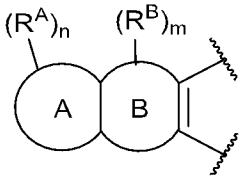
is 

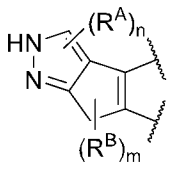
. In some embodiments, 

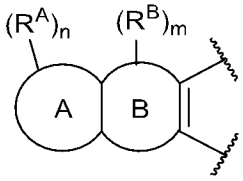
is 

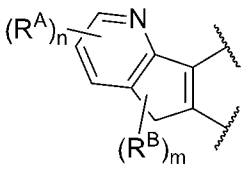
. In some embodiments, 

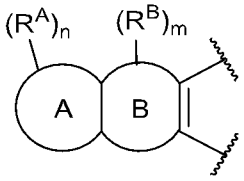
is 

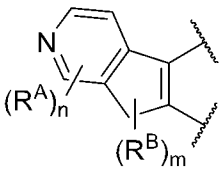
. In some embodiments, 

is 

. In some embodiments, 

is 

. In some embodiments, 

is 

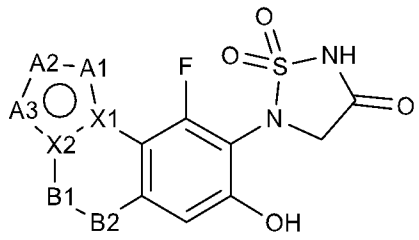
.

[0064] In some embodiments of Formula (I), n is 0, 1, 2, 3, or 4. In some embodiments, n is 1 or 2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[0065] In some embodiments of Formula (I), m is 0, 1, 2, 3, or 4. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 1 or 2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[0066] In some embodiments of a compound of Formula (I), each of R^1, R^2, R^3, and R^4 is hydrogen, Ring A is a 5-membered heteroaryl, and Ring B is a 6-membered cycloalkyl. In some embodiments of a compound of Formula (I), each of R^1, R^2, R^3, and R^4 is hydrogen, Ring A is a 5-membered heteroaryl, and Ring B is a 6-membered cycloalkyl, where m is 0 and n is 1. In some embodiments of a compound of Formula (I), each of R^1, R^2, R^3, and R^4 is hydrogen, Ring A is a 5-membered heteroaryl, and Ring B is a 6-membered cycloalkyl, where m is 0, n is 1, and R^A is a cycloalkyl or a heterocycloalkyl. In some embodiments of a compound of Formula (I), each of R^1, R^2, R^3, and R^4 is hydrogen, Ring A is a 5-membered heteroaryl, and Ring B is a 6-membered cycloalkyl, where m is 0, n is 1, and R^A is a cycloalkyl or a heterocycloalkyl, further substituted with -C_1-C_6alkyl.

[0067] In some embodiments of a compound of Formula (I), the compound of Formula (I) is of Formula (Ia):



Formula (Ia),

wherein

A1 is CR^{A1}, N, or NR^{AN1};

A2 is O, S, CR^{A2}, N, or NR^{AN2};

A3 is O, S, CR^{A3}, N, or NR^{AN3};

each of R^{A1}, R^{A2}, and R^{A3} is independently hydrogen or R^{A};

each of R^{AN1}, R^{AN2}, and R^{AN3} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

X1 is C or N;

X2 is C or N;

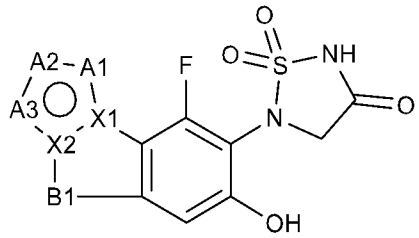
B1 is $C(R^{B1})(R^{B2})$ or NR^{BN1};

B2 is $C(R^{B3})(R^{B4})$ or NR^{BN2};

each of R^{B1}, R^{B2}, R^{B3} and R^{B4} is independently hydrogen or R^{B}; and

each of R^{BN1} and R^{BN2} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

[0068] In some embodiments of a compound of Formula (I), the compound of Formula (I) is of Formula (Ib)



Formula (Ib),

wherein

A1 is CR^{A1}, N, or NR^{AN1};

A2 is O, S, CR^{A2}, N, or NR^{AN2};

A3 is O, S, CR^{A3}, N, or NR^{AN3};

each of R^{A1}, R^{A2}, and R^{A3} is independently hydrogen or R^{A};

each of R^{AN1}, R^{AN2}, and R^{AN3} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

X1 is or N;

X2 is C or N;

B1 is $C(R^{B1})(R^{B2})$ or NR^{BN1};

each of R^{B1} and R^{B2} is independently hydrogen or R^{B}; and

R^{BN1} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

[0069] In some embodiments of a compound of Formula (Ia) or (Ib), A1 is CR^{A1}, N, or NR^{AN1}. In some embodiments, A1 is CR^{A1}. In some embodiments, A1 is N. In some embodiments, A1 is NR^{AN1}.

[0070] In some embodiments of a compound of Formula (Ia) or (Ib), A2 is O, S, CR^{A2}, N, or NR^{AN2}. In some embodiments, A2 is O or S. In some embodiments A2 is O. In some embodiments A2 is S. In some embodiments A2 is CR^{A2}. In some embodiments A2 is N. In some embodiments A2 is NR^{AN2}.

[0071] In some embodiments of a compound of Formula (Ia) or (Ib), A3 is O, S, CR^{A3}, N, or NR^{AN3}. In some embodiments, A3 is O or S. In some embodiments A3 is O. In some embodiments A3 is S. In some embodiments A3 is CR^{A3}. In some embodiments A3 is N. In some embodiments A3 is NR^{AN3}.

[0072] In some embodiments of a compound of Formula (Ia) or (Ib), each of R^{A1}, R^{A2}, and R^{A3} is independently hydrogen or R^A. In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is R^A. In some embodiments, R^{A2} is hydrogen. In some embodiments, R^{A2} is R^A. In some embodiments, R^{A3} is hydrogen. In some embodiments, R^{A3} is R^A.

[0073] In some embodiments of a compound of Formula (Ia) or (Ib), R^{A1} is hydrogen, halogen, 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, or heterocycloalkyl. In some embodiments, R^{A1} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is halogen. In some embodiments, R^{A1} is C_1-C_6alkyl. In some embodiments, R^{A1} is C_1-C_6haloalkyl.

[0074] In some embodiments of a compound of Formula (Ia) or (Ib), R^{A2} is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -SF_5, -SH, -SR^a, -NR^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, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{A2} is cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein the alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{A2} is cycloalkyl. In some embodiments, R^{A2} is heterocycloalkyl. In some embodiments, R^{A2} is C_1-C_6alkylene(cycloalkyl). In some embodiments, R^{A2} is C_1-C_6alkylene(heterocycloalkyl). In some embodiments, R^{A2} is C_1-C_6heteroalkylene(cycloalkyl). In some embodiments, R^{A2} is C_1-C_6heteroalkylene(heterocycloalkyl).

[0075] In some embodiments of a compound of Formula (Ia) or (Ib), R^{A3} is hydrogen, halogen, 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, or heterocycloalkyl. In some embodiments, R^{A3} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^{A3} is hydrogen. In some embodiments, R^{A3} is halogen. In some embodiments, R^{A3} is C_1-C_6alkyl. In some embodiments, R^{A3} is C_1-C_6haloalkyl.

[0076] In some embodiments of a compound of Formula (Ia) or (Ib), each of R^{AN1}, R^{AN2}, and R^{AN3} is independently hydrogen, -CN, -NO_2, -OC(=O)R^a, -OC(=O)NR^cR^d, -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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{AN1} 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, or heterocycloalkyl. In some embodiments, R^{AN1} is hydrogen or C_1-C_3alkyl. In some embodiments, R^{AN1} is hydrogen. In some embodiments, R^{AN1} is C_1-C_3alkyl. In some embodiments, R^{AN2} 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{AN2} is 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), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{AN2} is hydrogen. In some embodiments, R^{AN2} is C_1-C_6alkyl. In some embodiments, R^{AN2} is C_1-C_6haloalkyl. In some embodiments, R^{AN2} is C_1-C_6hydroxyalkyl. In some embodiments, R^{AN2} is C_1-C_6aminoalkyl. In some embodiments, R^{AN2} is C_1-C_6heteroalkyl. In some embodiments, R^{AN2} is cycloalkyl. In some embodiments, R^{AN2} is heterocycloalkyl. In some embodiments, R^{AN2} is C_1-C_6alkylene(cycloalkyl). In some embodiments, R^{AN2} is C_1-C_6alkylene(heterocycloalkyl). In some embodiments, R^{AN2} is C_1-C_6heteroalkylene(cycloalkyl). In some embodiments, R^{AN2} is C_1-C_6heteroalkylene(heterocycloalkyl). In some embodiments, R^{AN3} 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{AN3} is 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), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, R^{AN3} is hydrogen. In some embodiments, R^{AN3} is C_1-C_6alkyl. In some embodiments, R^{AN3} is C_1-C_6haloalkyl. In some embodiments, R^{AN3} is C_1-C_6hydroxyalkyl. In some embodiments, R^{AN3} is C_1-C_6aminoalkyl. In some embodiments, R^{AN3} is C_1-C_6heteroalkyl. In some embodiments, R^{AN3} is cycloalkyl. In some embodiments, R^{AN3} is heterocycloalkyl. In some embodiments, R^{AN3} is C_1-C_6alkylene(cycloalkyl). In some embodiments, R^{AN3} is C_1-C_6alkylene(heterocycloalkyl). In some

embodiments, R^{AN3} is C_1-C_6heteroalkylene(cycloalkyl). In some embodiments, R^{AN3} is C_1-C_6heteroalkylene(heterocycloalkyl).

[0077] In some embodiments of a compound of Formula (Ia) or (Ib), X1 is C or N. In some embodiments, X1 is C. In some embodiments, X1 is N.

[0078] In some embodiments of a compound of Formula (Ia) or (Ib), X2 is C or N. In some embodiments, X2 is C. In some embodiments, X2 is N.

[0079] In some embodiments of a compound of Formula (Ia) or (Ib), B1 is $C(R^{B1})(R^{B2})$ or NR^{BN1}. In some embodiments, B1 is $C(R^{B1})(R^{B2})$. In some embodiments, B1 is NR^{BN1}. In some embodiments of a compound of Formula (Ia), B2 is $C(R^{B3})(R^{B4})$ or NR^{BN2}. In some embodiments, B2 is $C(R^{B3})(R^{B4})$. In some embodiments, B2 is NR^{BN2}.

