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(54) Title: PROLYL HYDROXYLASE DOMAIN-CONTAINING PROTEIN (PHD) INHIBITORS AND USES THEREOF

(57) Abstract: Described herein are PHD inhibitors and pharmaceutical compositions comprising said inhibitors. The subject compounds and compositions are useful for the treatment of a disease or disorder associated with PHD.

PROLYL HYDROXYLASE DOMAIN-CONTAINING PROTEIN (PHD) INHIBITORS AND USES THEREOF

[0001] This patent application claims the benefit of International Application No. PCT/CN2021/127023, filed October 28, 2021 and International Application No. PCT/CN2022/112270, filed August 12, 2022; which are incorporated herein by reference in their entirety.

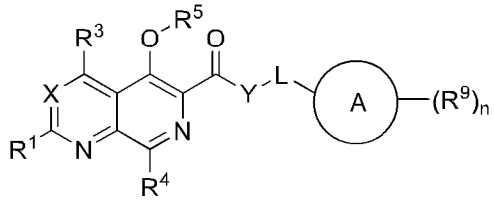
BACKGROUND

[0002] Hypoxia-inducible factor (HIF) mediates gene expression in response to changes in cellular oxygen concentration. HIF is a heterodimer having an oxygen-regulated subunit (HIF-α) and a constitutively expressed subunit (HIF-β). HIF prolyl hydroxylase, which is also known as prolyl hydroxylase domain-containing protein (PHD), exists as three isoforms in humans (PHD1 , PHD2, and PHD3). PHDs act as oxygen sensors modulating the hypoxia-inducible factor ("HIF") degradation pathway. Briefly, PHDs are responsible for hydroxylation of HIFα, a subunit of HIF, which initiates the pathway that eventually results in the degradation of HIFα by the proteasome. There are three subtypes of PHDs, including PHD1, PHD2 and PHD3. Inhibition of PHDs has been indicated as a promising therapy for the HIFα related disease, such as anemia and inflammatory bowel disease (IBD).

[0003] Inhibitors of PHDs coordinate erythropoiesis by inducing both renal and hepatic erythropoietin ("EPO") synthesis, which stimulates the production of red blood cells in the bone marrow, and by regulating the metabolism of iron, an indispensable component of functional red blood cells. Inhibitors of PHDs could also suppress the production of hepatic hepcidin, which has negative effects on iron mobilization. It is also speculated that inhibitors of PHDs might upregulate the expression several iron metabolism gene, such as DMT1 and DCYTB. Because of the central role HIF prolyl hydrolase plays in cellular oxygen sensing, inhibitors of PHD may be useful in treating cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, and cancer, among others.

SUMMARY

[0004] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

R^1 is hydrogen, halogen, -W-CN, -W-NO_2, -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-SH, -W-SR^a, -W-$S(=O)R^a$, -W-$S(=O)_2R^a$, -W-$S(=O)_2NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, 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_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a};

each R^{1a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{1a} on the same atom are taken together to form an oxo;

W is absent or C_1-C_6alkylene;

X is N or CR^2;

R^2 is hydrogen, fluoro, chloro, bromo, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^4 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Y is -O-, -S-, or -NR^6-;

R^6 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

L is -$(CR^7R^8)_p$-;

each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{7a};

each R^{7a} is independently halogen, -CN, -NO_2, -OH, -OR^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, or C_1-C_6heteroalkyl;

p is 0-4;

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

each R^9 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl,

heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{9a};

or two R^9 on the same atom are taken together to form an oxo;

each R^{9a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{9a} on the same atom are taken together to form an oxo;

n is 0-4;

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

each R^c and R^d are 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, 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, -OC_1-C_6alkyl, -$S(=O)C_1$-C_6alkyl, -$S(=O)_2C_1$-C_6alkyl, -$S(=O)_2NH_2$, -$S(=O)_2NHC_1$-C_6alkyl, -$S(=O)_2N(C_1$-C_6alkyl$)_2$, -NH_2, -NHC_1-C_6alkyl, -$N(C_1$-C_6alkyl$)_2$, -$NHC(=O)OC_1$-C_6alkyl, -$C(=O)C_1$-C_6alkyl, -C(=O)OH, -$C(=O)OC_1$-C_6alkyl, -$C(=O)NH_2$, -$C(=O)N(C_1$-C_6alkyl$)_2$, -$C(=O)NHC_1$-C_6alkyl, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or

two R on the same atom are taken together to form an oxo.

[0005] Also disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0006] Also disclosed herein is a method of treating a disease or disorder associated with PHD, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein.

[0007] Also disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein, wherein the disease or disorder is cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, or cancer.

[0008] Also disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein, wherein the disease or disorder is stroke, myocardial infarction, congestive heart failure, atherosclerosis, chronic venous insufficiency, cardiac cirrhosis, acute decompensated heart failure, heart failure following a heart attack, peripheral artery disease, occlusive artery disease, diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, impaired glucose tolerance, non-alcoholic liver steatosis, chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension, mountain sickness, acute respiratory failure, interstitial lung disease, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, acute kidney failure, acute kidney injury, renal ischemia reperfusion injury, hepatic ischemia reperfusion injury, diabetic foot ulcers, pressure ulcers, venous ulcers, arterial ulcers, epidermolysis bullosa, pemphigus, Sjogren's syndrome, anemia, inflammatory bowel disease (IBD), chronic kidney disease (CKD), Parkinson's disease (PD), or Alzheimer's disease (AD). In some embodiments of a method disclosed herein, the disease or disorder is Parkinson's disease (PD). In some embodiments of a method disclosed herein, the disease or disorder is Alzheimer's disease (AD). In some embodiments of a method disclosed herein, the disease or disorder is anemia, inflammatory bowel disease (IBD), or chronic kidney disease (CKD). In some embodiments of a method disclosed herein, the disease or disorder is anemia. In some embodiments of a method disclosed herein, the disease or disorder is inflammatory bowel disease (IBD). In some embodiments of a method disclosed herein, the disease or disorder is ulcerative colitis ("UC") or Crohn's disease ("CD"). In some embodiments of a method disclosed herein, the disease or disorder is chronic kidney disease (CKD).

[0009] Also disclosed herein is a method of stabilizing hypoxia inducible factor (HIF) in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein. In some embodiments, the HIF is HIF-1α.

[0010] In some embodiments of a method disclosed herein, the method further comprises administration of an additional active agent.

INCORPORATION BY REFERENCE

[0011] 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

[0012] In the following description, certain specific details are set forth in order 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.

[0013] 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.

[0014] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0015] "oxo" refers to =O.

[0016] "Carboxyl" refers to -COOH.

[0017] "Cyano" refers to -CN.

[0018] "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.

[0019] "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.

[0020] "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.

[0021] "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.

[0022] "Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. 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.

[0023] "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.

[0024] "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.

[0025] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0026] "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.

[0027] "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.

[0028] "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.

[0029] "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.

[0030] "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.

[0031] "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.

[0032] 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 (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) 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.

[0033] 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.

[0034] 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.

[0035] "Treatment" of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition.

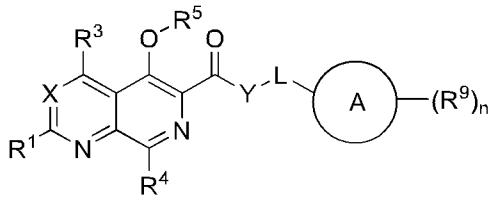
[0036] As used herein, a "disease or disorder associated with PHD" or, alternatively, "a PHD-mediated disease or disorder" means any disease or other deleterious condition in which PHD, or a mutant thereof, is known or suspected to play a role.

[0037] As used herein, a "disease or disorder associated with PHD2" or, alternatively, "a PHD2-mediated disease or disorder" means any disease or other deleterious condition in which PHD2, or a mutant thereof, is known or suspected to play a role.

Compounds

[0038] Described herein are compounds of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof useful in the treatment of a disease or disorder associated with PHD.

[0039] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

R^1 is hydrogen, halogen, -W-CN, -W-NO_2, -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-SH, -W-SR^a, -W-$S(=O)R^a$, -W-$S(=O)_2R^a$, -W-$S(=O)_2NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, 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_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted;

W is absent or C_1-C_6alkylene;

X is N or CR^2;

R^2 is hydrogen, fluoro, chloro, bromo, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^4 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Y is -O-, -S-, or -NR^6-;

R^6 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

L is -$(CR^7R^8)_p$-;

each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{7a};

each R^{7a} is independently halogen, -CN, -NO_2, -OH, -OR^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, or C_1-C_6heteroalkyl;

p is 0-4;

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

each R^9 is independently halogen, -CN, -NO_2, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted;

n is 0-4;

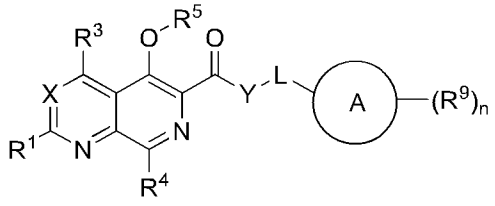
each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl);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

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, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted; and

each R^c and R^d are 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, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted;

or R^c and R^d are taken together with the atom to which they are attached to form an optionally substituted heterocycloalkyl.

[0040] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

R^1 is hydrogen, halogen, -W-CN, -W-NO_2, -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-SH, -W-SR^a, -W-$S(=O)R^a$, -W-$S(=O)_2R^a$, -W-$S(=O)_2NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, 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_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a};

each R^{1a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{1a} on the same atom are taken together to form an oxo;

W is absent or C_1-C_6alkylene;

X is N or CR^2;

R^2 is hydrogen, fluoro, chloro, bromo, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^4 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Y is -O-, -S-, or -NR^6-;

R^6 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

L is -$(CR^7R^8)_p$-;

each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{7a};

each R^{7a} is independently halogen, -CN, -NO_2, -OH, -OR^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, or C_1-C_6heteroalkyl;

p is 0-4;

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

each R^9 is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -

$NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{9a};

or two R^9 on the same atom are taken together to form an oxo;

each R^{9a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{9a} on the same atom are taken together to form an oxo;

n is 0-4;

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

each R^c and R^d are 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, 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, $-OC_1$-C_6alkyl, $-S(=O)C_1$-C_6alkyl, $-S(=O)_2C_1$-C_6alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_6alkyl, $-S(=O)_2N(C_1$-C_6alkyl$)_2$, $-NH_2$, $-NHC_1$-C_6alkyl, $-N(C_1$-C_6alkyl$)_2$, $-NHC(=O)OC_1$-C_6alkyl, $-C(=O)C_1$-C_6alkyl, -C(=O)OH, $-C(=O)OC_1$-C_6alkyl, $-C(=O)NH_2$, $-C(=O)N(C_1$-C_6alkyl$)_2$, $-C(=O)NHC_1$-C_6alkyl, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or

two R on the same atom are taken together to form an oxo.

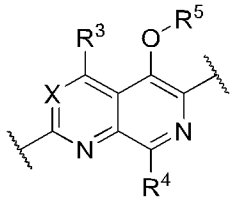
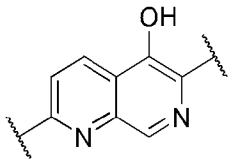
[0041] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X is CR^2.

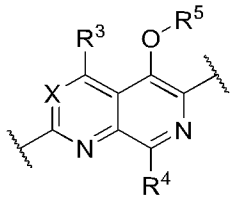
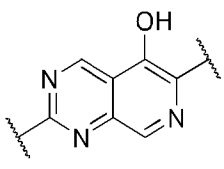
[0042] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen, fluoro, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen.

[0043] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^3 is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^3 is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^3 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^3 is hydrogen.

[0044] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^4 is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^4 is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^4 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^4 is hydrogen.

[0045] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^5 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^5 is C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^5 is hydrogen.

[0046] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,  is  .

[0047] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,  is  .

[0048] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y is -O- or -NR^6-. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y is -NR^6-. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y is -O-. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y is -S-.

[0049] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^6 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^6 is C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^6 is hydrogen.

[0050] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1-4. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1-3. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1 or 2. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 2. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 3.

[0051] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6hydroxyalkyl; or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^7 and R^8 are independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^7 and R^8 are hydrogen.

[0052] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{7a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{7a} is independently halogen, -OH, -OR^a, C_1-C_6alkyl.

[0053] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring A is aryl or heteroaryl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring A is phenyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or

stereoisomer thereof, Ring A is 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring A is 6-membered heteroaryl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring A is 6-membered pyridyl.

[0054] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 1-3. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 2-4. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 2 or 3. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 1 or 2. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 0. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 1. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 2. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 3.

[0055] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^9 is independently halogen, -CN, -OH, -OR^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, or C_1-C_6heteroalkyl.

[0056] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^9 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, C_1-C_6alkyl, or C_1-C_6haloalkyl.

[0057] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^9 is independently halogen or -CN.

[0058] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^9 is -CN.

[0059] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is halogen, -W-CN, -OH, -W-OR^a, -W-OC(=O)R^a, -W-OC(=O)OR^b, -W-OC(=O)NR^cR^d, -W-SR^a, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-C(=O)R^a, -W-C(=O)OR^b, -W-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, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}. In some embodiments, R^1 is independently substituted with 1, 2, 3, or 4 R^{1a}. In some embodiments, R^1 is independently substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is halogen. In some embodiments, R^1 is -W-CN. In some embodiments, R^1 is -W-NO_2. In some embodiments, R^1 is -OH. In some embodiments, R^1 is -W-OR^a. In some embodiments, R^1 is -W-OC(=O)R^a. In some embodiments, R^1 is -W-OC(=O)OR^b. In some embodiments, R^1 is -W-OC(=O)NR^cR^d. In some embodiments, R^1 is -W-SH. In some embodiments, R^1 is

-W-SR^a. In some embodiments, R^1 is -W-S(=O)R^a. In some embodiments, R^1 is -W-S(=O)$_2$R^a. In some embodiments, R^1 is -W-S(=O)$_2$NR^{c}R^d. In some embodiments, R^1 is -W-NR^{c}R^d. In some embodiments, R^1 is -W-NR^{b}C(=O)NR^{c}R^d. In some embodiments, R^1 is -W-NR^{b}C(=O)R^a. In some embodiments, R^1 is -W-NR^{b}C(=O)OR^b. In some embodiments, R^1 is -W-NR^{b}S(=O)$_2$R^a. In some embodiments, R^1 is -W-C(=O)R^a. In some embodiments, R^1 is -W-C(=O)OR^b. In some embodiments, R^1 is -W-C(=O)NR^{c}R^d. In some embodiments, R^1 is optionally substituted C_1-C_6alkyl. In some embodiments, R^1 is optionally substituted C_1-C_6haloalkyl. In some embodiments, R^1 is optionally substituted C_1-C_6hydroxyalkyl. In some embodiments, R^1 is optionally substituted C_1-C_6aminoalkyl. In some embodiments, R^1 is optionally substituted C_1-C_6heteroalkyl. In some embodiments, R^1 is optionally substituted C_2-C_6alkenyl. In some embodiments, R^1 is optionally substituted C_2-C_6alkynyl. In some embodiments, R^1 is optionally substituted cycloalkyl. In some embodiments, R^1 is optionally substituted heterocycloalkyl. In some embodiments, R^1 is optionally substituted aryl. In some embodiments, R^1 is optionally substituted heteroaryl. In some embodiments, R^1 is optionally substituted C_1-C_6alkylene(cycloalkyl). In some embodiments, R^1 is optionally substituted C_1-C_6alkylene(heterocycloalkyl). In some embodiments, R^1 is optionally substituted C_1-C_6alkylene(aryl). In some embodiments, R^1 is optionally substituted C_1-C_6alkylene(heteroaryl).

[0060] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, halogen, -W-CN, -W-NO$_2$, -OH, -W-OR^a, -W-OC(=O)R^a, -W-OC(=O)OR^b, -W-OC(=O)NR^{c}R^d, -W-SH, -W-SR^a, -W-S(=O)R^a, -W-S(=O)$_2$R^a, -W-S(=O)$_2$NR^{c}R^d, -W-NR^{c}R^d, -W-NR^{b}C(=O)NR^{c}R^d, -W-NR^{b}C(=O)R^a, -W-NR^{b}C(=O)OR^b, -W-NR^{b}S(=O)$_2$R^a, -W-C(=O)R^a, -W-C(=O)OR^b, -W-C(=O)NR^{c}R^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, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}.