[0080] In some embodiments of a compound of Formula (Ia) or (Ib), each of R^{B1} and R^{B2} is independently hydrogen or R^B. In some embodiments of a compound of Formula (Ia), each of R^{B1}, R^{B2}, R^{B3} and R^{B4} is independently hydrogen or R^B. In some embodiments, R^{B1} is hydrogen. In some embodiments, R^{B1} is R^B. In some embodiments, R^{B2} is hydrogen. In some embodiments, R^{B2} is R^B. In some embodiments, R^{B3} is hydrogen. In some embodiments, R^{B3} is R^B. In some embodiments, R^{B4} is hydrogen. In some embodiments, R^{B4} is R^B. In some embodiments, R^{B1} and R^{B2} are taken together to form an oxo. In some embodiments, R^{B1} and R^{B2} are taken together to form a cycloalkyl (e.g., cyclopropyl) or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}. In some embodiments, R^{B3} and R^{B4} are taken together to form an oxo. In some embodiments, R^{B3} and R^{B4} are taken together to form a cycloalkyl (e.g., cyclopropyl) or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}.

[0081] In some embodiments of a compound of Formula (Ia) or (Ib), R^{B1} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^{B1} is hydrogen. In some embodiments, R^{B1} is halogen.

[0082] In some embodiments of a compound of Formula (Ia) or (Ib), R^{B2} is hydrogen, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{B2} is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -SF_5, -SH, -SR^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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{B2} is hydrogen. In some embodiments, R^{B2} is halogen.

[0083] In some embodiments of a compound of Formula (Ia), R^{B3} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^{B3} is hydrogen.

[0084] In some embodiments of a compound of Formula (Ia), R^{B4} is hydrogen, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{B4} is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -SF_5, -SH, -SR^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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{B4} is hydrogen. In some embodiments, R^{B4} is -NR^cR^d.

[0085] In some embodiments of a compound of Formula (Ia), or (Ib), R^{BN1} is independently hydrogen, -CN, -NO_2, -$OC(=O)R^a$, -$OC(=O)NR^cR^d$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{BN1} 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, or heterocycloalkyl, wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{BN1} is hydrogen.

[0086] In some embodiments of a compound of Formula (Ia), R^{BN2} is hydrogen, -CN, -NO_2, -$OC(=O)R^a$, -$OC(=O)NR^cR^d$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^b)R^b$, -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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{BN2} 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, or heterocycloalkyl, wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}. In some embodiments, R^{BN2} is hydrogen.

[0087] In some embodiments of Formula (I), (Ia), or (Ib), each R^A 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11} (e.g., 1, 2, 3, 4 or 5 R^{11}). In some embodiments, each R^A 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, each R^A is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -SF_5, -SH, -SR^a, -NR^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, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, each R^A is independently halogen, -CN, -NO_2, -OH, amino, C_1-C_6alkyl, C_1-C_6alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}. In some embodiments, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl). In some embodiments, R^A is C_1-C_6alkyl. In some embodiments, R^A is C_1-C_6haloalkyl. In some embodiments, R^A is C_1-C_6hydroxyalkyl. In some embodiments, R^A is C_1-C_6aminoalkyl. In some embodiments, R^A is C_1-C_6heteroalkyl. In some embodiments, R^A is heterocycloalkyl. In some embodiments, R^A is C_1-C_6alkylene(cycloalkyl). In some embodiments, R^A is C_1-C_6alkylene(heterocycloalkyl). In some embodiments, R^A is C_1-C_6heteroalkylene(cycloalkyl). In some embodiments, R^A is C_1-C_6heteroalkylene(heterocycloalkyl). In some embodiments, two R^A on the same atom are taken together to form an oxo.

[0088] In some embodiments of Formula (I), (Ia), or (Ib), each R^B 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}. In some embodiments, each R^B is independently halogen, 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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12} (e.g., 1, 2, 3, 4 or 5 R^{12}). In some embodiments, R^B is halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, or $-OC(=O)NR^cR^d$. In some embodiments, R^B is halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments, R^B is C_1-C_6alkyl. In some embodiments, R^B is C_1-C_6haloalkyl. In some embodiments, R^B is C_1-C_6hydroxyalkyl. In some embodiments, R^B is C_1-C_6aminoalkyl. In some embodiments, R^B is C_1-C_6heteroalkyl. In some embodiments, R^B is C_2-C_6alkenyl. In some embodiments, R^B is C_2-C_6alkynyl. In some embodiments, two R^B on the same atom are taken together to form an oxo. In some embodiments, In some embodiments, two R^B on the same atom or adjacent atoms are taken together to form a cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}. In some embodiments, two R^B on the same atom are taken together to form a 3-5 membered cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}. In some embodiments, two R^B on the same atom are taken together to form a cycloalkyl. In some embodiments, two R^B on the same atom are taken together to form a heterocycloalkyl.

[0089] In some embodiments of Formula (Ia) or (Ib), B1 is $C(R^{B1})(R^{B2})$, each of X1 and X2 is C, A1 is CR^{A1}, A2 is NR^{AN2}, and A3 is N. In some embodiments of Formula (Ia) or (Ib), B1 is $C(R^{B1})(R^{B2})$, each of X1 and X2 is C, A1 is CR^{A1}, A2 is NR^{AN2}, and A3 is N, where each of R^{B1} and R^{B2} are is hydrogen, R^{A1} is hydrogen, and R^{AN2} is a cycloalkyl or a heterocycloalkyl optionally substituted with C_1-C_6alkyl and/or C_1-C_6haloalkyl.

[0090] In some embodiments of a compound of Formula (I), (Ia), or (Ib) 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, 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. In some embodiments, 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, or heteroaryl. In some embodiments, each R^a is independently C_1-C_6alkyl. In some embodiments, each R^a is independently C_1-C_6haloalkyl. In some embodiments, each R^a is independently C_1-C_6hydroxyalkyl. In some embodiments, each R^a is independently C_1-C_6aminoalkyl. In some embodiments, each R^a is independently C_1-C_6heteroalkyl. In some embodiments, each R^a is independently C_2-C_6alkenyl. In some embodiments, each R^a is independently C_2-C_6alkynyl. In some embodiments, each R^a is independently cycloalkyl. In some embodiments, each R^a is independently heterocycloalkyl.

[0091] In some embodiments of a compound of Formula (I), (Ia), or (Ib) 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, 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. In some embodiments, 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, or heterocycloalkyl. In some embodiments, R^b is hydrogen. In some embodiments, R^b is C_1-C_6alkyl. In some embodiments, R^b is C_1-C_6haloalkyl. In some embodiments, R^b is C_1-C_6hydroxyalkyl.

[0092] In some embodiments of a compound of Formula (I), (Ia), or (Ib) 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, 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. In some embodiments, R^c 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, R^c is hydrogen. In some embodiments, R^c is C_1-C_6heteroalkyl. In some embodiments, R^d 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, R^d is hydrogen. In some embodiments, R^d is C_1-C_6heteroalkyl. In some embodiments, 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.

[0093] In some embodiments of a compound of Formula (I), (Ia), or (Ib) disclosed herein, 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. In some embodiments, each R is independently halogen, -CN, -OH, -SH, $-NH_2$, $-C(=O)C_1$-C_3alkyl, C_1-C_3alkyl, or C_1-C_3alkoxy. In some embodiments R is halogen. In some embodiments, R is -CN. In some embodiments, R is -OH. In some embodiments, R is -SH. In some embodiments, R is $-NH_2$. In some embodiments, R is $-C(=O)C_1$-C_3alkyl. In some embodiments, R is C_1-C_3alkyl. In some embodiments, R is C_1-C_3alkoxy. In some embodiments, two R on the same atom form an oxo.

[0094] In some embodiments of a compound of Formula (I), (Ia), or (Ib) disclosed herein, 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, or heteroaryl, wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R. In some embodiments, R^{11} is halogen. In some embodiments, R^{11} is -CN. In some embodiments, R^{11} is $-NO_2$. In some embodiments, R^{11} is -OH. In some embodiments, R^{11} is $-OR^a$. In some embodiments, R^{11} is $-OC(=O)R^a$. In some embodiments, R^{11} is $-OC(=O)OR^b$. In some embodiments, R^{11} is $-OC(=O)NR^cR^d$. In some embodiments, R^{11} is $-SF_5$. In some embodiments, R^{11} is -SH. In some embodiments, R^{11} is $-SR^a$. In some embodiments, R^{11} is $-S(=O)R^a$. In some embodiments, R^{11} is $-S(=O)_2R^a$. In some embodiments, R^{11} is $-S(=O)_2NR^cR^d$. In some embodiments, R^{11} is $-S(=O)(=NR^b)R^b$. In some embodiments, R^{11} is $-NR^cR^d$. In some embodiments, R^{11} is $-NR^bC(=O)NR^cR^d$. In some embodiments, R^{11} is $-NR^bC(=O)R^a$. In some embodiments, R^{11} is $-NR^bC(=O)OR^b$. In some embodiments, R^{11} is $-NR^bS(=O)_2R^a$. In some embodiments, R^{11} is $-N=S(=O)(R^b)_2$. In some embodiments, R^{11} is $-C(=O)R^a$. In some embodiments, R^{11} is $-C(=O)OR^b$. In some embodiments, R^{11} is $-C(=O)NR^cR^d$. In some embodiments, R^{11} is $-P(=O)(R^b)_2$. In some embodiments, each R^{11} is independently C_1-C_6alkyl. In some embodiments, each R^{11} is independently C_1-C_6haloalkyl. In some embodiments, each R^{11} is independently C_1-C_6hydroxyalkyl. In some embodiments, each R^{11} is independently C_1-C_6aminoalkyl. In some embodiments, each R^{11} is independently C_1-C_6heteroalkyl. In some embodiments, each R^{11} is independently C_2-C_6alkenyl. In some embodiments, each R^{11} is independently C_2-C_6alkynyl.

[0095] In some embodiments of a compound of Formula (I), (Ia), or (Ib) disclosed herein, each R^{12} 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. In some embodiments, each R^{12} 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, or $-N(C_1$-C_3alkyl$)_2$. In some embodiments, each R^{12} is independently halogen. In some embodiments, each R^{12} is independently 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. In some embodiments, each R^{12} is independently C_1-C_3alkyl.