[0061] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, halogen, -W-CN, -W-NO$_2$, -OH, -W-OR^a, -W-OC(=O)R^a, -W-OC(=O)OR^b, -W-OC(=O)NR^{c}R^d, -W-SH, -W-SR^a, -W-S(=O)R^a, -W-S(=O)$_2$R^a, -W-S(=O)$_2$NR^{c}R^d, -W-NR^{c}R^d, -W-NR^{b}C(=O)NR^{c}R^d, -W-NR^{b}C(=O)R^a, -W-NR^{b}C(=O)OR^b, -W-NR^{b}S(=O)$_2$R^a, -W-C(=O)R^a, -W-C(=O)OR^b, -W-C(=O)NR^{c}R^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, monocyclic heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}. In some embodiments, R^1 is a monocyclic ring. In some embodiments, R^1 is an optionally substituted monocyclic heterocycloalkyl.

[0062] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, halogen, -W-CN, -W-NO$_2$, -OH, -W-OR^a, -W-

$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-SH, -W-SR^a, -W-$S(=O)R^a$, -W-$S(=O)_2R^a$, -W-$S(=O)_2NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, 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, bicyclic heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}. In some embodiments, R^1 is a bicyclic ring. In some embodiments, R^1 is an optionally substituted bicyclic heterocycloalkyl.

[0063] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is halogen, -W-CN, -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}.

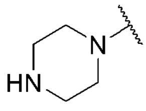
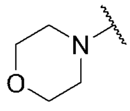
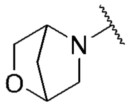
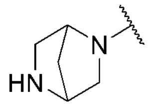
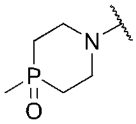
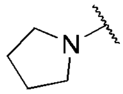
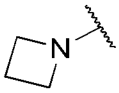
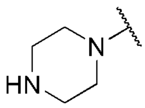
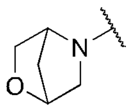
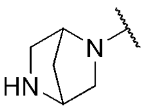
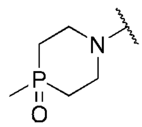
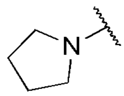
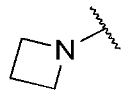
[0064] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, cycloalkyl, or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally and independently substituted with one or more R^{1a}.

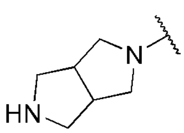
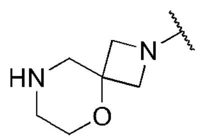
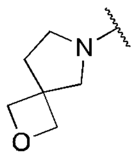
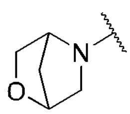
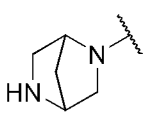
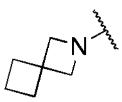
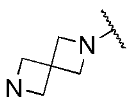
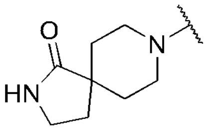
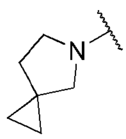
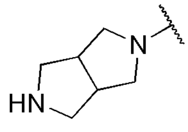
[0065] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-NR^cR^d, -W-$NR^bC(=O)R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, or heterocycloalkyl optionally and independently substituted with one or more R^{1a}.

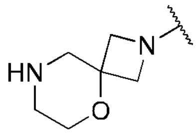
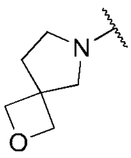
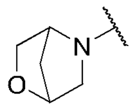
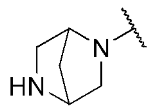
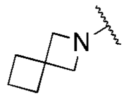
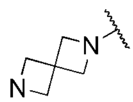
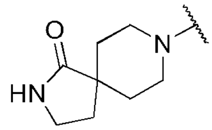
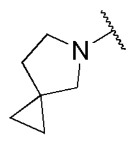
[0066] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-NR^cR^d, -W-$NR^bC(=O)R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, or heterocycloalkyl.

[0067] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -W-OR^a, -W-NR^cR^d, -W-$C(=O)R^a$, or heterocycloalkyl optionally and independently substituted with one or more R^{1a}.

[0068] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is heterocycloalkyl optionally and independently substituted with one or more R^{1a}. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is a monocyclic heterocycloalkyl optionally and independently substituted with one or more R^{1a}. In some embodiments, R^1 is a 4 membered, optionally substituted monocyclic heterocycloalkyl. In some embodiments, R^1 is a 5 membered, optionally substituted monocyclic heterocycloalkyl. In some embodiments, R^1 is a 6 membered, optionally substituted

monocyclic heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is attached to the rest of the fragment of formula (I) via a nitrogen atom of R^1. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is  ,  ,  ,  ,  ,  , or  , each of which is optionally substituted with one or more R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is optionally substituted with 1 or 2 R^{1a}.

[0069] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is a bicyclic heterocycloalkyl optionally and independently substituted with one or more R^{1a}. In some embodiments, R^1 is a spiro bicyclic heterocycloalkyl. In some embodiments, R^1 is a fused bicyclic heterocycloalkyl. In some embodiments, R^1 is a bridged bicyclic heterocycloalkyl. In some embodiments, R^1 is a 8-10 membered, optionally substituted bicyclic heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is  ,  ,  ,  ,  ,  ,  ,  , or  , each of which is optionally substituted with one or more R^{1a} (e.g., 1, 2, or 3 R^{1a}). In some embodiments, R^1 is  , which

is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is  , which is unsubstituted or substituted with 1 or 2 R^{1a}.

[0070] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally and independently substituted with one or more R^{1a}.

[0071] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is piperidinyl optionally substituted with one or more R^{1a}.

[0072] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is 3,6-diazabicyclo[3.1.1]heptane, 2,5-diazabicyclo[2.2.1]heptane, 6-oxa-3-azabicyclo[3.1.1]heptane, or 2-oxa-5-azabicyclo[2.2.1]heptane, each optionally and independently substituted with one or more R^{1a}. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is 2-oxa-5-azabicyclo[2.2.1]heptane optionally substituted with one or more R^{1a}. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is heterocycloalkyl optionally and independently substituted with one or more R^{1a} (e.g., 1 or 2 R^{1a}). In some embodiments, R^1 is monocyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is 5-

7 membered (e.g., 6 membered) monocyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}, and wherein the monocyclic heterocycloalkyl contains 1-3 ring nitrogen atoms.

[0073] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is bicyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}. In some embodiments, R^1 is 7-9 membered bicyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}, and wherein the bicyclic heterocycloalkyl contains 0-1 ring oxygen and 1-2 ring nitrogen atoms.

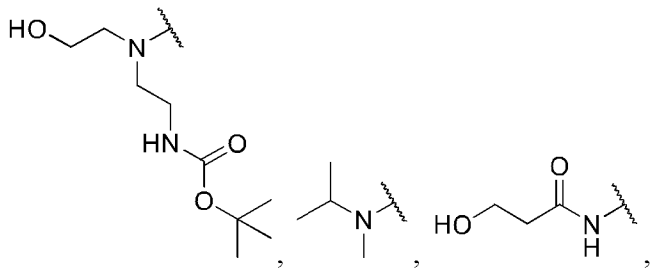
[0074] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is unsubstituted.

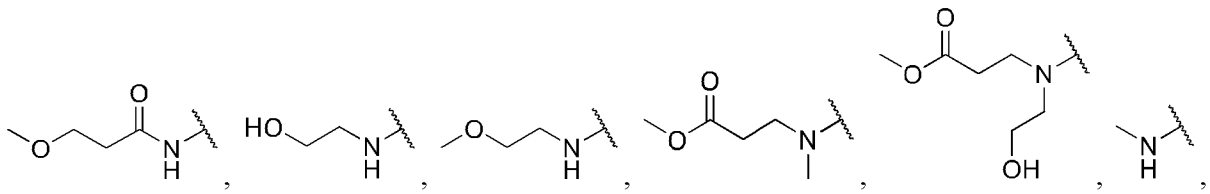
[0075] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -W-OR^a. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -OR^a. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -O-C_1-C_6alkylene(cycloalkyl) or -O-C_1-C_6alkylene(heterocycloalkyl), each optionally and independently substituted with one or more R^{1a}.

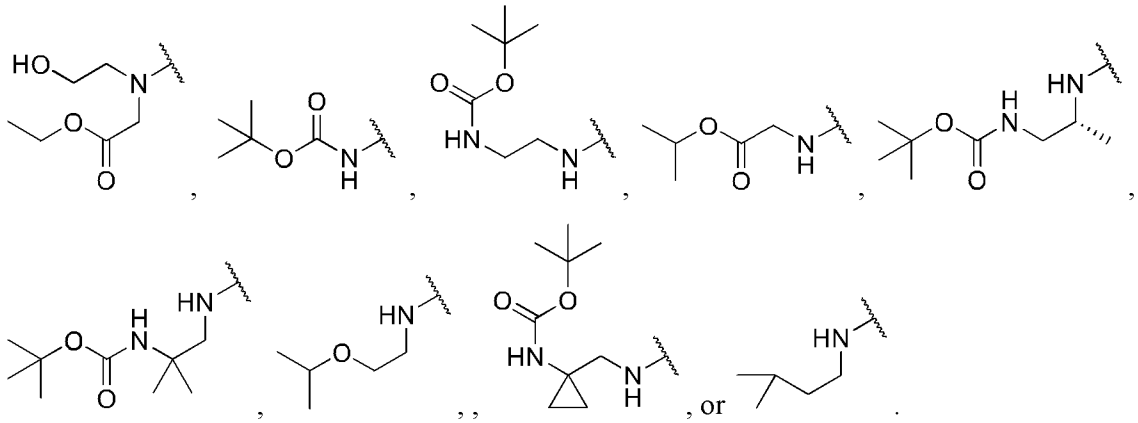
[0076] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -W-$NR^bC(=O)R^a$.

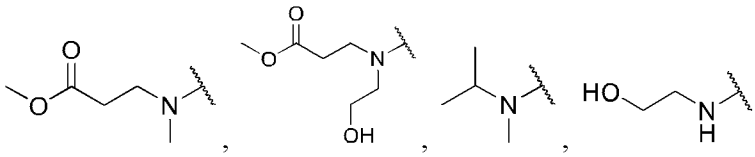
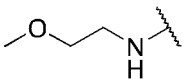
[0077] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is -W-NR^cR^d.

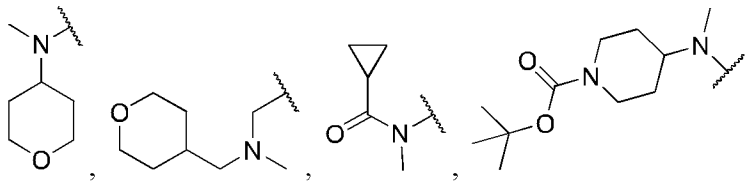
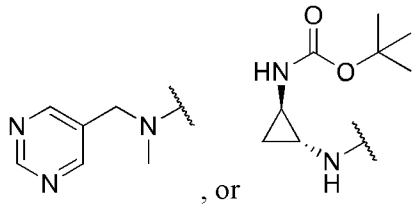
[0078] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is







[0079] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is  or  .

[0080] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is   or .

[0081] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, W is absent. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, W is C_1-C_2alkylene. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, W is C_1alkylene.

[0082] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{1a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or two R^{1a} on the same atom are taken together to form an oxo.

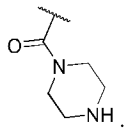
[0083] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{1a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl,

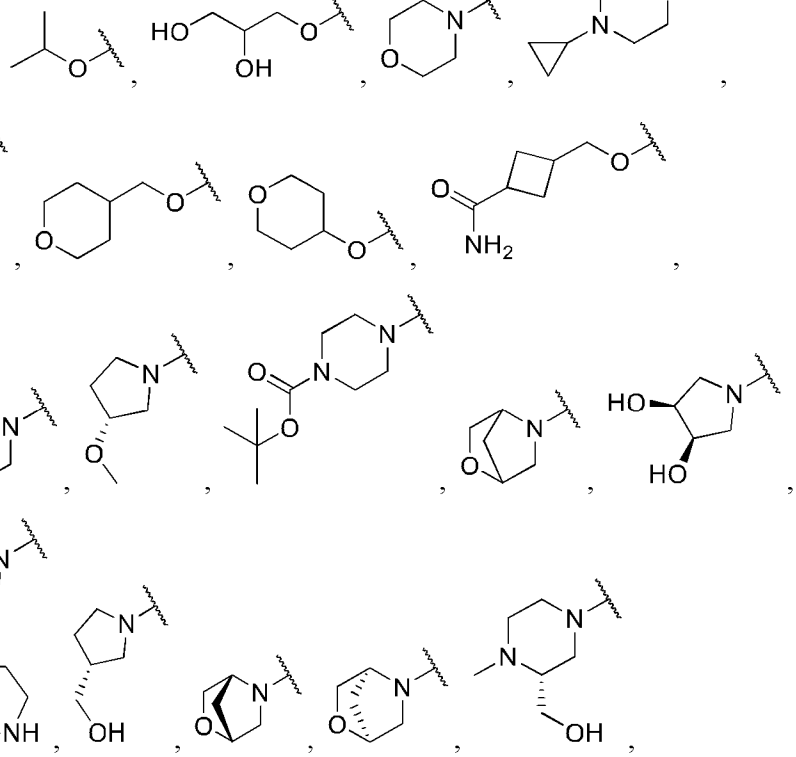
C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl; or two R^{1a} on the same atom are taken together to form an oxo.

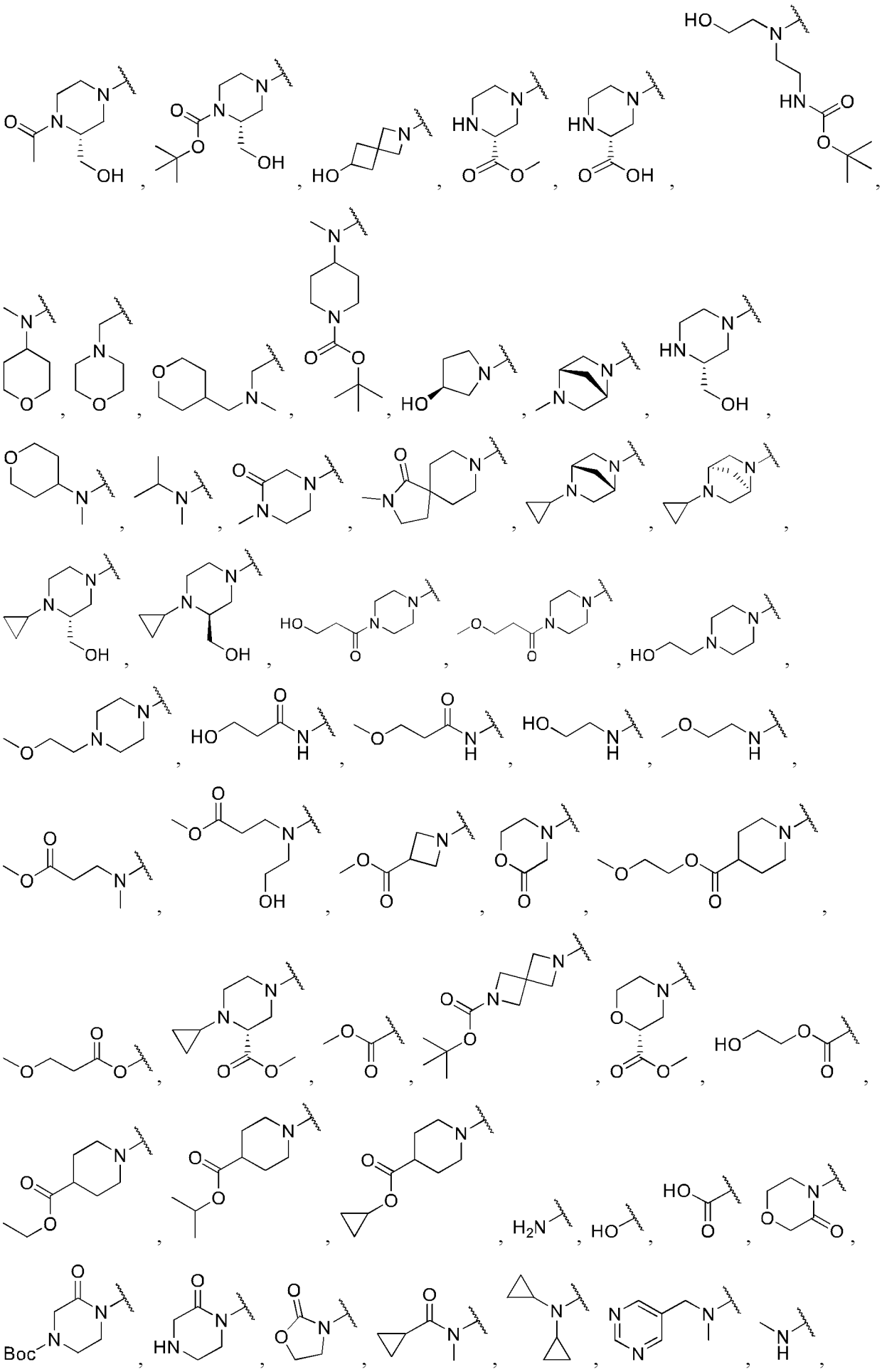
[0084] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{1a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$NR^bC(=O)R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl; or two R^{1a} on the same atom are taken together to form an oxo.