[0096] In some embodiments of a compound disclosed herein, one or more of R, R^1, R^2, R^3, R^4, R^{11}, R^{12}, R^A, R^B, R^{A1}, R^{A2}, R^{A3}, R^{AN1}, R^{AN2}, R^{AN3}, R^{B1}, R^{B2}, R^{B3} R^{B4}, R^{BN1}, R^{BN2} R^a, R^b, R^c, and R^d groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[0097] In some embodiments of a compound disclosed herein, one or more ^1H 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^{11}, R^{12}, R^A, R^B, R^{A1}, R^{A2}, R^{A3}, R^{AN1}, R^{AN2}, R^{AN3}, R^{B1}, R^{B2}, R^{B3} R^{B4}, R^{BN1}, R^{BN2} R^a, R^b, R^c, and R^d.

[0098] 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^{11}, R^{12}, R^A, R^B, R^{A1}, R^{A2}, R^{A3}, R^{AN1}, R^{AN2}, R^{AN3}, R^{B1}, R^{B2}, R^{B3} R^{B4}, R^{BN1}, R^{BN2} R^a, R^b,

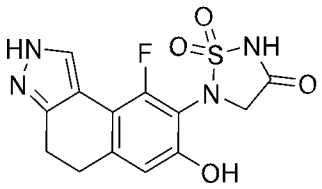
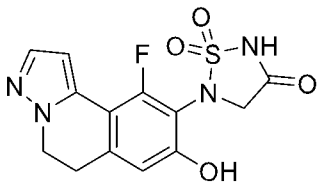
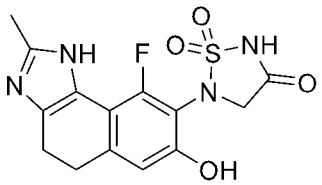
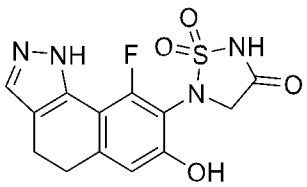
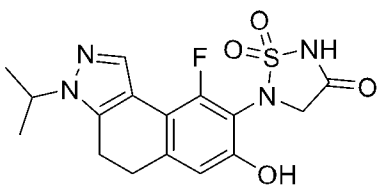
R^c, and R^d is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

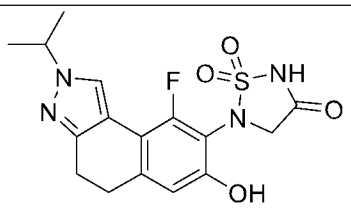
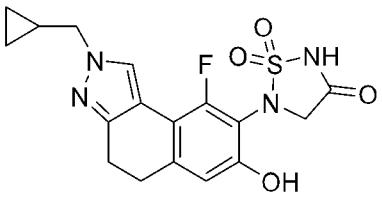
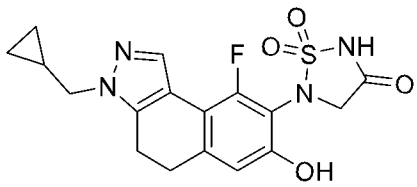
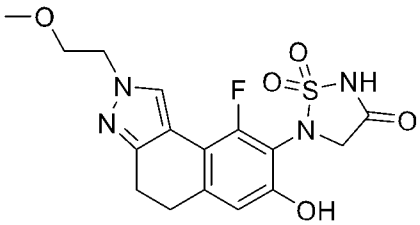
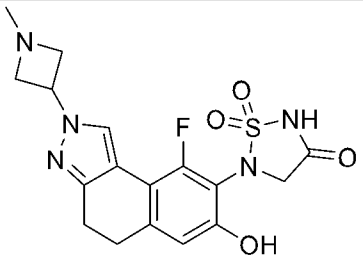
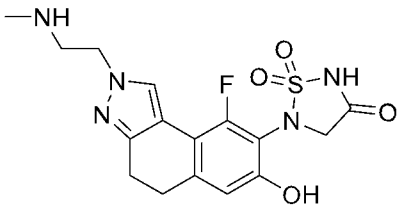
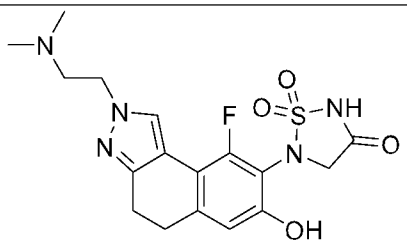
[0099] In some embodiments of a compound disclosed herein, one or more ^1H of Ring A or Ring B are replaced with one or more deuteriums.

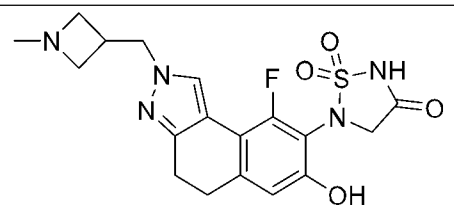
[00100] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00101] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 1.

TABLE 1

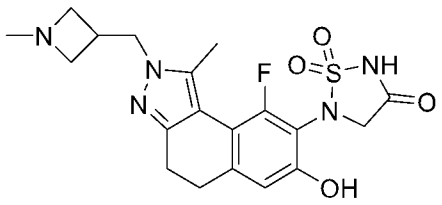
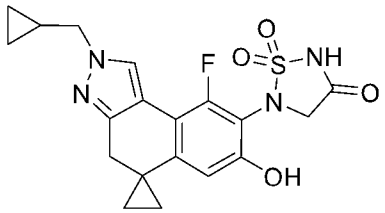
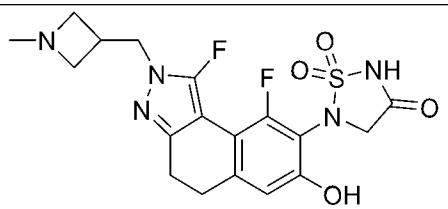
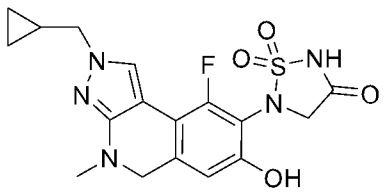
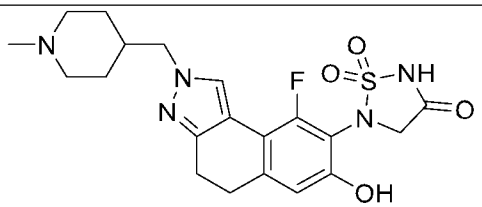
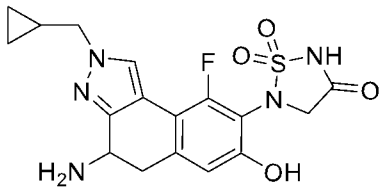
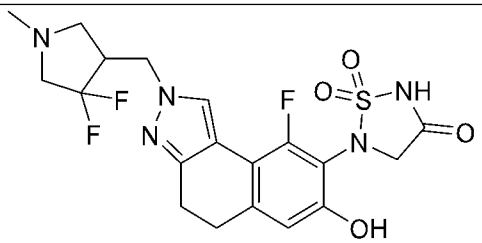
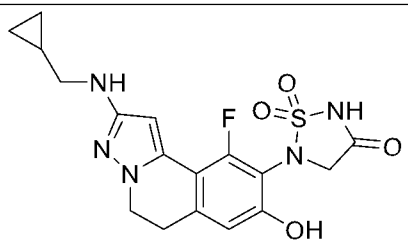
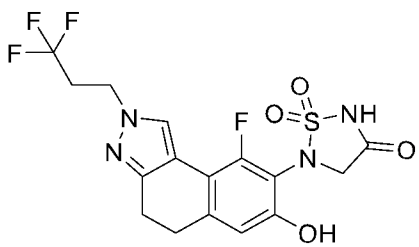
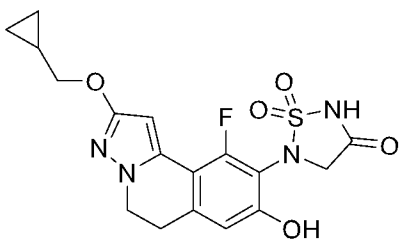
Ex.	Structure
1	
2	
3	
4	
5	

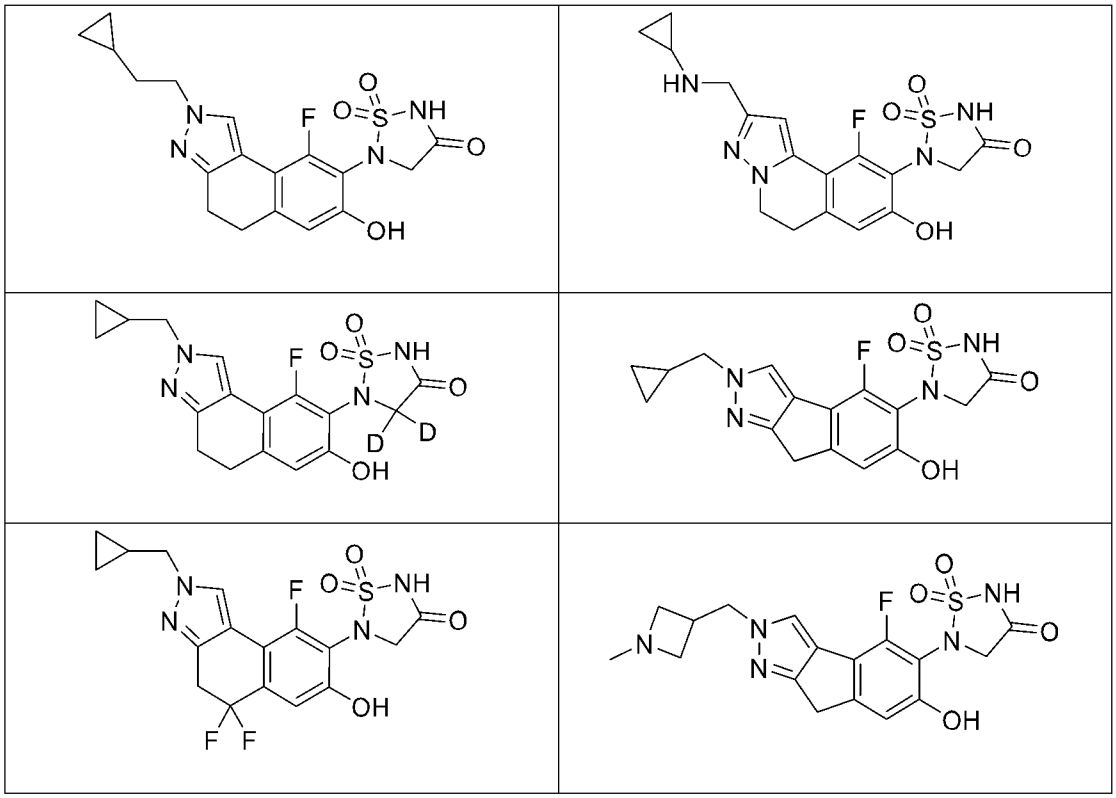
6	
7	
8	
9	
10	
11	
12	

13	

[00102] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 2.

TABLE 2

Structure	Structure
	
	
	
	
	



Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00103] 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

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

Solvates

[00114] In some embodiments, the compounds described herein exist as solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering the compounds in the form of such solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering a composition comprising the compounds in the form of such solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents.

Tautomers

[00115] 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

[00116] Disclosed herein are methods of modulating the activity of a protein phosphatase enzyme such as by contacting the enzyme with an effective amount of a PTPN1/2 inhibitor described herein, or a pharmaceutically acceptable salt thereof, or a composition thereof.

[00117] Also disclosed herein is a method of treating a disease or disorder, comprising administering to a subject in need thereof a compound described herein (e.g., compounds of Formula (I), (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein. The disease or disorder can be associated with protein tyrosine phosphatase enzyme. The disease or disorder can be cancer. The disease or disorder can be a metabolic disorder (e.g., diabetes).

[00118] 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 thereof, or a pharmaceutical composition comprising a compound of the disclosure to the subject in need thereof.

[00119] Also disclosed herein is a method of treating a cancer responsive to inhibition of PTPN1/2 activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00120] 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 thereof, to the subject in need thereof, where the subject may have a disease or disorder.

[00121] Also disclosed herein is a method of inhibiting a protein tyrosine phosphatase enzyme, the method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. Also disclosed herein is a method of modulating a protein tyrosine phosphatase enzyme, the method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the subject has a disease or disorder.

[00122] Also disclosed herein is a method for treating a disease or disorder associated with PTPN1/2 activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00123] In some embodiments, the disease or disorder is cancer.

[00124] In some embodiments, the cancer is selected from bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, prostate cancer, marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). In some embodiments, the cancer is melanoma.

[00125] In some embodiments, the disease or disorder is a metabolic disease.

[00126] In some embodiments, the metabolic disease is selected from non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, metabolic syndrome, phenylketonuria, proliferative retinopathy, and Kearns-Sayre disease. In some embodiments, diabetes may be Type 1 diabetes. In some embodiments, diabetes may be Type 2 diabetes. In some embodiments, diabetes may be gestational diabetes.

Dosing

[00127] 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.

Pharmaceutical Compositions/Formulations

[00128] 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.

[00129] 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

[00130] 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.

[00131] 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.

[00132] **Abbreviations** used herein are as follows:

ACN: acetonitrile

BrettPhos: dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine

BrettPhos Pd G3: methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)

DCM: dichloromethane

DIPEA: *N*, *N*-diisopropyl ethyl amine

DMF: *N*,*N*-dimethylformamide

DMSO: Dimethyl sulfoxide

EA: ethyl acetate

IC_{50}: half inhibition concentration

i-PrOH: isopropyl alcohol

MS: mass spectrometry

NaH: sodium hydride

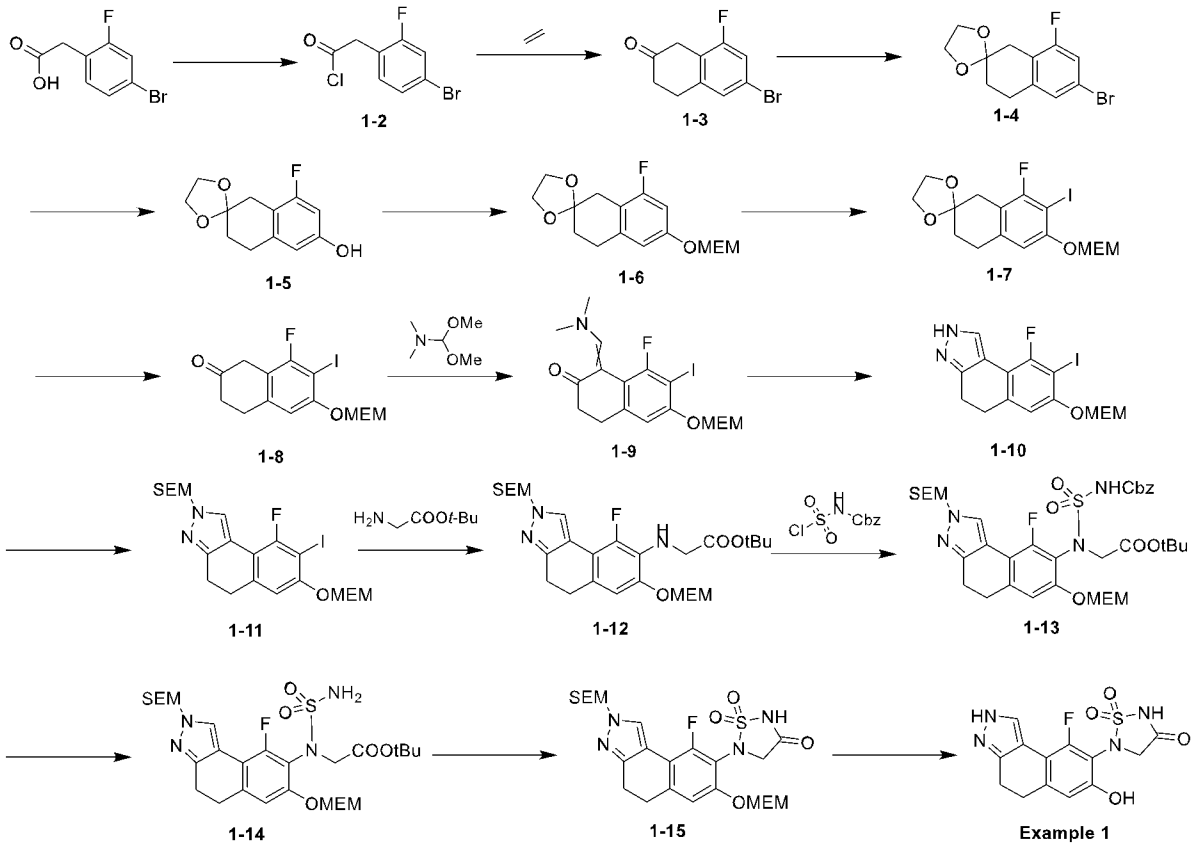
NH_4Cl: ammonium chloride

t-BuBrettPhos Pd G3: methanesulfonato(2-di-t-butylphosphino-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)

TFA: trifluoroacetic acid

THF: tetrahydrofuran

Example 1: Preparation of 5-(9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



Step 1: Preparation of Compound 1-2

[00133] To a solution of 2-(4-bromo-2-fluorophenyl)acetic acid (50.0 g, 215 mmol) in dichloromethane (DCM) (500 mL) and N,N-dimethylformamide (DMF) (3.31 mL, 42.9 mmol) was added oxalyl chloride (36.3 mL, 429 mmol) dropwise at 0℃. The resulting mixture was stirred at 25℃ for 16 hours. The resulting mixture was concentrated under reduced pressure to afford **Compound 1-2** (54.0 g, crude) which was used for next step without further purification.

Step 2: Preparation of Compound 1-3

[00134] To a solution of **Compound 1-2** (37.8 g, 150 mmol) in DCM (500 mL) was added dry aluminium chloride (60.1 g, 451 mmol). The mixture was stirred at 25℃ under nitrogen atmosphere for 15 minutes. Then ethylene was bubbled into the reaction mixture and the mixture was stirred at 25℃ for 7 hours. The resulting mixture was quenched with ice-water (500 mL) and extracted with ethylacetate

(EA) (200 mL ×3). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford 6-bromo-8-fluoro-3,4-dihydronaphthalen-2(1H)-one (30.4 g, 58% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.14 (dd, J = 8.8, 1.6 Hz, 1H), 3.51 (s, 2H), 3.06 (t, J = 6.4 Hz, 2H), 2.58 (t, J = 6.4 Hz, 2H)

Step 3: Preparation of Compound 1-4

[00135] To a solution of **Compound 1-3** (36.6 g, 151 mmol) in toluene (300 mL) were added ethylene glycol (10.1 mL, 181 mmol) and *p*-toluenesulfonic acid (5.19 g, 30.1 mmol). The reaction mixture was stirred at 110℃ for 16 hours. The resulting mixture was cooled down, diluted with ice-water (500 mL), and extracted with EA (200 mL ×3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressured to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-4** (25.8 g, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 7.03 (dd, J = 8.8, 1.6 Hz, 1H), 4.09 - 3.99 (m, 4H), 2.98 (t, J = 6.8 Hz, 2H), 2.85 (s, 2H), 1.92 (t, J = 6.8 Hz, 2H).

Step 4: Preparation of Compound 1-5

[00136] To a solution of **Compound 1-4** (24.0 g, 83.6 mmol) in DMF (350 mL) and water (3 mL), *t*-BuBrettPhos Pd G3 (1.79 g, 2.09 mmol) and cesium carbonate (Cs_2CO_3) (54.5 g, 167 mmol) were added. The reaction mixture was stirred at 80℃ for 16 hours under nitrogen atmosphere. The reaction mixture was cooled down, diluted with ice-water (500 mL), and extracted with EA (200 mL ×3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-5** (16.3 g, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 6.45 - 6.26 (m, 2H), 4.01 - 3.87 (m, 4H), 2.80 (t, J = 6.8 Hz, 2H), 2.67 (s, 2H), 1.80 (t, J = 6.8 Hz, 2H).