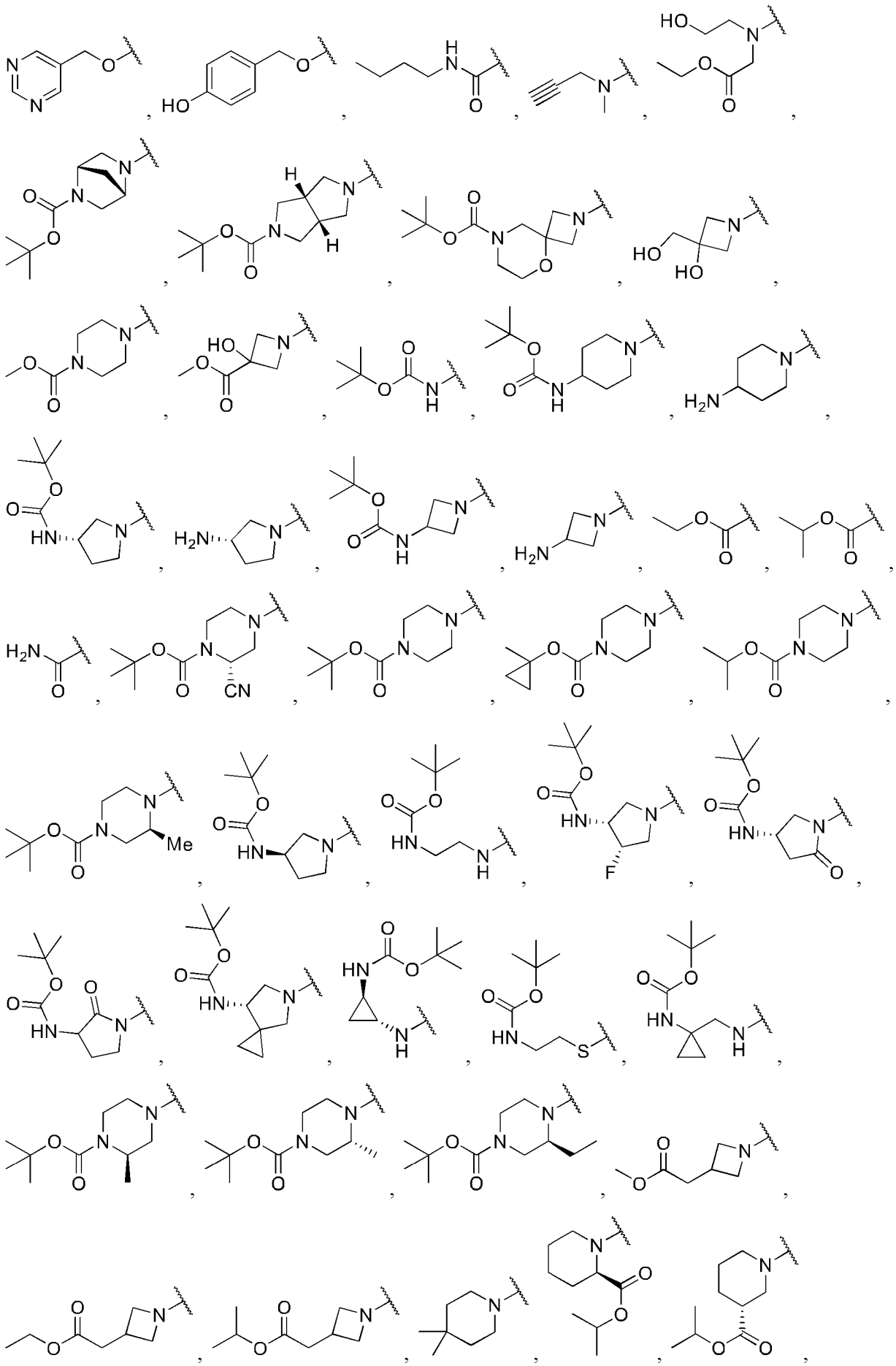
[0085] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{1a} is independently halogen, -OH, -OR^a, -$NR^bC(=O)R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6heteroalkyl, or cycloalkyl; or two R^{1a} on the same atom are taken together to form an oxo.

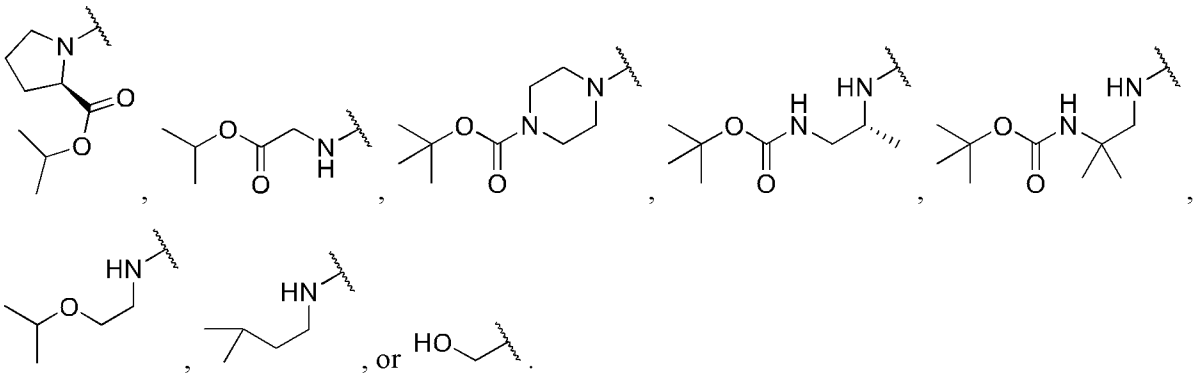
[0086] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{1a} is independently C_1-C_6alkyl (e.g., methyl), C_1-C_6haloalkyl, or -$C(=O)OR^b$ (e.g., -$C(=O)O(C_1$-C_6alkyl)).

[0087] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{1a} is -$C(=O)NR^cR^d$. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{1a} is -$C(=O)NH_2$. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{1a} is  .

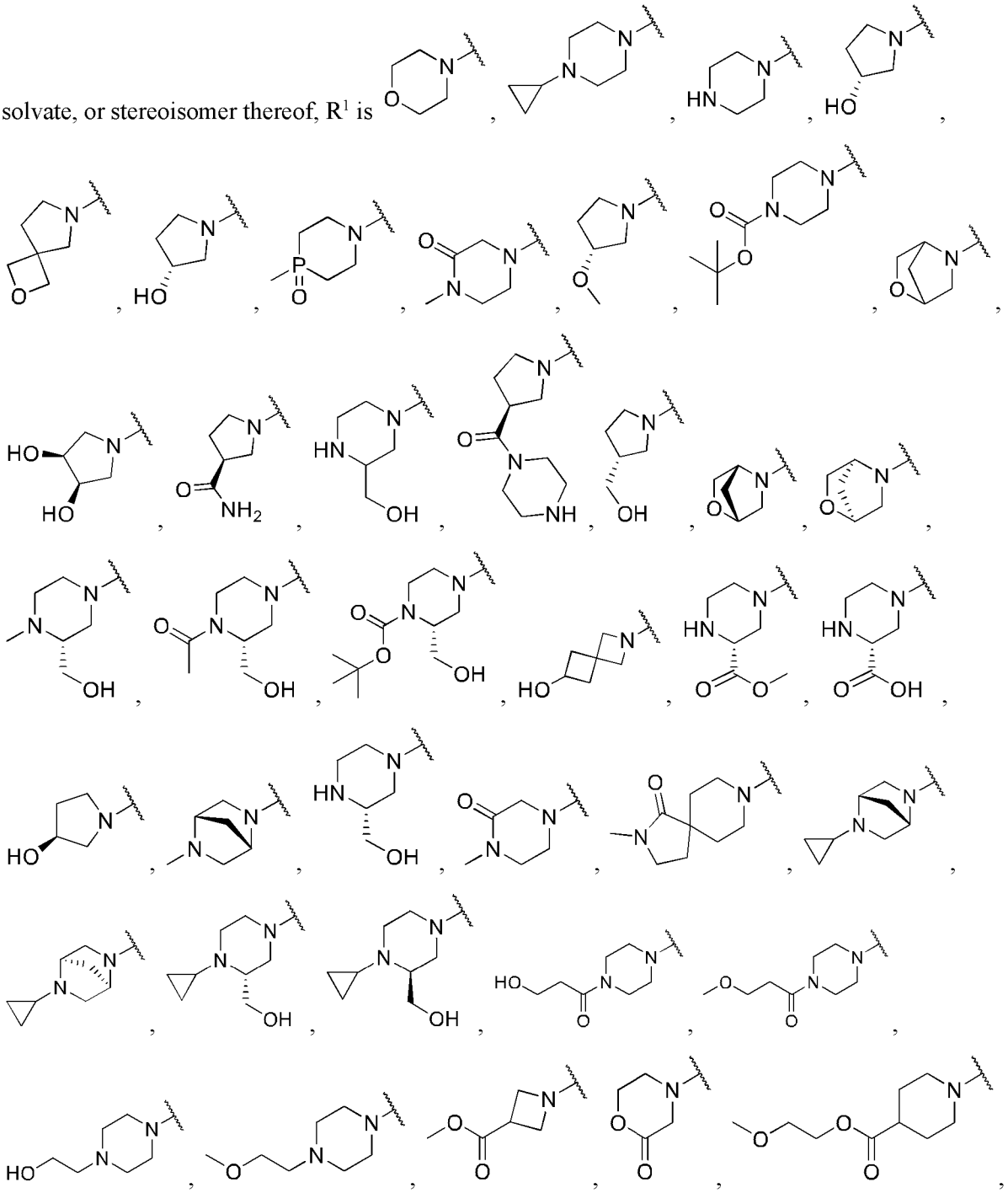
[0088] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is  .