Step 5: Preparation of Compound 1-6

[00137] To a stirring mixture of **Compound 1-5** (13.9 g, 62.0 mmol) in tetrahydrofuran (THF) (150 mL) was added sodium hydride (NaH) (4.96 g, 124 mmol, 60% wt. in mineral oil) at 0℃. The reaction mixture was stirred at 0℃ for 30 minutes, then 2-methoxyethoxymethyl chloride (11.6 g, 93.0 mmol) was added. The reaction mixture was stirred at 25℃ for 16 hours. The resulting mixture was quenched with ice-water (300 mL) and extracted with EA (100 mL ×3). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified by silica gel chromatography to afford **Compound 1-6** (13.3 g, 78% yield). LCMS: 237.0 $[M-(OCH_2CH_2OCH_3)]^+$.

Step 6: Preparation of Compound 1-7

[00138] To a solution of 2,2,6,6-tetramethylpiperidine (8.56 g, 60.6 mmol) in THF (70 mL) was added dropwise *n*-BuLi (22.0 mL, 2.5 M) at −70℃. The mixture was stirred at −70℃ for 1 hour. Then a solution of **Compound 1-6** (8.60 g, 27.5 mmol) in THF (10 mL) was added dropwise at −70℃. The mixture was stirred at −70℃ for 1 hour. The solution of iodine (12.6 g, 49.6 mmol) in THF (10 mL) was added dropwise at −70℃. The reaction mixture was stirred at 25℃ for 3 hours. The resulting mixture

was quenched with aqueous $Na_2S_2O_3$ solution and extracted with EA (30 mL ×3). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified by silica gel chromatography to afford **Compound 1-7** (13.3 g, 78% yield). LCMS: 363.0 $[M-(OCH_2CH_2OCH_3)]^+$.

Step 7: Preparation of Compound 1-8

[00139] To a solution of **Compound 1-7** (5.0 g, 11.4 mmol) in methanol (MeOH) (5 mL) was added formic acid (15 mL) and water (2.5 mL). The reaction mixture was stirred at 25℃ for 4 hours. The resulting mixture was concentrated under reduced pressure to give the crude residue. The residue was lyophilized to afford **Compound 1-8** (3.80 g, 84% yield) which was used directly for next step reaction without further purification. LCMS: 417.0 $[M+Na]^+$.

Step 8: Preparation of Compound 1-9

[00140] The mixture of **Compound 1-8** (3.80 g, 9.64 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (11.5 g, 96.4 mmol) was stirred at 25℃ for 1 hour. The resulting mixture was concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-9** (3.30 g, 75% yield). LCMS: 450.0 $[M+H]^+$.

Step 9: Preparation of Compound 1-10

[00141] To a solution of **Compound 1-9** (3.30 g, 7.34 mmol) in MeOH (50 mL) was added hydrazinium hydroxide (0.92 g, 80% wt. in water). The reaction mixture was stirred at 25℃ for 16 hours. The resulting mixture was concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-10** (2.60 g, 85% yield). LCMS: 419.0 $[M+H]^+$.

Step 10: Preparation of Compound 1-11

[00142] To a solution of **Compound 1-10** (2.60 g, 6.21 mmol) in THF (50 mL) was added NaH (0.5 g, 12.5 mmol, 60% wt. in mineral oil) at 0℃. The mixture was stirred at 0℃ for half hour, then 2-(trimethylsilyl)ethoxymethyl chloride (1.30 g, 8.08 mmol) was added. The reaction was stirred at 25℃ for 2 hours. The resulting mixture was quenched with saturated ammonium chloride (NH_4Cl) aqueous solution (100 mL), and the aqueous layer was extracted with EA (100 mL ×3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-11** (3.3 g, 97% yield). LCMS: 549.0 $[M+H]^+$.

Step 11: Preparation of Compound 1-12

The mixture of *tert*-butyl glycinate (167 mg, 1.27 mmol), BrettPhos Pd G3 (165 mg, 0.18 mmol), BrettPhos (146 mg, 0.27 mmol) and Cs_2CO_3 (891 mg, 2.73 mmol) was added to the solution of **Compound 1-11** (500 mg, 0.91 mmol) in toluene (10 mL). The reaction mixture was stirred at 100℃ for 16 hours under nitrogen atmosphere. The resulting mixture was cooled down and diluted with ice-water (20 mL). The mixture was extracted with EA (10 mL ×3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-12** (330 mg, 66% yield). LCMS: 552.0 $[M+H]^+$.

Step 12: Preparation of Compound 1-13

[00143] To a solution of **Compound 1-12** (110 mg, 0.20 mmol) in DCM (10 mL) was added benzyl (chlorosulfonyl)carbamate (74.8 mg, 0.23 mmol) and DIEA (77.3 mg, 0.60 mmol). The reaction mixture was stirred at 25℃ for 1 hour. The resulting mixture was diluted with ice-water (10 mL), and the aqueous layer was extracted with DCM (10 mL ×3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-13** (110 mg, 72% yield). LCMS: 765.2 $[M+H]^+$.

Step 13: Preparation of Compound 1-14

[00144] To a solution of **Compound 1-13** (180 mg, 0.24 mmol) in isopropanol (*i*-PrOH) (5 mL) and DCM (1 mL) was added palladium on carbon (Pd/C) (20 mg, 10% wt., 55% H_2O). The reaction mixture was stirred at 25℃ for 16 hours under hydrogen atmosphere. The resulting mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford **Compound 1-14** (120 mg, 81% yield) which was used directly for next step reaction without further purification. LCMS: 631.4 $[M+H]^+$.

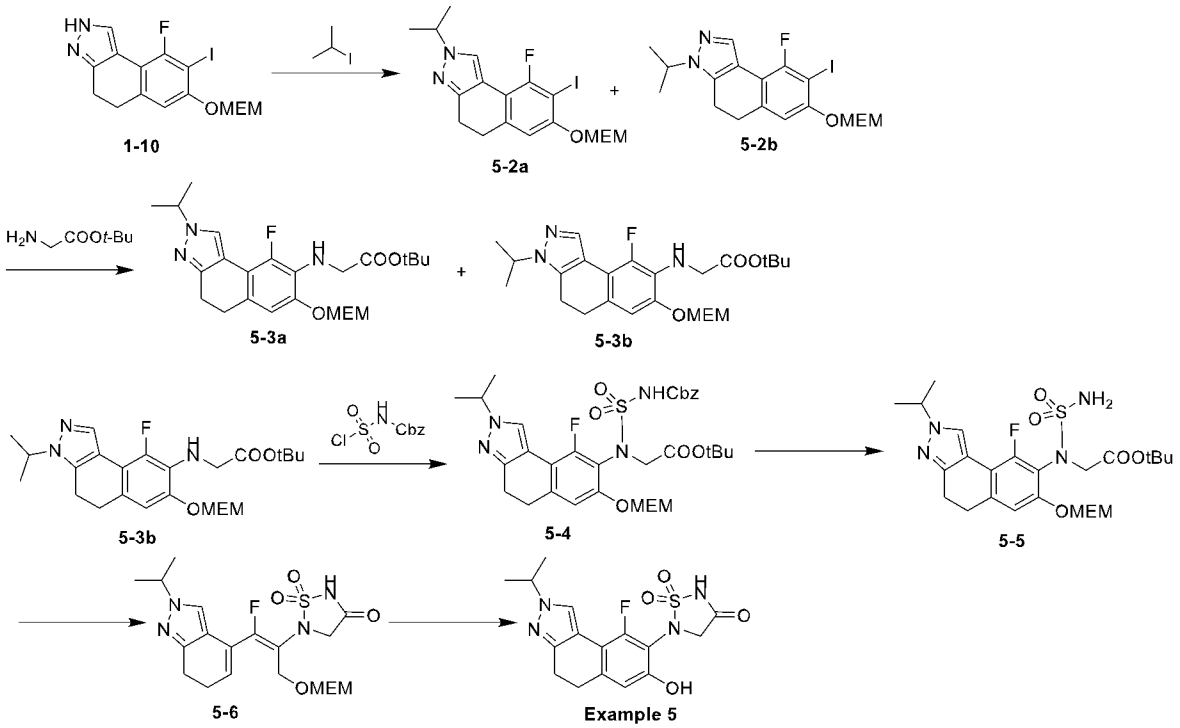
Step 14: Preparation of Compound 1-15

[00145] To a solution of **Compound 1-14** (120 mg, 0.19 mmol) in MeOH (3 mL) was added sodium methoxide (NaOMe) (0.18 mL, 5.4 M in MeOH). The reaction mixture was stirred at 25℃ for 3 hours. The resulting mixture was quenched with saturated NH_4Cl aqueous solution (2 mL). The layers were separated and the organic layer was concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 1-15** (80 mg, 76% yield). LCMS: 557.2 $[M+H]^+$.

Step 15: Preparation of 5-(9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 1)

[00146] The solution of **Compound 1-15** (80.0 mg, 0.14 mmol) in DCM (1 mL) and trifluoroacetic acid (TFA) (1 mL) was stirred at 25℃ for 4 hours. The resulting mixture was concentrated under reduced pressure to give the crude residue. The residue was purified with prep-HPLC to afford **5-(9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 1)** (28.3 mg, 44% yield). LCMS: 339.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.77 (d, J = 3.2 Hz, 1H), 6.67 (s, 1H), 4.34 (s, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H).

Example 5: Preparation of 5-(9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



[00147] Step 1: Preparation of Compound 5-2a and Compound 5-2b

To a mixture of **Compound 1-10** (430 mg, 1.02 mmol) and Cs_2CO_3 (1005 mg, 3.08 mmol) in DMF (5 mL) was added 2-iodopropane (210 mg, 1.23 mmol). The reaction was stirred at 25℃ for 4 hours. The resulting mixture was quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted with EA (25 mL ×3). The organic layer was washed with brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford a mixture of **Compound 5-2a** and **Compound 5-2b** (375 mg, 78% yield). LCMS: 461.0 $[M+H]^+$.

[00148] Step 2: Preparation of Compound 5-3a and Compound 5-3b

The mixture of *tert*-butyl glycinate (159 mg, 1.21 mmol), BrettPhos Pd G3 (158 mg, 0.17 mmol), BrettPhos (140 mg, 0.26 mmol) and Cs_2CO_3 (850 mg, 2.60 mmol) was added to the solution of **Compound 5-2a** and **Compound 5-2b** (400 mg, 0.86 mmol) in toluene (10 mL). The reaction mixture was stirred at 100℃ for 16 hours under nitrogen atmosphere. The resulting mixture was cooled down and diluted with ice-water (20 mL). The mixture was extracted with EA (10 mL ×3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified with prep-HPLC to afford **Compound 5-3a** (177 mg, 44% yield) and **Compound 5-3b** (124 mg, 31% yield). LCMS: 464.2 $[M+H]^+$.