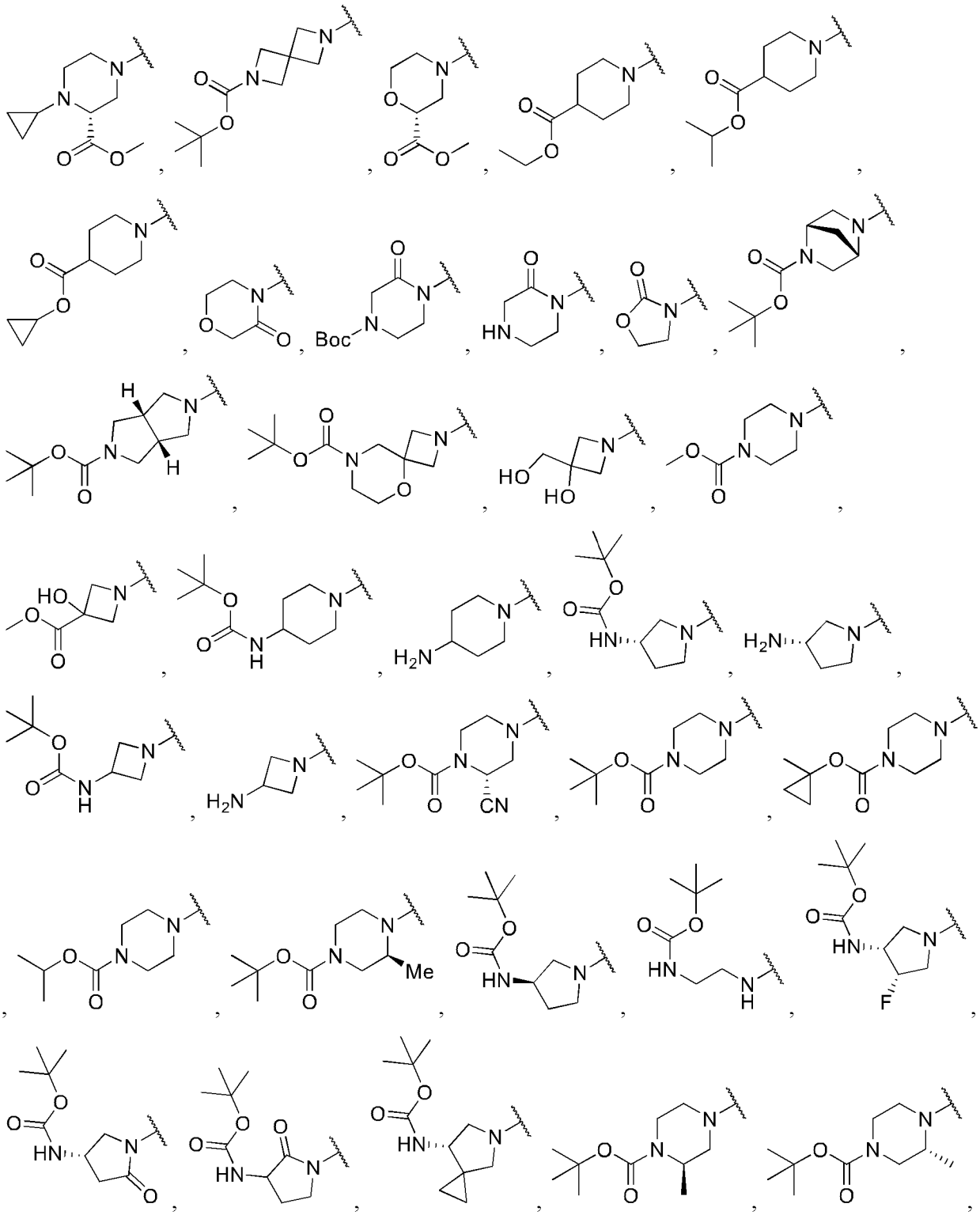


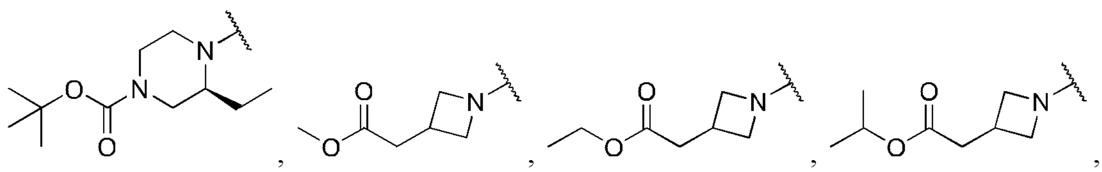


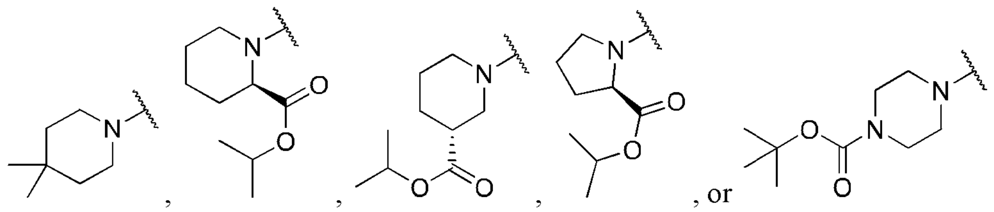


[0089] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is

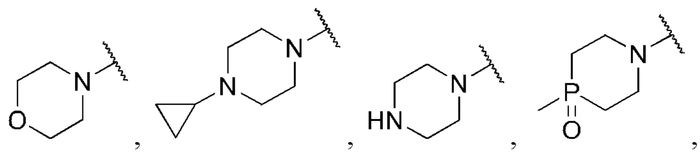


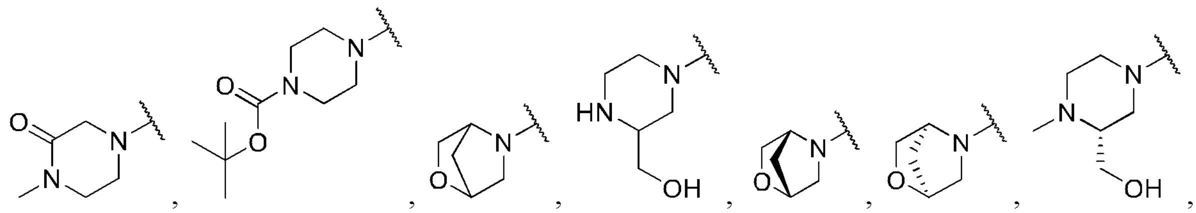


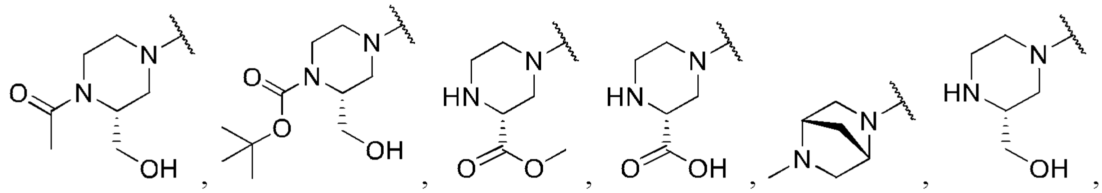


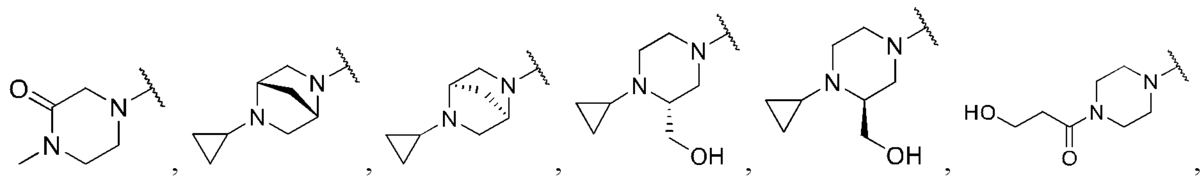


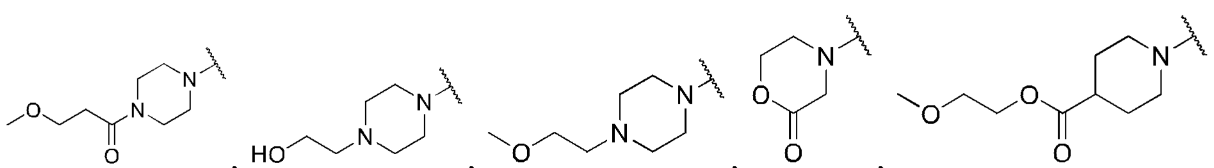
[0090] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is

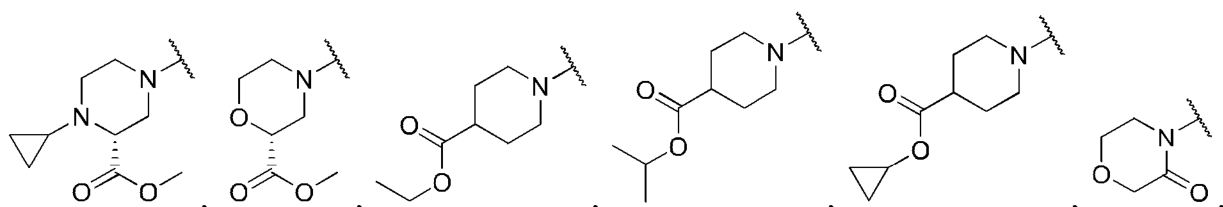


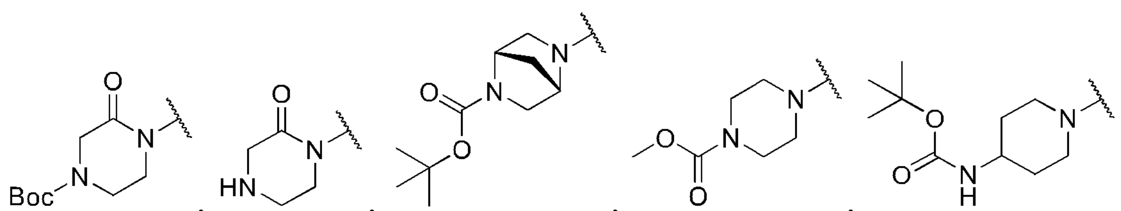


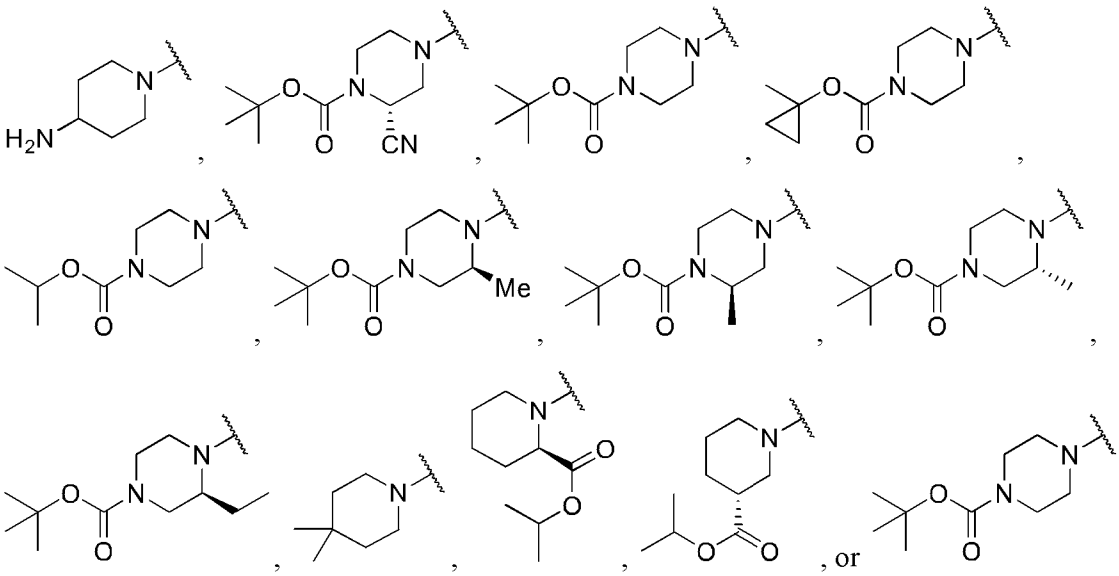


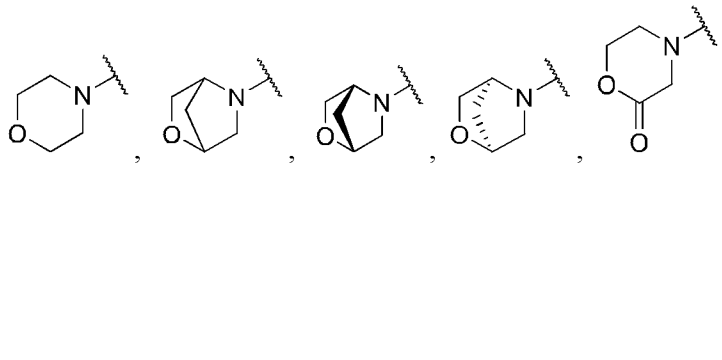


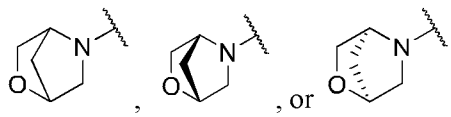


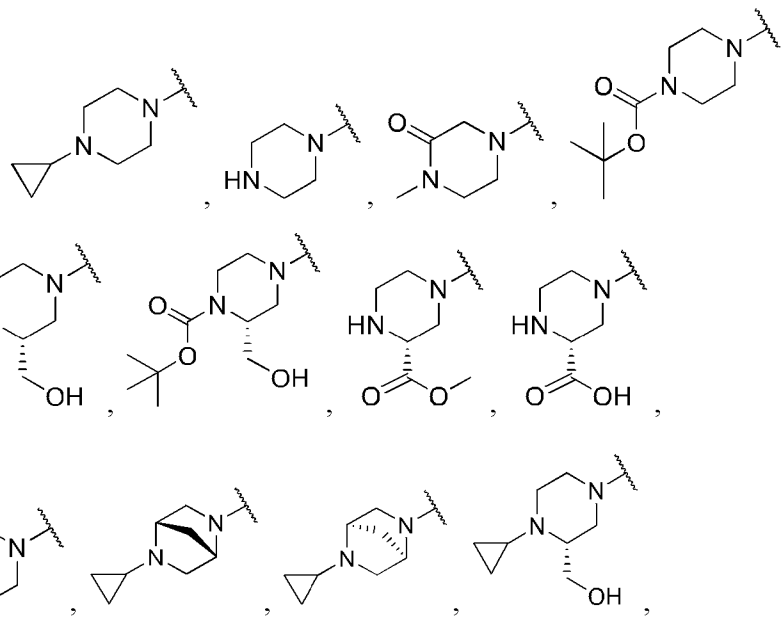


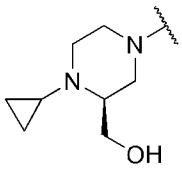
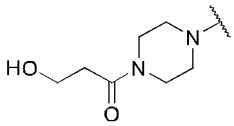
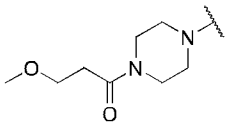
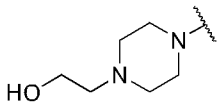
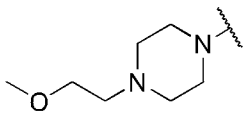
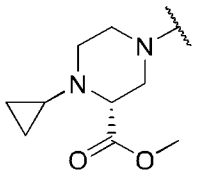
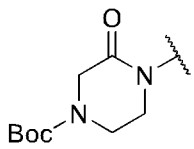
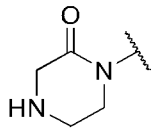
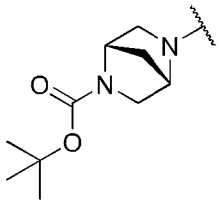
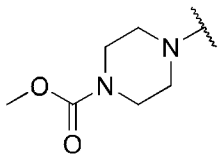
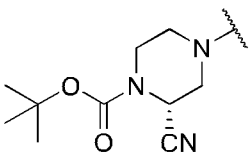
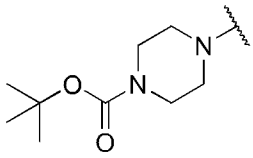
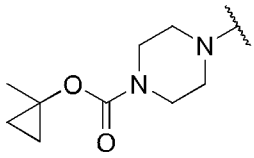
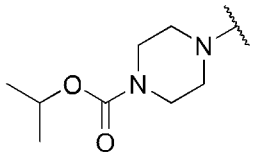
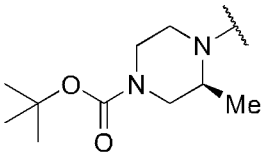
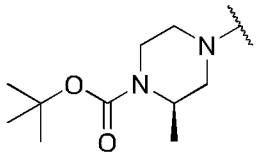
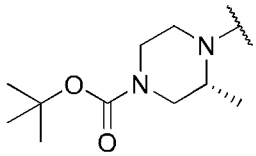
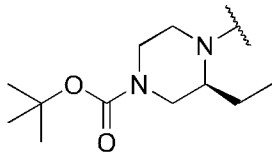




[0091] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is 

[0092] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is 

[0093] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is 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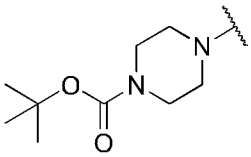
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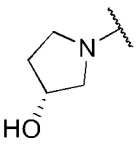
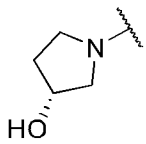
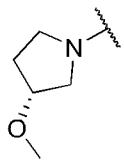
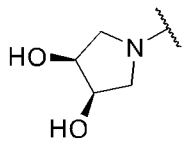
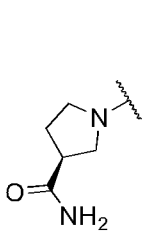
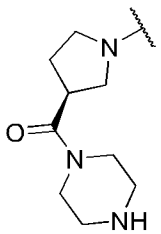
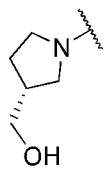
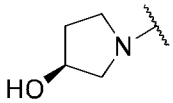
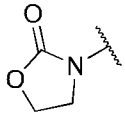
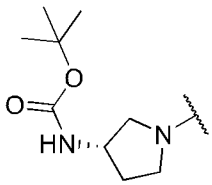
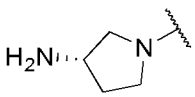
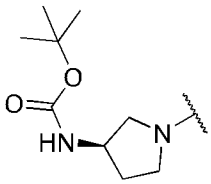
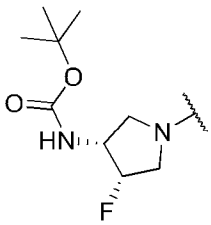
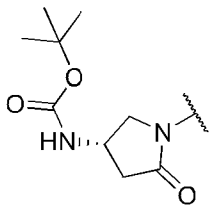
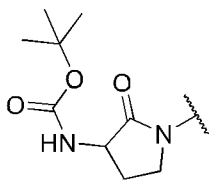
[0094] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is















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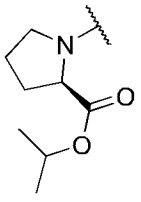
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[0095] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, 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, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl). In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C_1-C_6alkyl.

[0096] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, 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, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkylene(cycloalkyl), C_1-C_6alkylene(heterocycloalkyl), C_1-C_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl). In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen or

C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is hydrogen. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently C_1-C_6alkyl.

[0097] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, 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, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, 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). In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen, C_1-C_6alkyl or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are hydrogen. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d are independently C_1-C_6alkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^c is hydrogen, C_1-C_6hydroxyalkyl, C_1-C_6alkyl, C_1-C_6aminoalkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^d is hydrogen, C_1-C_6hydroxyalkyl, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, C_1-C_6alkylene(cycloalkyl), or C_1-C_6alkylene(heterocycloalkyl). In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^d is $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2OH$, or $-CH_2CH_2NHC(=O)O$-t-butyl.

[0098] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, 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.

[0099] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R is independently halogen, -CN, -OH, -OC_1-C_6alkyl, -NH_2, -NHC_1-C_6alkyl, -$N(C_1$-C_6alkyl$)_2$, -NHC(=O)OC_1-C_6alkyl, -C(=O)C_1-C_6alkyl, -C(=O)OH, -C(=O)OC_1-C_6alkyl, -C(=O)NH_2, -C(=O)$N(C_1$-C_6alkyl$)_2$, -C(=O)NHC_1-C_6alkyl, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R is independently halogen, -CN, -OH, -OC_1-C_6alkyl, -NH_2, -C(=O)C_1-C_6alkyl, -C(=O)OH, -C(=O)OC_1-C_6alkyl, -C(=O)NH_2, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R is independently halogen, -CN, -OH, -OC_1-C_6alkyl, -NH_2, C_1-C_6alkyl, or C_1-C_6haloalkyl.

[00100] In some embodiments of a compound disclosed herein, each R^1, R^9, R^a, R^b, R^c, R^d, the heterocycloalkyl formed when R^7 and R^8 are taken together, and the heterocycloalkyl formed when R^c and R^d are taken together, is optionally and independently substituted with one, two, three, or four substituents as defined herein. In some embodiments of a compound disclosed herein, each R^1, R^9, R^a, R^b, R^c, R^d, the heterocycloalkyl formed when R^7 and R^8 are taken together, and the heterocycloalkyl formed when R^c and R^d are taken together, is optionally and independently substituted with one, two, or three substituents as defined herein. In some embodiments of a compound disclosed herein, each R^1, R^9, R^a, R^b, R^c, R^d, the heterocycloalkyl formed when R^7 and R^8 are taken together, and the heterocycloalkyl formed when R^c and R^d are taken together, is optionally and independently substituted with one or two substituents as defined herein. In some embodiments of a compound disclosed herein, each R^1, R^9, R^a, R^b, R^c, R^d, the heterocycloalkyl formed when R^7 and R^8 are taken together, and the heterocycloalkyl formed when R^c and R^d are taken together, is optionally and independently substituted with one substituent as defined herein.

[00101] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or 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% of a total number of hydrogen and deuterium.

[00102] In some embodiments of a compound disclosed herein, one or more of R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or R^d groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[00103] In some embodiments of a compound disclosed herein, one or more hydrogens are replaced with one or more deuteriums in one or more of the following groups R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or R^d.

[00104] In some embodiments of a compound disclosed herein, one or more hydrogens of Ring A are replaced with one or more deuteriums.

[00105] 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.

[00106] In some embodiments the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is one of the compounds in Table 1.

TABLE 1

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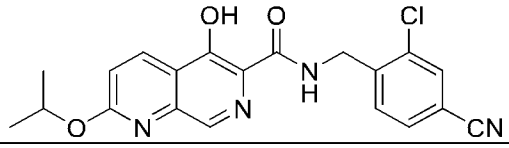
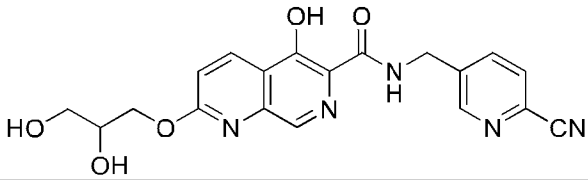
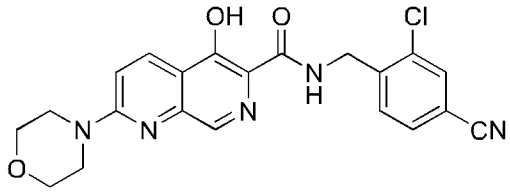
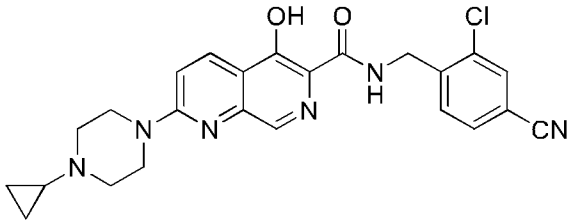
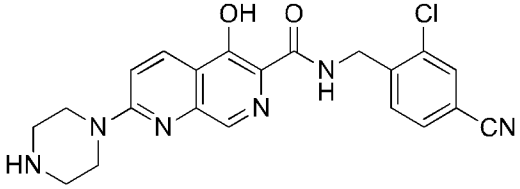
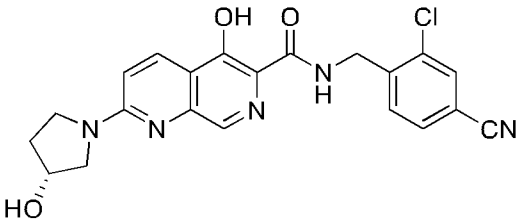
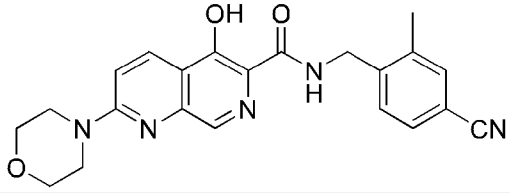
1	
2	
3	
4	
5	
6	
7	

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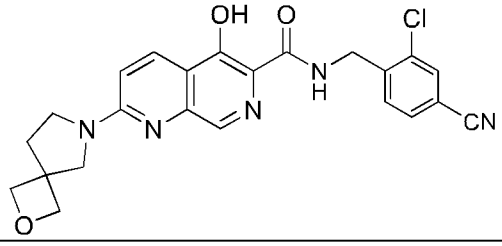
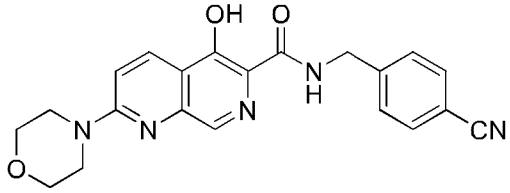
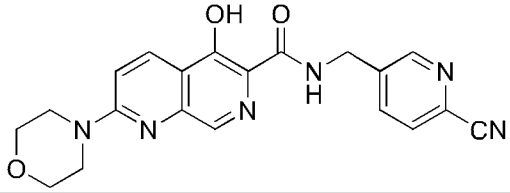
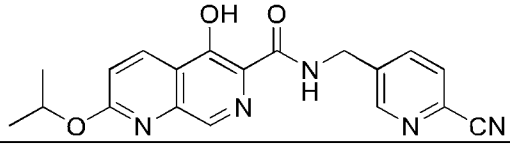
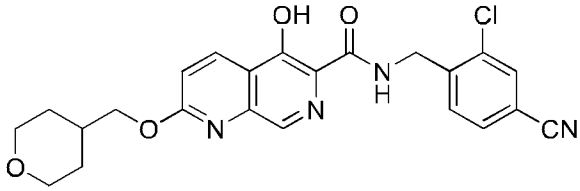
8	
9	
10	
11	
12	
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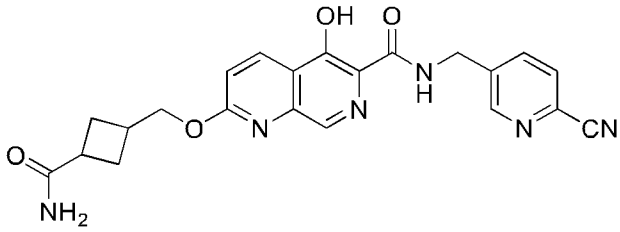
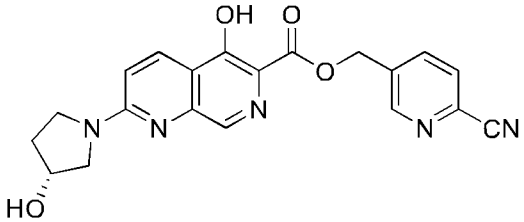
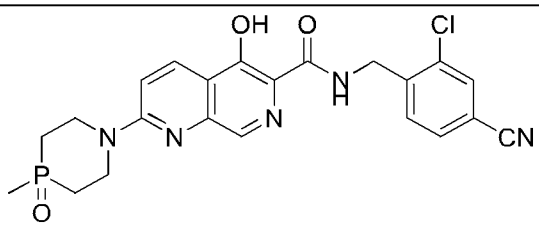
14	
15	
16	

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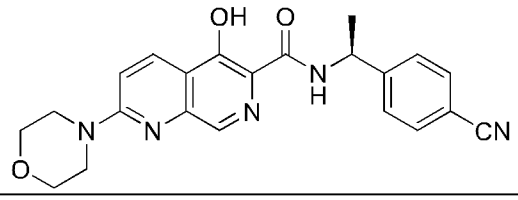
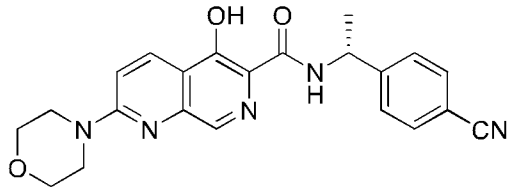
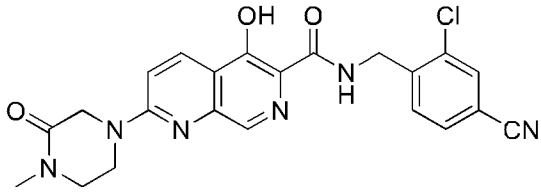
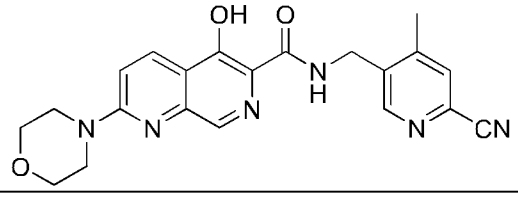
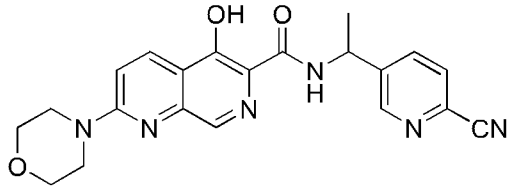
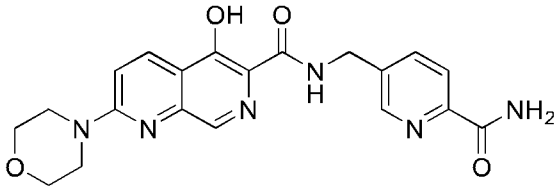
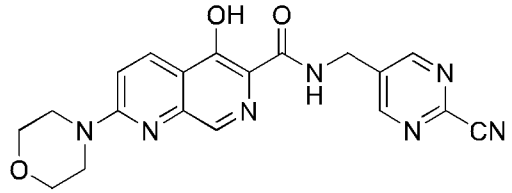
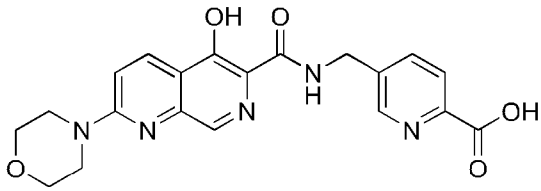
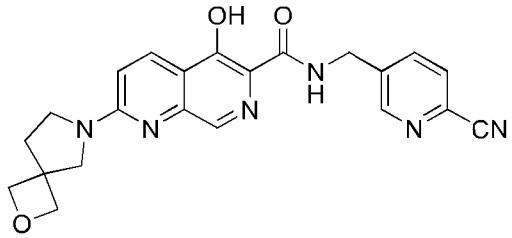
17	
18	
19	
20	
21	
22	
23	
24	
25	

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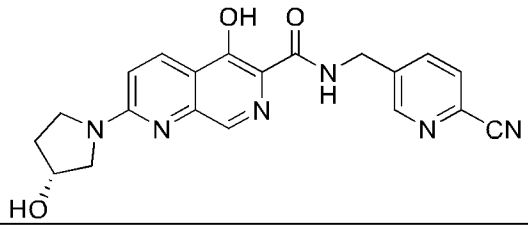
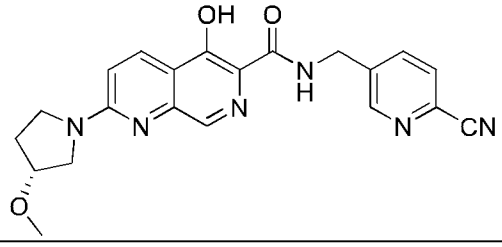
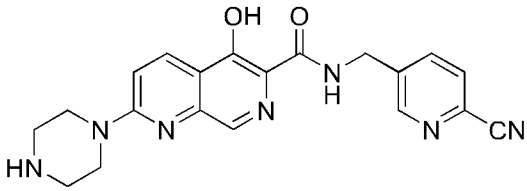
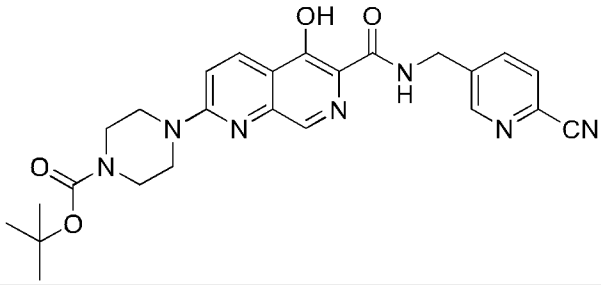
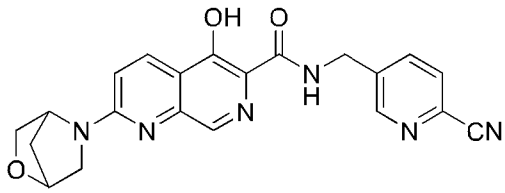
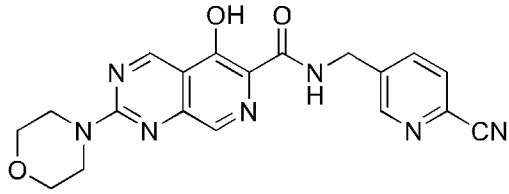
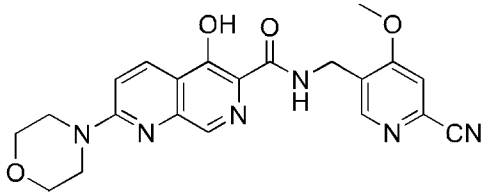
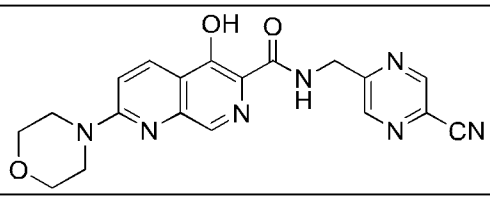
26	
27	
28	
29	
30	
31	
32	
33	

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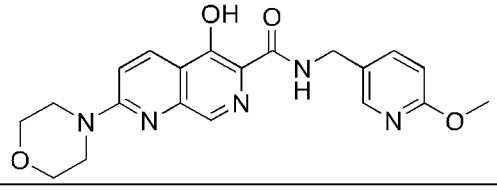
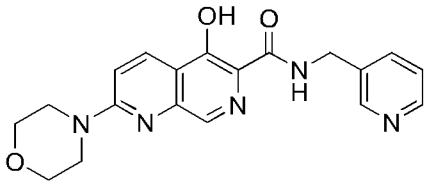
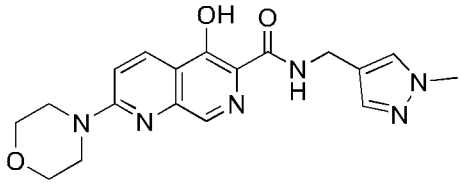
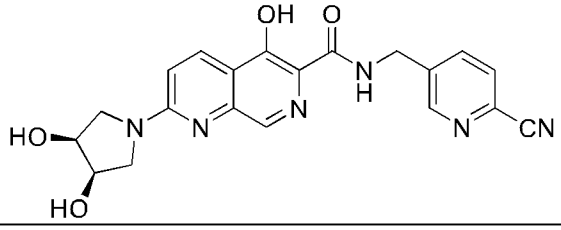
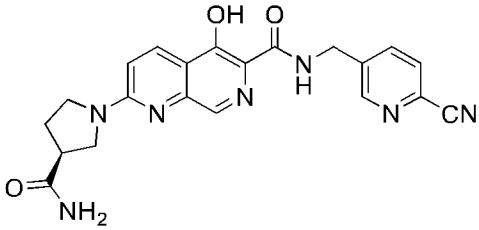
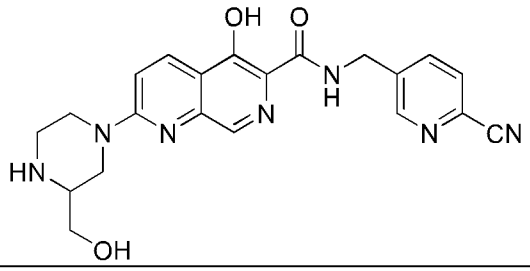
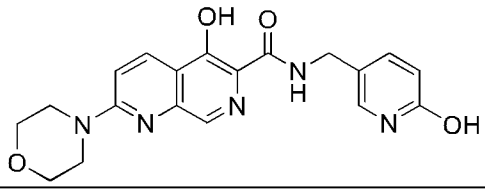
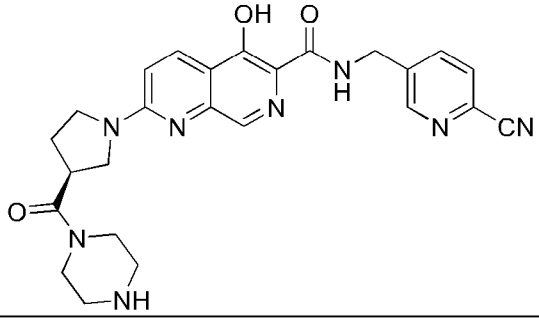
34	
35	
36	
37	
38	
39	
40	
41	