[00149] Step 3: Preparation of Compound 5-4

To the solution of **Compound 5-3a** (230 mg, 0.49 mmol) in DCM (10 mL) was added benzyl (chlorosulfonyl)carbamate (185 mg, 0.74 mmol) and DIEA (192 mg, 1.49 mmol). The reaction mixture was stirred at 25℃ for 1 hour. The resulting mixture was diluted with ice-water (10 mL) and extracted with DCM (10 mL ×3). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue. The residue was

purified with silica gel chromatography to afford **Compound 5-4** (180 mg, 53% yield). LCMS: 677.2 $[M+H]^+$.

[00150] Step 4: Preparation of Compound 5-5

To a solution of **Compound 5-4** (180 mg, 0.26 mmol) in *i*-PrOH (5 mL) and DCM (1 mL) was added Pd/C (20 mg, 10% wt., 55% H_2O). The reaction mixture was stirred at 25℃ for 16 hours under hydrogen atmosphere. The resulting mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford **Compound 5-5** (120 mg, 85% yield) which was used for next step without further purification. LCMS: 543.0 $[M+H]^+$.

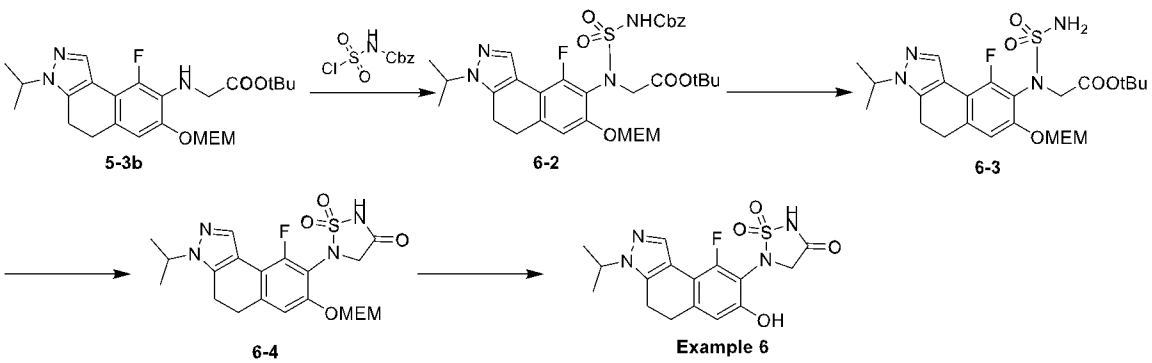
[00151] Step 5: Preparation of Compound 5-6

To the solution of **Compound 5-5** (120 mg, 0.22 mmol) in MeOH (3 mL) was added NaOMe (0.18 mL, 5.4 M in MeOH). The reaction mixture was stirred at 25℃ for 3 hours. The resulting mixture was quenched with saturated NH_4Cl aqueous solution (2 mL) and concentrated under reduced pressure to give the crude residue. The residue was purified with silica gel chromatography to afford **Compound 5-6** (90.0 mg, 87% yield). LCMS: 469.2 $[M+H]^+$.

[00152] Step 6: Preparation of 5-(9-fluoro-7-hydroxy-2-isopropyl-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Compound 5)

The solution of **Compound 5-6** (90.0 mg, 0.19 mmol) in DCM (1 mL) and TFA (1 mL) was stirred at 25℃ for 4 hours. The resulting mixture was concentrated under reduced pressure to give the crude residue. The residue was purified by prep-HPLC to afford **5-(9-fluoro-7-hydroxy-2-isopropyl-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Compound 5)** (6.30 mg, 8.7% yield). LCMS: 381.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 2.8 Hz, 1H), 6.67 (s, 1H), 4.57 - 4.47 (m, 1H), 4.29 (s, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 1.50 (d, J = 6.8 Hz, 6H).

Example 6: Preparation of 5-(9-fluoro-7-hydroxy-3-isopropyl-4,5-dihydro-3*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

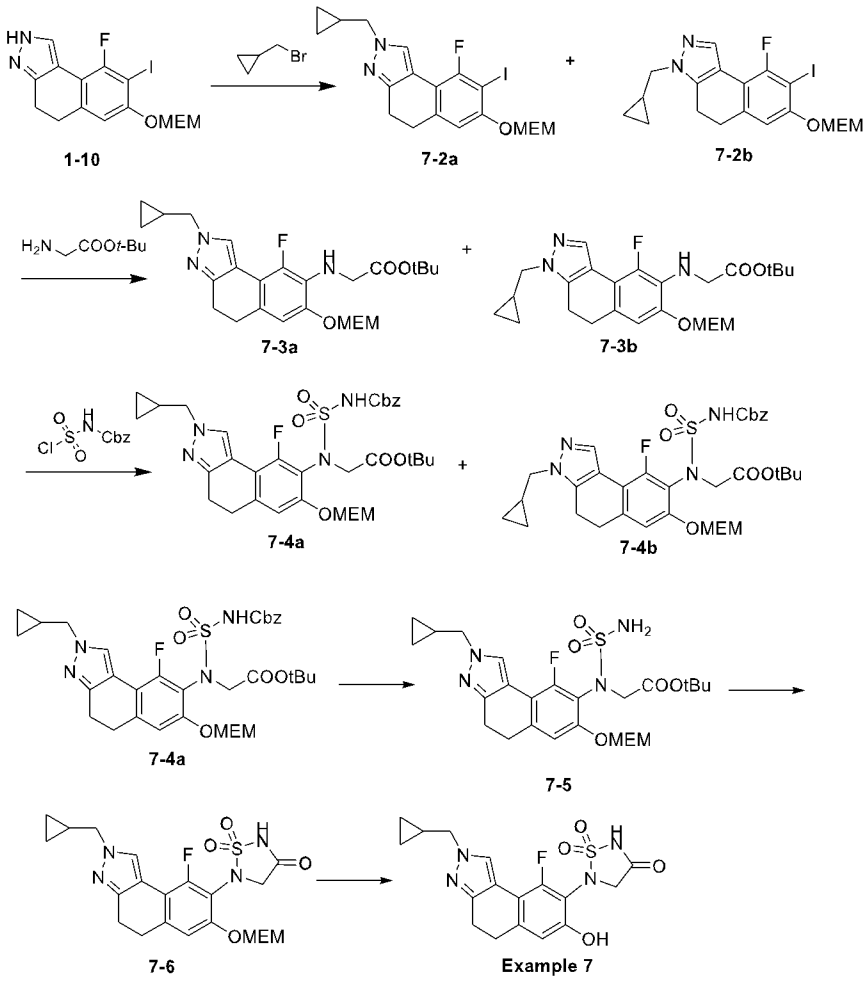


[00153] Step 1: Preparation of 5-(9-fluoro-7-hydroxy-3-isopropyl-4,5-dihydro-3*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 6)

The title compound was prepared in analogy to the preparation of **Example 5** by using **Compound 5-3b** instead of **Compound 5-3a**. **Example 6** (6.4 mg, 14% yield) was obtained. LCMS: 381.4 $[M+H]^+$. ^1H

NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 3.2 Hz, 1H), 6.67 (s, 1H), 4.62 - 4.55 (m, 1H), 4.31 (s, 2H), 3.04 - 2.95 (m, 2H), 2.95 - 2.85 (m, 2H), 1.48 (d, J = 6.8 Hz, 6H).

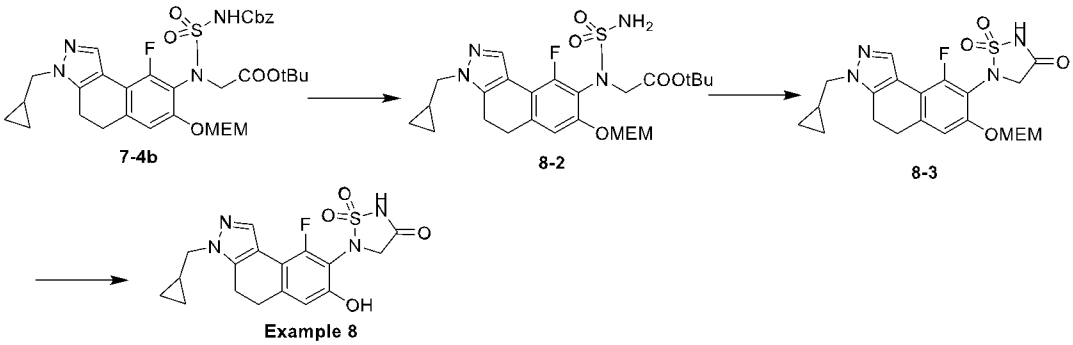
Example 7: Preparation of 5-(9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



[00154] Step 1: Preparation of 5-(2-(cyclopropylmethyl)-9-fluoro-7-hydroxy-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 7)

The title compound was prepared in analogy to the preparation of **Example 5** by using (bromomethyl)cyclopropane instead of 2-iodopropane. **Example 7** (16.1 mg, 21% yield) was obtained. LCMS: 393.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 2.8 Hz, 1H), 6.67 (s, 1H), 4.31 (s, 2H), 3.97 (d, J = 7.2 Hz, 2H), 2.98 - 2.94 (m, 2H), 2.85 - 2.82 (m, 2H), 1.36 - 1.24 (m, 1H), 0.65 - 0.56 (m, 2H), 0.45 - 0.36 (m, 2H).