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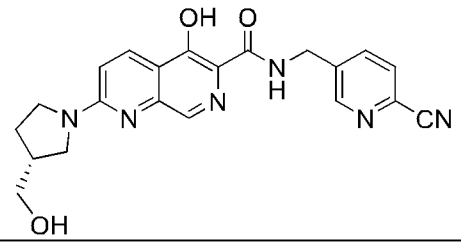
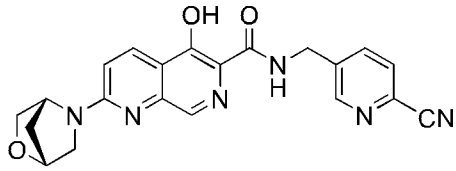
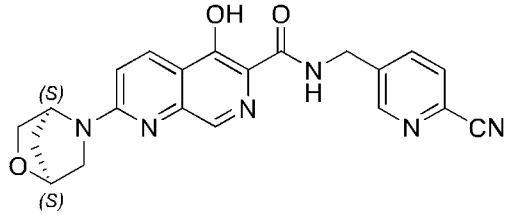
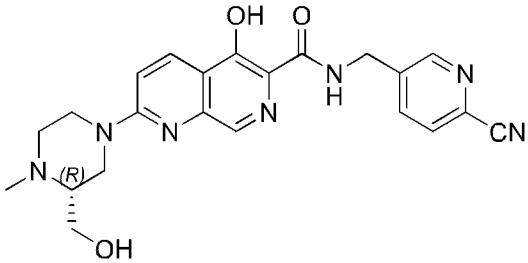
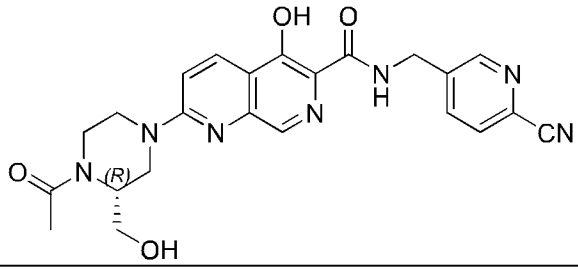
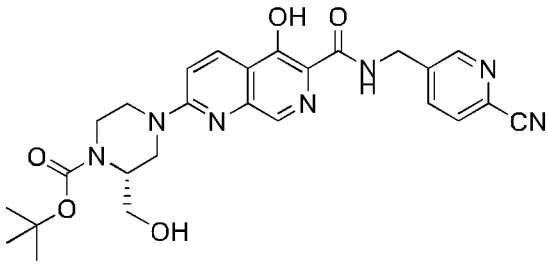
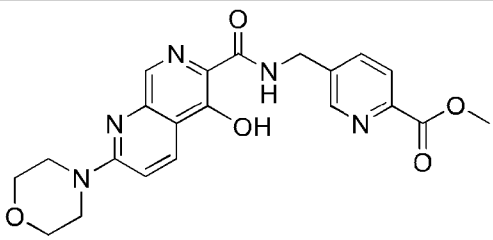
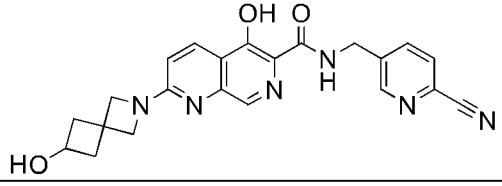
42	
43	
44	
45	
46	
47	
48	
49	

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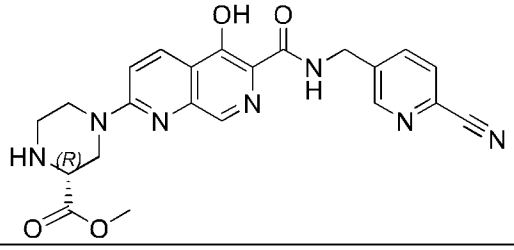
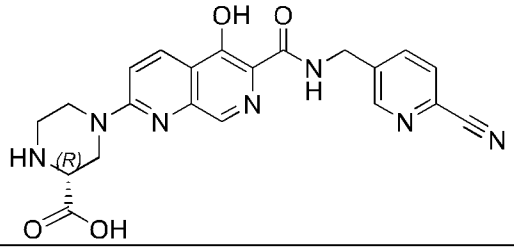
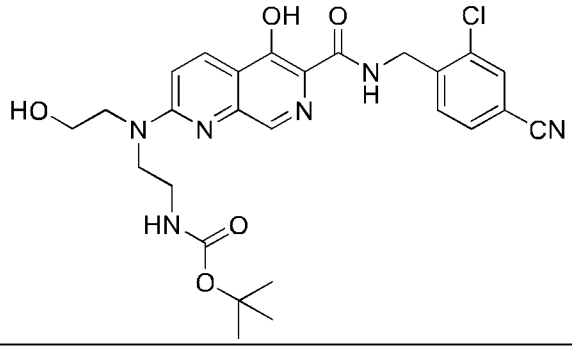
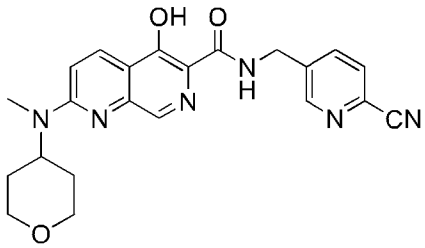
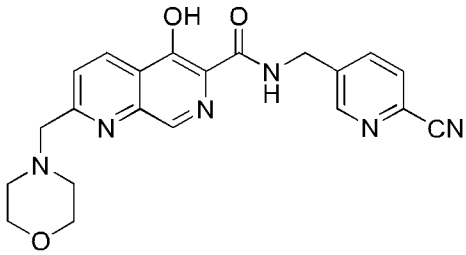
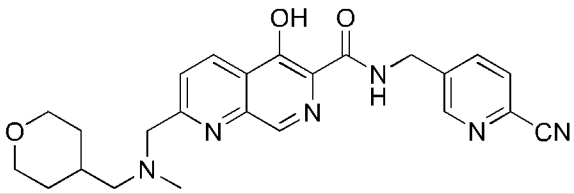
50	
51	
52	
53	
54	
55	

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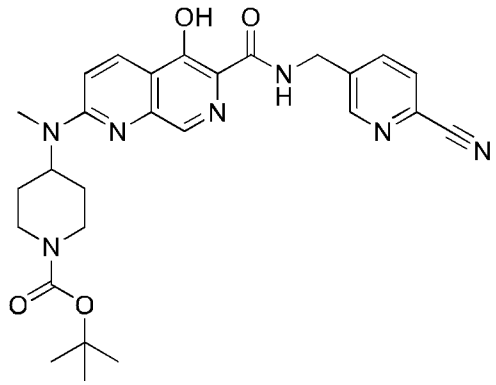
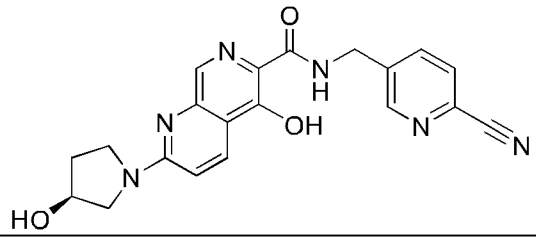
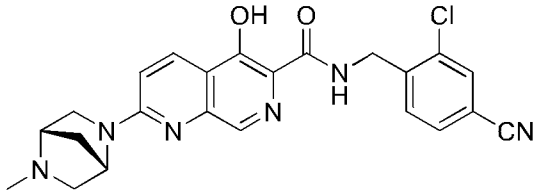
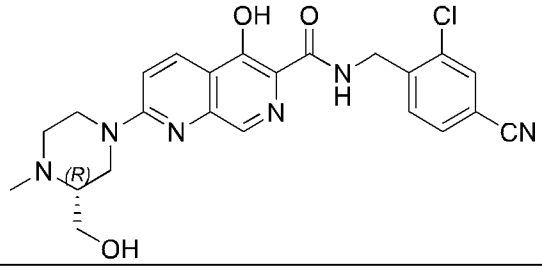
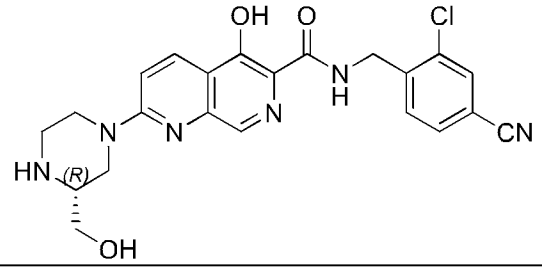
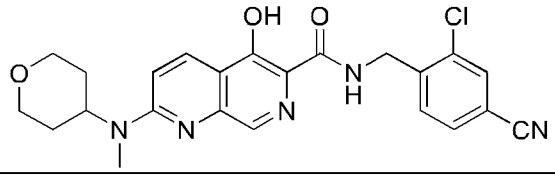
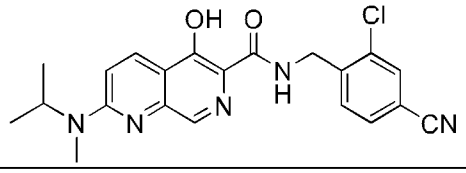
56	
57	
58	
59	
60	
61	
62	

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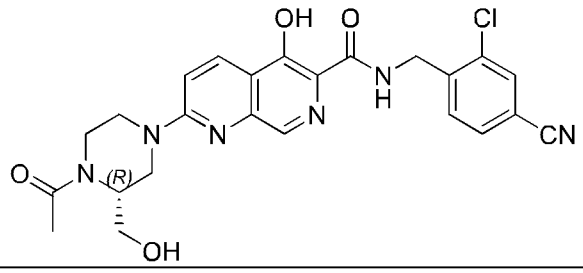
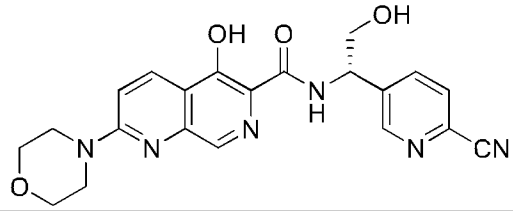
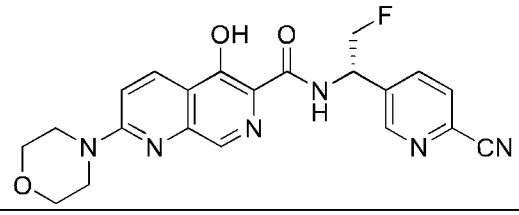
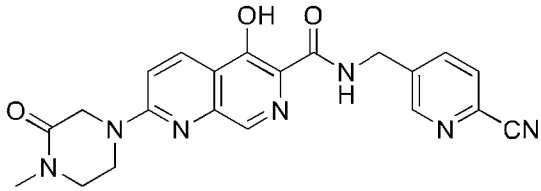
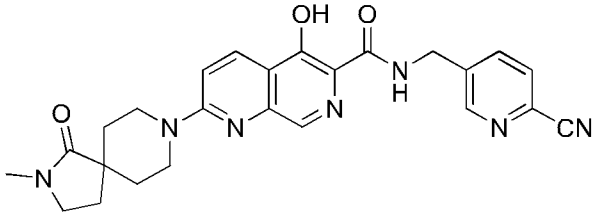
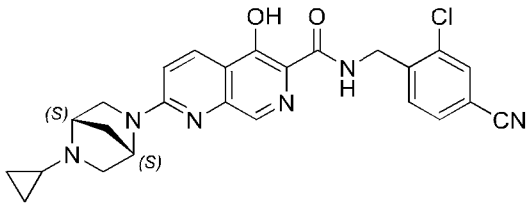
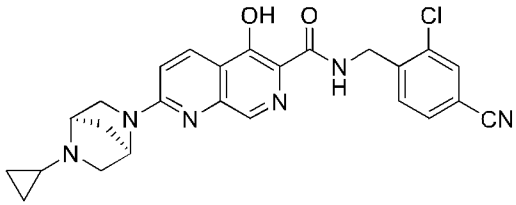
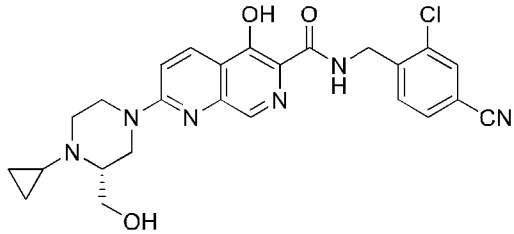
63	
64	
65	
66	
67	
68	
69	
70	

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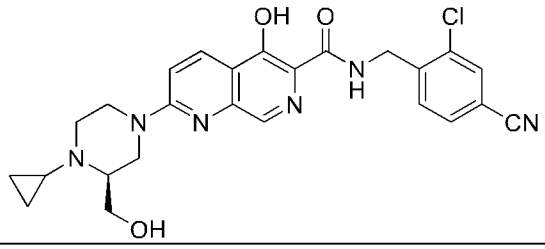
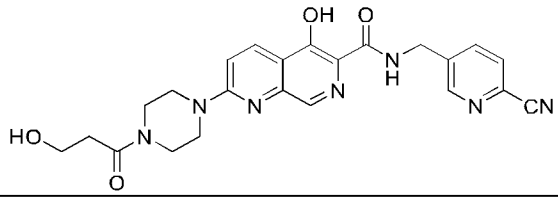
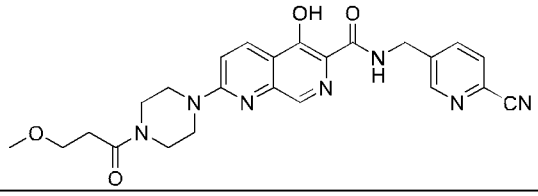
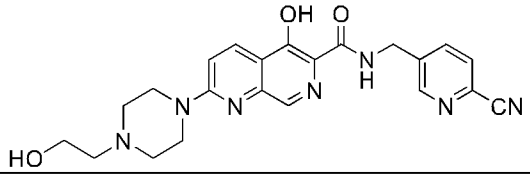
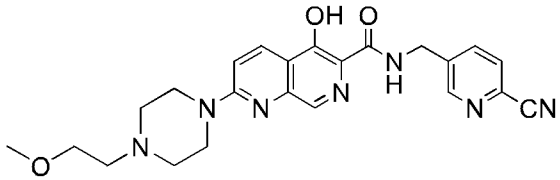
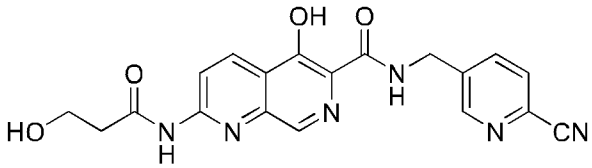
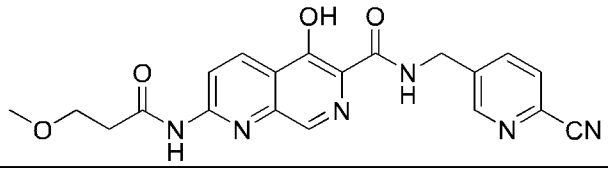
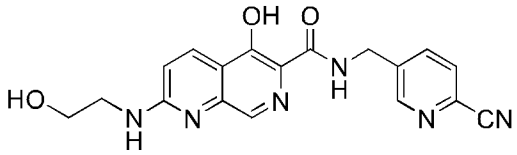
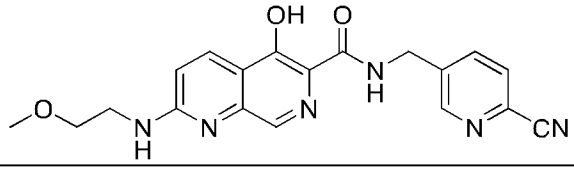
71	
72	
73	
74	
75	
76	
77	
78	
79	

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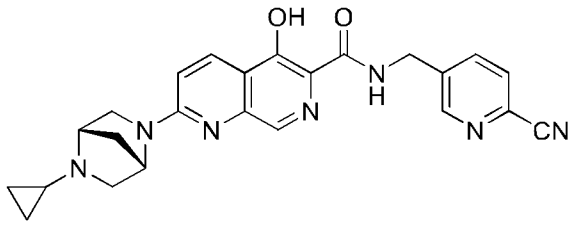
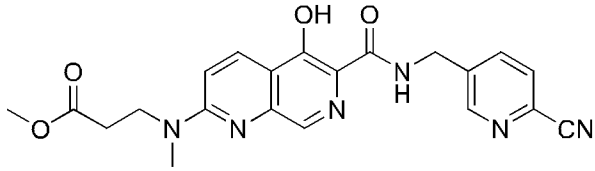
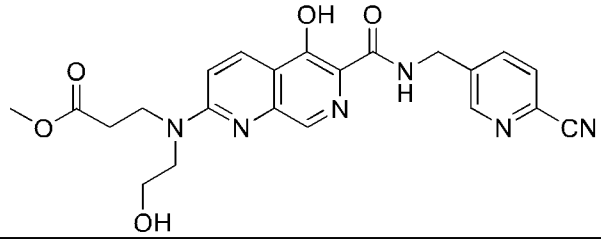
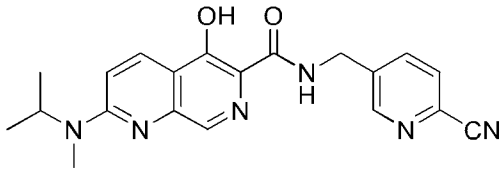
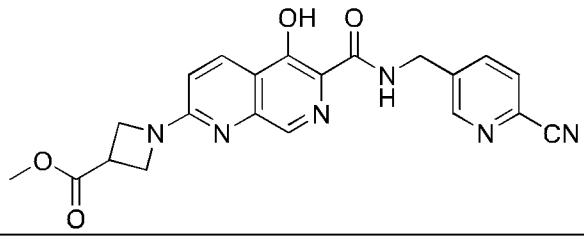
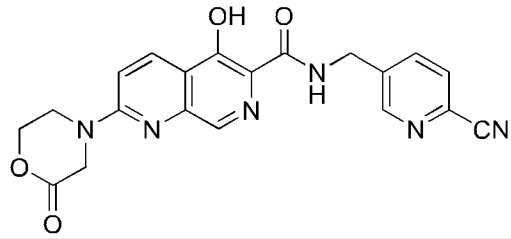
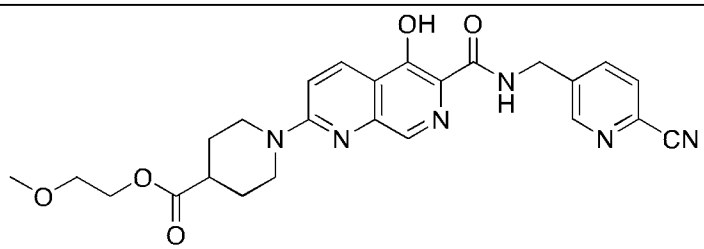
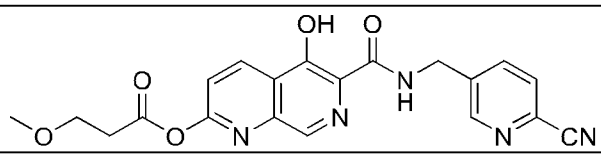
80	
81	
82	
83	
84	
85	
86	
87	

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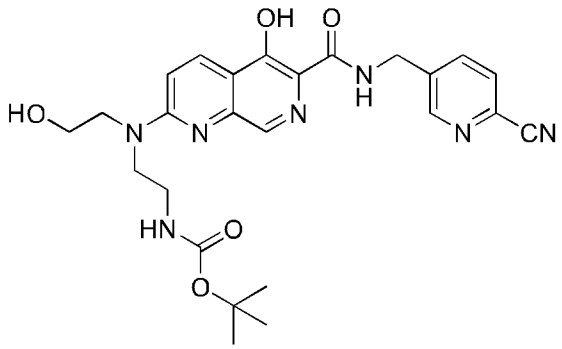
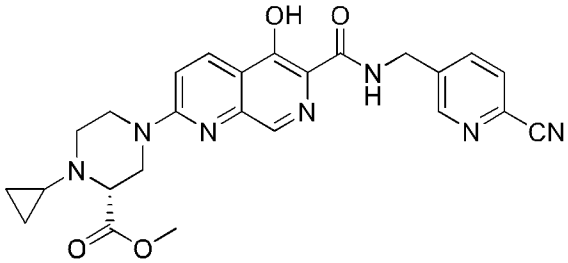
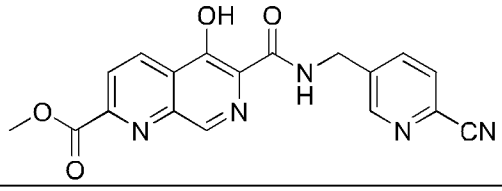
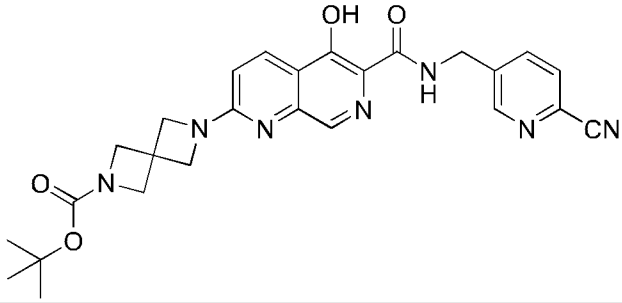
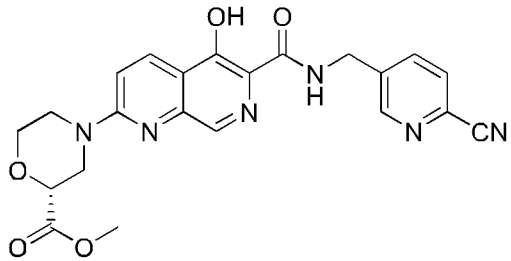
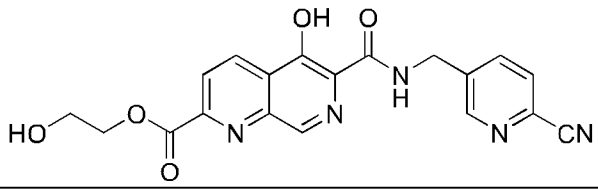
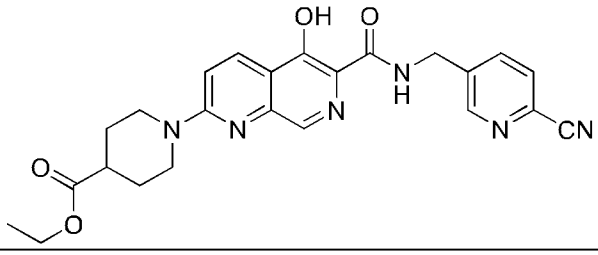
88	
89	
90	
91	
92	
93	
94	

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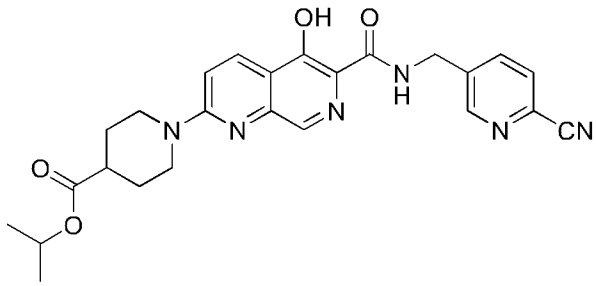
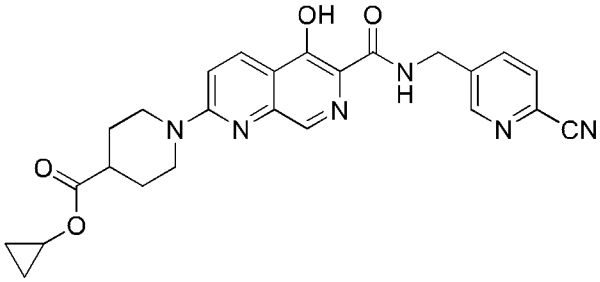
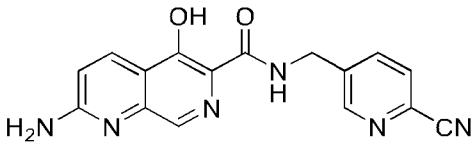
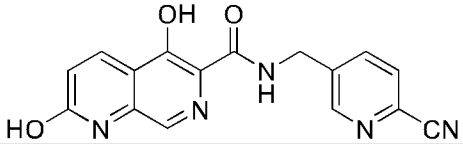
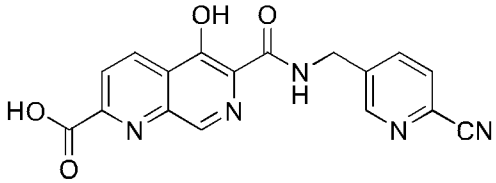
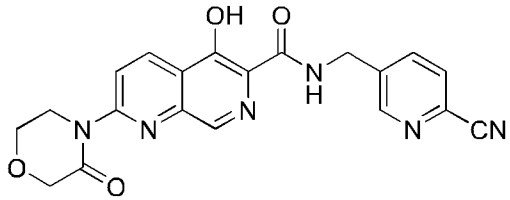
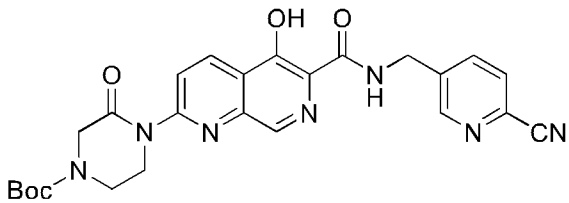
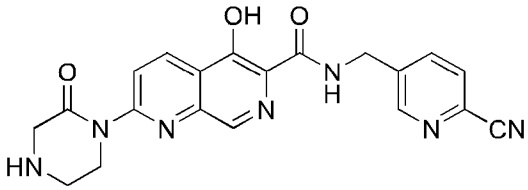
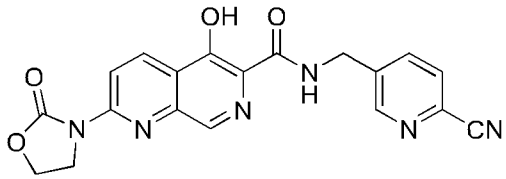
95	
96	
97	
98	
99	
100	
101	
102	
103	

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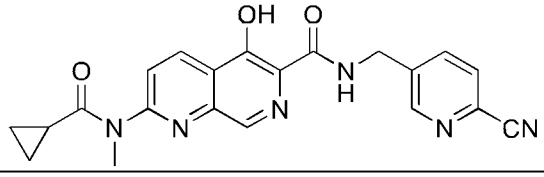
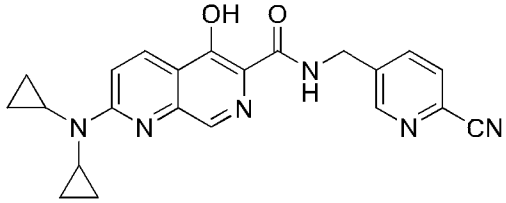
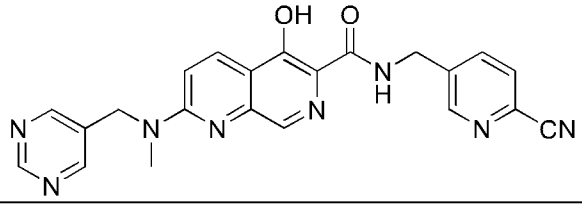
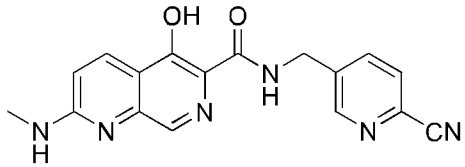
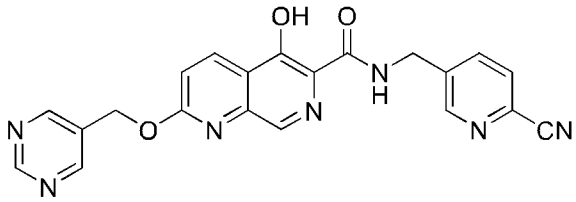
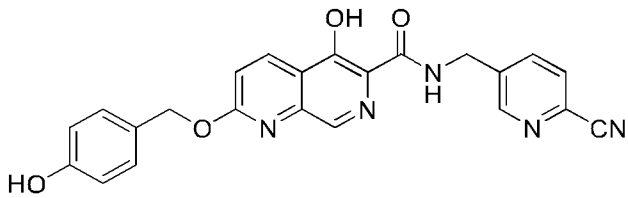
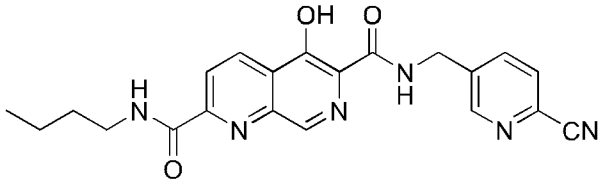
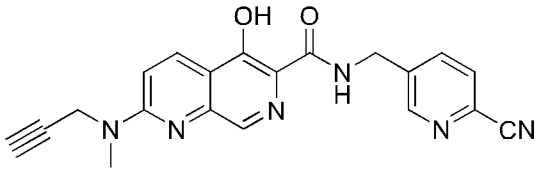
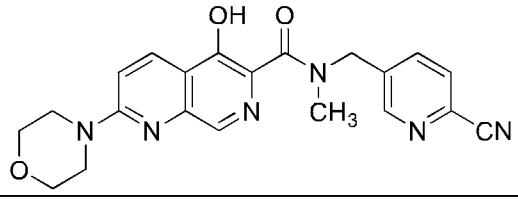
104	
105	
106	
107	
108	
109	
110	
111	
112	