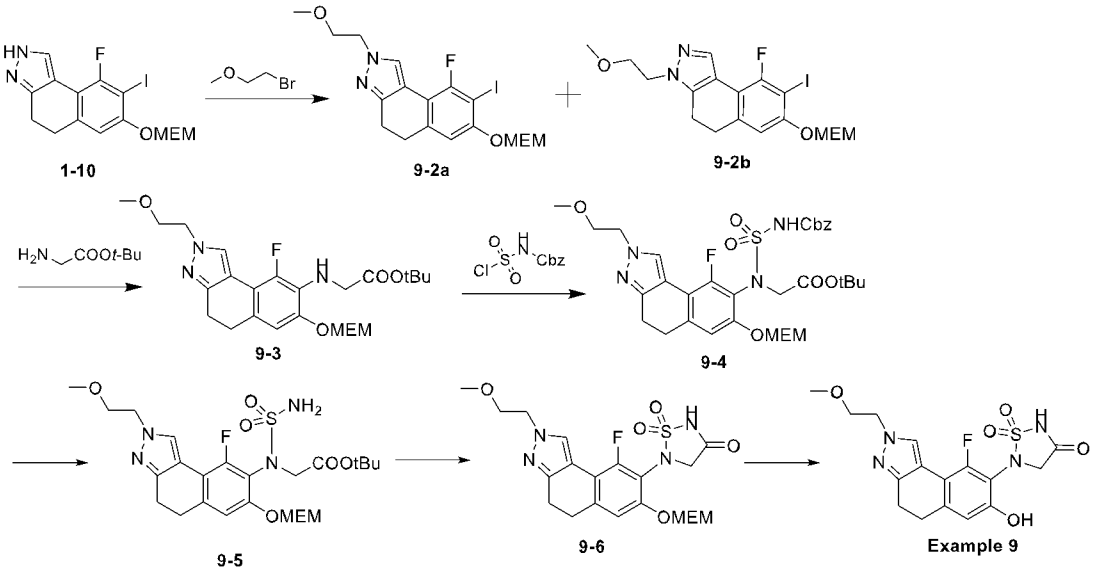
Example 8: Preparation of 5-(3-(cyclopropylmethyl)-9-fluoro-7-hydroxy-4,5-dihydro-3*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



[00155] Step 1: Preparation of 5-(3-(cyclopropylmethyl)-9-fluoro-7-hydroxy-4,5-dihydro-3*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 8)

The title compound was prepared in analogy to the preparation of **Example 5** by using **Compound 7-4b** instead of **Compound 5-4**. **Example 8** (7.47 mg, 13% yield) was obtained. LCMS: 393.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 3.2 Hz, 1H), 6.68 (s, 1H), 4.30 (s, 2H), 4.00 (d, J = 6.8 Hz, 2H), 3.03 - 2.95 (m, 2H), 2.93 - 2.87 (m, 2H), 1.31 - 1.18 (m, 1H), 0.62 - 0.53 (m, 2H), 0.40 - 0.36 (m, 2H).

Example 9: Preparation of 5-(9-fluoro-7-hydroxy-2-(2-methoxyethyl)-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



[00156] Step 1: Preparation of 5-(9-fluoro-7-hydroxy-2-(2-methoxyethyl)-4,5-dihydro-2*H*-benzo[*e*]indazol-8-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Example 9)

The title compound was prepared in analogy to the preparation of **Example 5** by using 1-bromo-2-methoxyethane instead of 2-iodopropane. **Example 9** (22.7 mg, 33% yield) was obtained. LCMS: 397.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.79 (d, J = 3.2 Hz, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 6.62 (s, 1H), 4.23 (t, J = 5.6 Hz, 2H), 4.00 (s, 2H), 3.68 (t, J = 5.6 Hz, 2H), 3.24 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H).

[00157] Example 100: PTPN2 Enzymatic assay

For PTPN2 inhibition assay using 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) as a substrate, 5 μL PTPN2 solution (diluted to 0.2 nM in reaction buffer: 50 mM Tris-HCl, pH 7.2, 50 mM NaCl, 0.01% Triton X-100, 1 mM DTT) was incubated with compounds or dimethylsulfoxide (DMSO) (0.5% v/v) for 10 minutes at room temperature in 384 well plate. Reactions were initiated by the addition of 5 μL DiFMUP (10 μM), and the fluorescence (excitation at 360 nm, emission at 460 nm) of the resulting solutions was measured on CLARIO Star Plusacu microplate reader (BMG) after 30 min incubation at room temperature. The experiment is carried out in duplicate. The value for the low control (DMSO and buffer) was set to 100% inhibition, and the value for high control (DMSO and PTPN2) was set to 0% inhibition. The % inhibition was calculated by 100*(average high control - compound well) / (average high control - average low control). IC_{50} values were determined from non-linear regression equation fitting by XLfit.

[00158] The results are found in Table 3.

TABLE 3

Ex. No.	Binding Activity IC_{50}
1	A
5	A
6	A
7	A
8	A
9	A

$0 < A \leq 20$ nM; 20 nM $< B \leq 50$ nM; 50 nM $< C \leq 500$ nM; 500 nM $< D \leq 1000$ nM ; $E > 1000$ nM

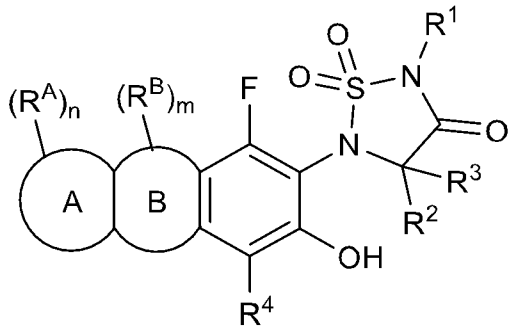
NT: not tested

[00159] 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 thereof:



Formula (I),

wherein:

Ring A is heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^A 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

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

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

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

Ring B is 5, 6 or 7 membered cycloalkyl or heterocycloalkyl;

each R^B 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12};

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

or two R^B on the same atom or adjacent atoms are taken together to form a cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12};

each R^{12} 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;

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

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^2 is hydrogen, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^3 is hydrogen, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

R^4 is hydrogen, halogen, -OH, -CN, $-NO_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, or C_2-C_6alkynyl;

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;

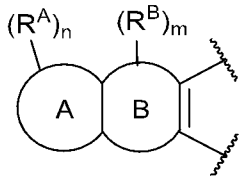
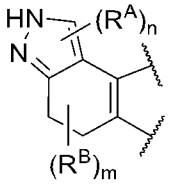
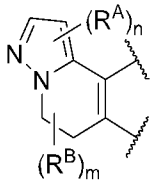
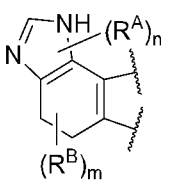
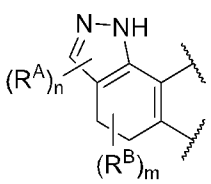
or two R on the same atom form an oxo.

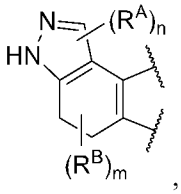
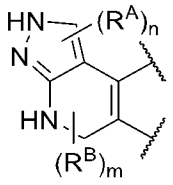
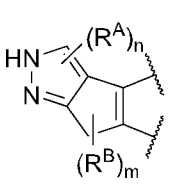
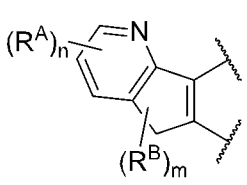
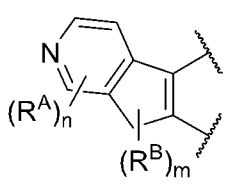
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is heteroaryl.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is a 6-membered heteroaryl.
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyridine, pyrimidine, or pyrazine.
5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is a 5-membered heteroaryl.
6. The compound of any one of claims 1, 2, or 5, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyrrole, pyrazole, imidazole, triazole, oxazole, or thiazole.
7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein Ring B is 5 or 6 membered cycloalkyl or heterocycloalkyl.
8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein Ring B is 6 membered cycloalkyl.
9. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein Ring B is 6 membered heterocycloalkyl containing 1-2 ring nitrogen atoms.
10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.
11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen or C_1-C_3alkyl.
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.
13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the hydrogen is deuterium.
14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or C_1-C_3alkyl.
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.
16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein the hydrogen is deuterium.
17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

19. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof,

wherein  is  ,  ,  ,  ,

 ,  ,  ,  , or  .

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

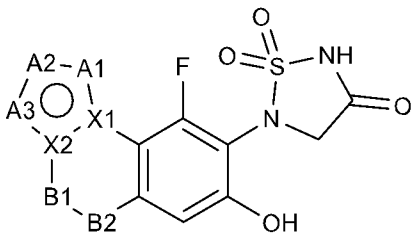
22. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein n is 1.

23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2.

24. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein m is 0.

25. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2.

26. The compound of any one of claims 1, 2, 5 to 18, or 20 to 25, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure of Formula (Ia),



Formula (Ia)

wherein,

A1 is CR^{A1}, N, or NR^{AN1};

A2 is O, S, CR^{A2}, N, or NR^{AN2};

A3 is O, S, CR^{A3}, N, or NR^{AN3};

each of R^{A1}, R^{A2}, and R^{A3} is independently hydrogen or R^A;

each of R^{AN1}, R^{AN2}, and R^{AN3} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, -

$NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

X1 is C or N;

X2 is C or N;

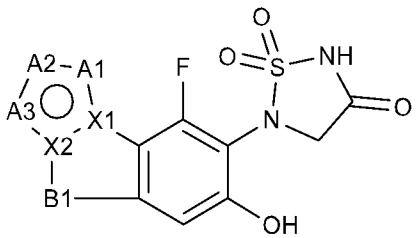
B1 is $C(R^{B1})(R^{B2})$ or NR^{BN1};

B2 is $C(R^{B3})(R^{B4})$ or NR^{BN2};

each of R^{B1}, R^{B2}, R^{B3} and R^{B4} is independently hydrogen or R^B; and

each of R^{BN1} and R^{BN2} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

27. The compound of any one of claims 1, 2, 5 to 7, 10 to 18, or 20 to 25, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure of Formula (Ib),



Formula (Ib)

wherein,

A1 is CR^{A1}, N, or NR^{AN1};

A2 is O, S, CR^{A2}, N, or NR^{AN2};

A3 is O, S, CR^{A3}, N, or NR^{AN3};

each of R^{A1}, R^{A2}, and R^{A3} is independently hydrogen or R^A;

each of R^{AN1}, R^{AN2}, and R^{AN3} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11};

X1 is C or N;

X2 is C or N;

B1 is $C(R^{B1})(R^{B2})$ or NR^{BN1};

each of R^{B1} and R^{B2} is independently hydrogen or R^B; and

R^{BN1} is independently hydrogen, -CN, $-NO_2$, $-OC(=O)R^a$, $-OC(=O)NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-N=S(=O)(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-P(=O)(R^b)_2$, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

28. The compound of claim 26 or 27, or a pharmaceutically acceptable salt thereof, wherein A1 is CR^{A1}.

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R^{A1} is hydrogen.

30. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R^{A1} is R^A.

31. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R^{A1} is hydrogen, halogen, 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, or heterocycloalkyl.

32. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R^{A1} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

33. The compound of claim 26 or 27, or a pharmaceutically acceptable salt thereof, wherein A1 is NR^{AN1}.

34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein R^{AN1} 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, or heterocycloalkyl.

35. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein R^{AN1} is hydrogen or C_1-C_3alkyl.

36. The compound of any one of claims 26 to 35, or a pharmaceutically acceptable salt thereof, wherein A2 is O or S.

37. The compound of any one of claims 26 to 35, or a pharmaceutically acceptable salt thereof, wherein A2 is N.

38. The compound of any one of claims 26 to 35, or a pharmaceutically acceptable salt thereof, wherein A2 is CR^{A2}.

39. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein R^{A2} is hydrogen.

40. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein R^{A2} is R^{A}.

41. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein R^{A2} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-SF_5$, -SH, $-SR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}.

42. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein R^{A2} is cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein the alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

43. The compound of any one of claims 26 to 35, or a pharmaceutically acceptable salt thereof, wherein A2 is NR^{AN2}.

44. The compound of claim 43, or a pharmaceutically acceptable salt thereof, wherein R^{AN2} 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}.

45. The compound of claim 43, or a pharmaceutically acceptable salt thereof, wherein R^{AN2} is 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), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

46. The compound of any one of claims 26 to 45, or a pharmaceutically acceptable salt thereof, wherein A3 is O or S.

47. The compound of any one of claims 26 to 45, or a pharmaceutically acceptable salt thereof, wherein A3 is N.

48. The compound of any one of claims 26 to 45, or a pharmaceutically acceptable salt thereof, wherein A3 is CR^{A3}.

49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{A3} is hydrogen.

50. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{A3} is R^{A}.

51. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{A3} is hydrogen, halogen, 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, or heterocycloalkyl.

52. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{A3} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

53. The compound of any one of claims 26 to 45, or a pharmaceutically acceptable salt thereof, wherein A3 is NR^{AN3}.

54. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{AN3} 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_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently optionally substituted with one or more R^{11}.

55. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{AN3} is 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), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

56. The compound of any one of claims 26 to 55, or a pharmaceutically acceptable salt thereof, wherein X1 is C.

57. The compound of any one of claims 26 to 55, or a pharmaceutically acceptable salt thereof, wherein X1 is N.

58. The compound of any one of claims 26 to 57, or a pharmaceutically acceptable salt thereof, wherein X2 is C.

59. The compound of any one of claims 26 to 57, or a pharmaceutically acceptable salt thereof, wherein X2 is N.

60. The compound of any one of claims 26 to 59, or a pharmaceutically acceptable salt thereof, wherein B1 is $C(R^{B1})(R^{B2})$.

61. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{B1} and R^{B2} are taken together to form an oxo.

62. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{B1} and R^{B2} are taken together to form a cycloalkyl (e.g., cyclopropyl) or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}.

63. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{B1} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

64. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{B1} is hydrogen.

65. The compound of any one of claims 60, 63 or 64, or a pharmaceutically acceptable salt thereof, wherein R^{B2} is hydrogen, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

66. The compound of any one of claims 60, 63 or 64, or a pharmaceutically acceptable salt thereof, wherein R^{B2} is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -SF_5, -SH, -SR^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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}.

67. The compound of any one of claims 60, 63 or 64, or a pharmaceutically acceptable salt thereof, wherein R^{B2} is hydrogen.

68. The compound of any one of claims 26 to 59, or a pharmaceutically acceptable salt thereof, wherein B1 is NR^{BN1}.

69. The compound of claim 68, or a pharmaceutically acceptable salt thereof, wherein R^{BN1} 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, or heterocycloalkyl, wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}.

70. The compound of any one of claims 26, or 28 to 69, or a pharmaceutically acceptable salt thereof, wherein B2 is $C(R^{B3})(R^{B4})$.

71. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein R^{B3} and R^{B4} are taken together to form an oxo.

72. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein R^{B3} and R^{B4} are taken together to form a cycloalkyl (e.g., cyclopropyl) or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}.

73. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein R^{B3} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

74. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein R^{B3} is hydrogen.

75. The compound of any one of claims 70, 73 or 74, or a pharmaceutically acceptable salt thereof, wherein R^{B4} is hydrogen, 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, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^{12}.

76. The compound of any one of claims 70, 73 or 74, or a pharmaceutically acceptable salt thereof, wherein R^{B4} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-SF_5$, -SH, $-SR^a$, $-NR^cR^d$, 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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}.

77. The compound of any one of claims 70, 73 or 74, or a pharmaceutically acceptable salt thereof, wherein R^{B4} is hydrogen.

78. The compound of any one of claims 26, or 28 to 69, or a pharmaceutically acceptable salt thereof, wherein B2 is NR^{BN2}.

79. The compound of claim 78, or a pharmaceutically acceptable salt thereof, wherein R^{BN2} 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, or heterocycloalkyl, wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}.

80. The compound of any one of claims 1 to 79, or a pharmaceutically acceptable salt thereof, wherein each R^A 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, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

81. The compound of any one of claims 1 to 80, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-SF_5$, -SH, $-SR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-

C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

82. The compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently halogen, -CN, -NO_2, -OH, amino, C_1-C_6alkyl, C_1-C_6alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6heteroalkylene(cycloalkyl), or C_1-C_6heteroalkylene(heterocycloalkyl), wherein each alkyl, heteroalkyl, alkylene, heteroalkylene, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{11}.

83. The compound of any one of claims 1 to 82, or a pharmaceutically acceptable salt thereof, wherein two R^B on the same atom are taken together to form an oxo.

84. The compound of any one of claims 1 to 83, or a pharmaceutically acceptable salt thereof, wherein two R^B on the same atom are taken together to form a 3-5 membered cycloalkyl or heterocycloalkyl, each of which is optionally substituted with one or more R^{12}.

85. The compound of any one of claims 1 to 82, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently halogen, 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, heteroalkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R^{12}.

86. The compound of any one of claims 1 to 82, or 85, or a pharmaceutically acceptable salt thereof, wherein each R^B is independently halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

87. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1.

88. A pharmaceutical composition comprising a compound of any one of claims 1 to 87, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

89. A method of modulating a protein tyrosine phosphatase enzyme, comprising administering to a subject in need of a compound of any one of claims 1 to 87, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 88.

90. A method of inhibiting a protein tyrosine phosphatase enzyme, comprising administering to a subject in need of a compound of any one of claims 1 to 87, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 88.

91. The method of claim 89 or 90, wherein the protein tyrosine phosphatase enzyme is protein tyrosine phosphatase non-receptor type 1 (PTPN1), or protein tyrosine phosphatase nonreceptor type 2 (PTPN2).

92. The method of any one of claims 89 to 91, wherein the subject has a disease or disorder.

93. A method of treating a disease or disorder, comprising administering to a subject in need of a compound of any one of claims 1 to 87, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 88.

94. The method of claim 92 or 93, wherein the disease or disorder is associated with protein tyrosine phosphatase enzyme.

95. The method of any one of claims 92 to 94, wherein the disease or disorder is cancer.

96. The method of claim 95, wherein the cancer is selected from bladder cancer, bone cancer, brain cancer, breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, head, spine and neck cancer, Kaposi's sarcoma, kidney cancer, leukemia, liver cancer, lymphoma, melanoma, multiple myeloma, pancreatic cancer, penile cancer, testicular germ cell cancer, thymoma carcinoma, thymic carcinoma, lung cancer, ovarian cancer, prostate cancer, marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

97. The method of claim 95, wherein the cancer is melanoma.

98. The method of one of claims 92 to 94, wherein the disease or disorder is a metabolic disease.

99. The method of claim 98, wherein the metabolic disease is selected from non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, metabolic syndrome, phenylketonuria, proliferative retinopathy, and Kearns-Sayre disease.

100. The method of claim 99, wherein the diabetes is Type I diabetes.

101. The method of claim 99, wherein the diabetes is Type II diabetes.

102. The method of claim 99, wherein the diabetes is gestational diabetes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/143223

A. CLASSIFICATION OF SUBJECT MATTER

C07D285/10(2006.01)i; C07D417/02(2006.01)i; A61K31/433(2006.01)i; A61P35/00(2006.01)i; A61P3/00(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)

CNTXT,VCN,DWPI,CNKI,Caplus(STN),Registry(STN),MARPAT(STN): INSILICO MEDICINE, PROTEIN, TYROSINE, PHOSPHATASE, INHIBIT, fused ring, thiadiazolidin, cancer, tumor, diabetes, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007067612 A1 (NOVARTIS AG, et al.) 14 June 2007 (2007-06-14) claims 1-83,example 18	1,7-19,21-25, 80-86,88-102
PX	WO 2023150150 A1 (NERIO THERAPEUTICS, INC.) 10 August 2023 (2023-08-10) claims 1-58, table 2	1-102
A	WO 2007067612 A1 (NOVARTIS AG, et al.) 14 June 2007 (2007-06-14) claims 1-83,example 18	2-6,20,26-79,87
A	WO 2022192598 A1 (KUMQUAT BIOSCIENCES INC.) 15 September 2022 (2022-09-15) whole document	1-102
A	WO 2022056281 A1 (CALICO LIFE SCIENCES LLC, et al.) 17 March 2022 (2022-03-17) whole document	1-102
A	WO 2020186199 A1 (CALICO LIFE SCIENCES LLC, et al.) 17 September 2020 (2020-09-17) whole document	1-102

☑ 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
21 March 2024	**01 April 2024**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**YANG,Jie** Telephone No. **(+86) 010-53962314**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014130608 A1 (MERCK SHARP & DOHME CORP., et al.) 28 August 2014 (2014-08-28) whole document	1-102
A	WO 2007067615 A2 (NOVARTIS AG. et al.) 14 June 2007 (2007-06-14) whole document	1-102
A	WO 03082841 A1 (NOVARTIS AG, et al.) 09 October 2003 (2003-10-09) whole document	1-102

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International application No.
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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.: **89-102**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 89-102 are directed to methods of treatment of the human/animal body, and the search report is established based on the use of the claimed compound or composition for manufacturing medicaments for treating disease or disorder.

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/CN2023/143223

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International application No.
PCT/CN2023/143223

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2023/143223

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