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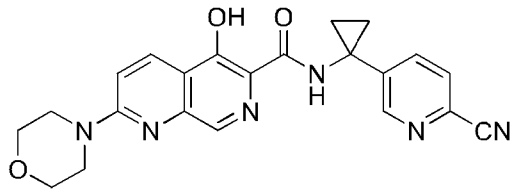
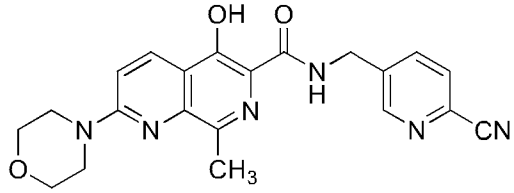
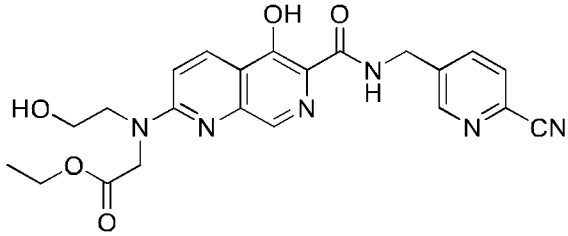
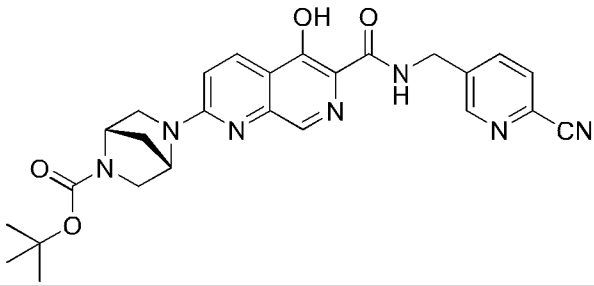
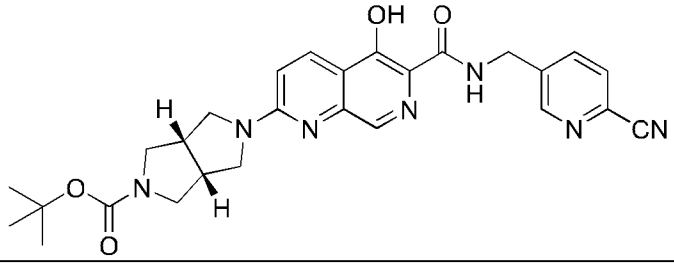
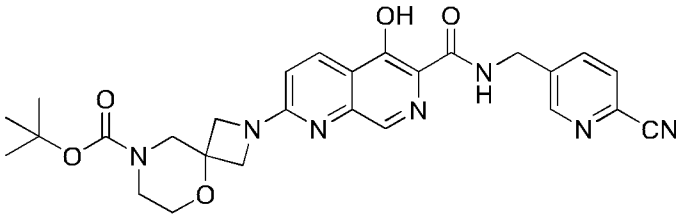
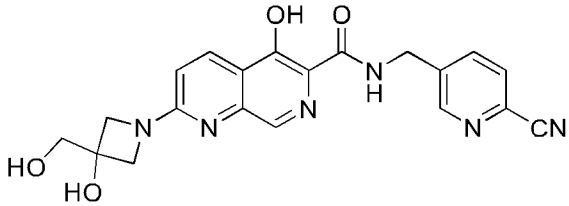
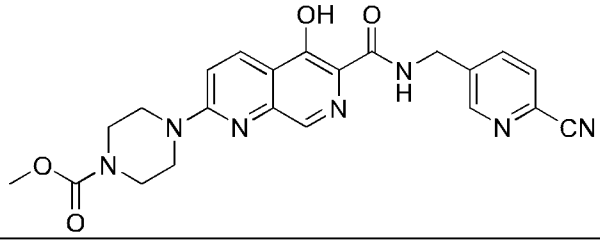
113	
114	
115	
116	
117	
118	
119	
120	

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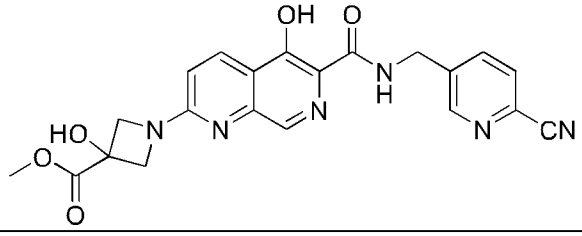
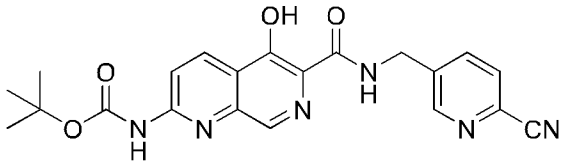
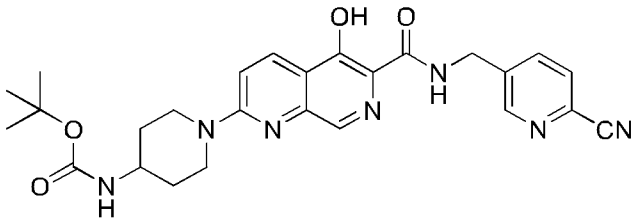
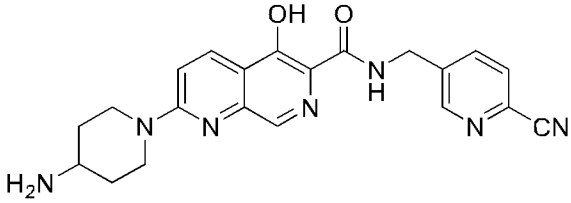
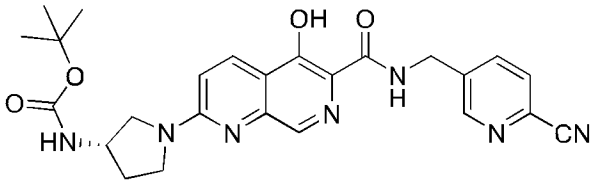
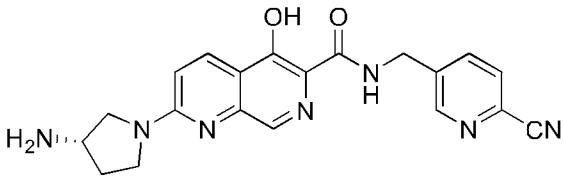
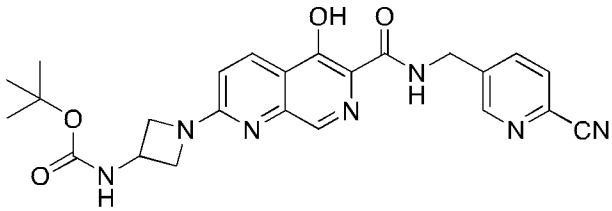
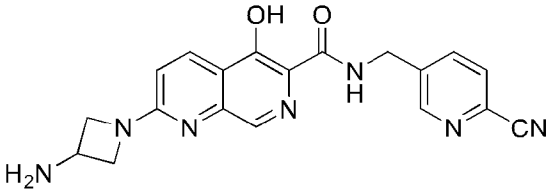
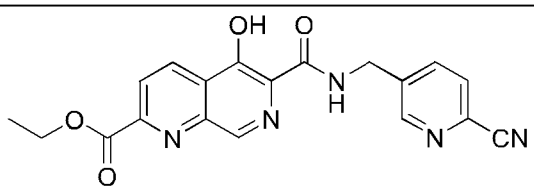
121	
122	
123	
124	
125	
126	
127	
128	
129	

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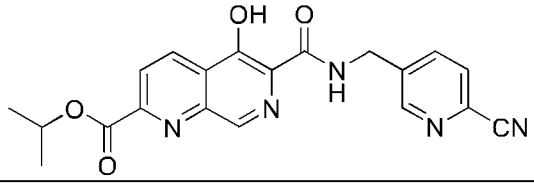
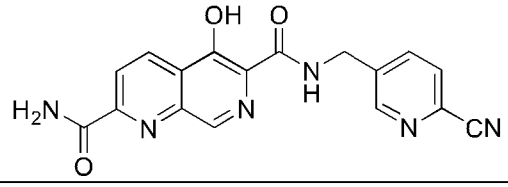
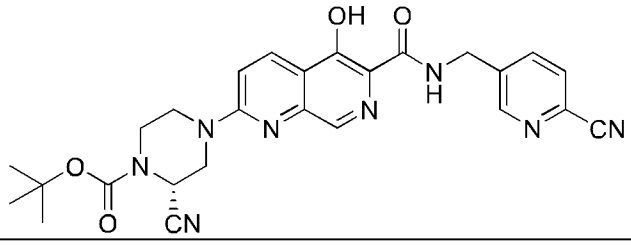
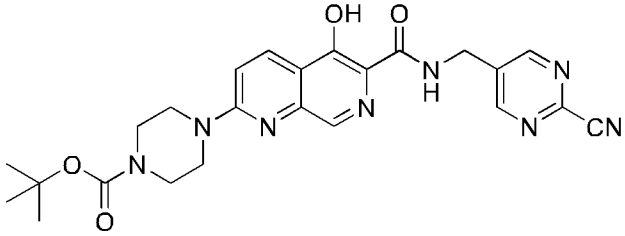
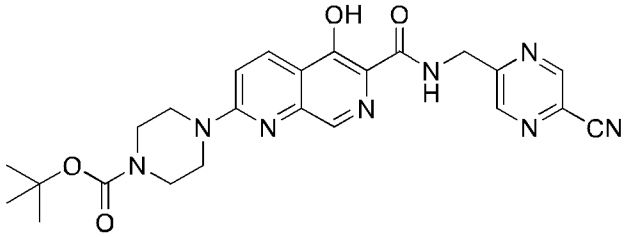
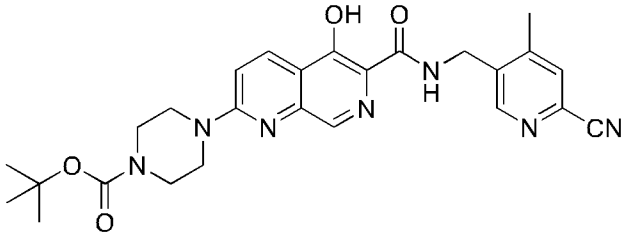
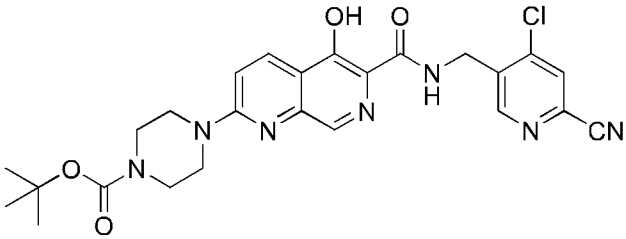
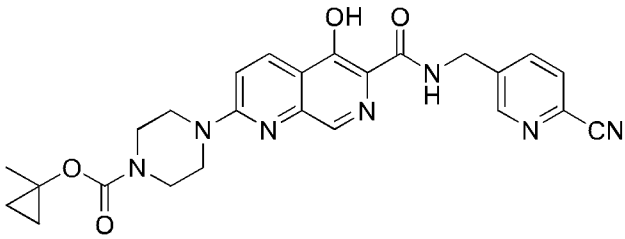
130	
131	
132	
133	
134	
135	
136	
137	

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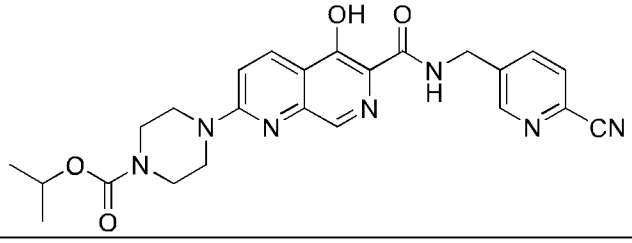
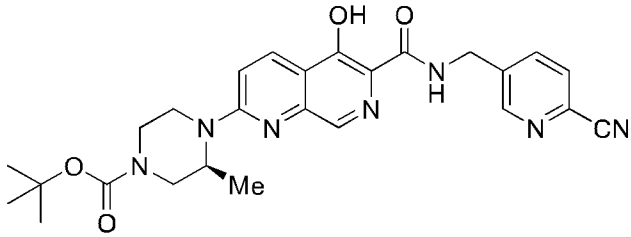
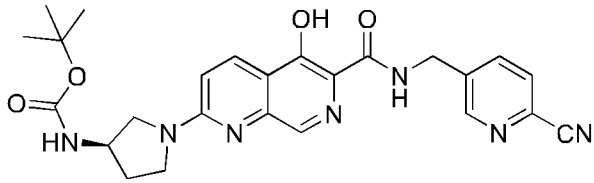
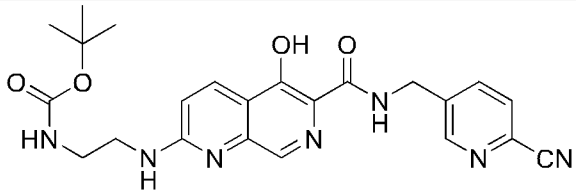
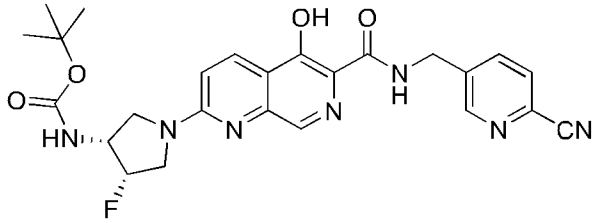
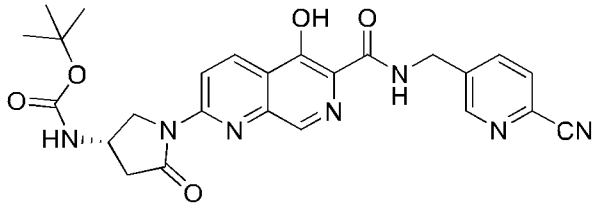
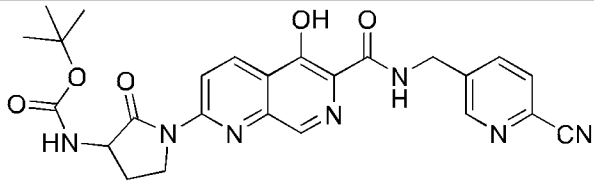
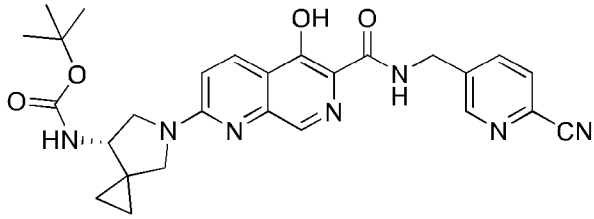
138	
139	
140	
141	
142	
143	
144	
145	

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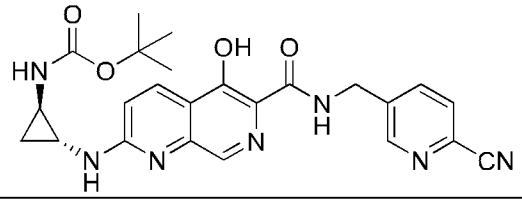
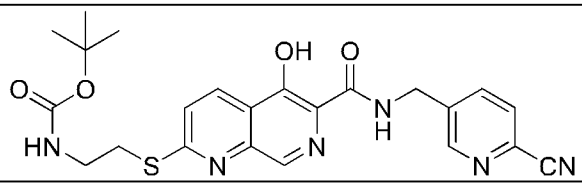
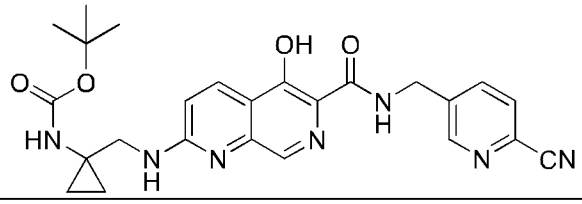
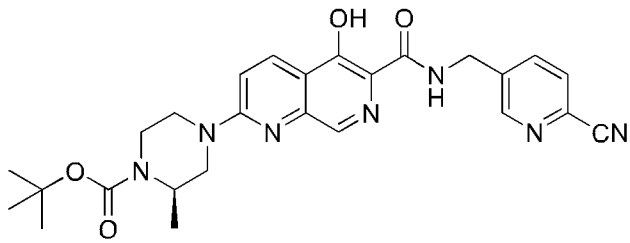
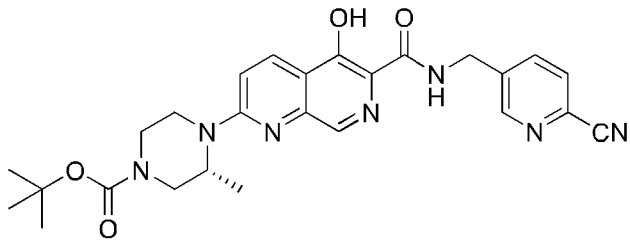
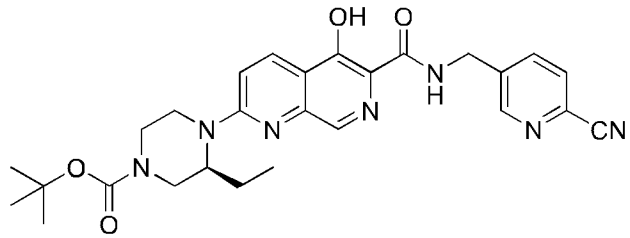
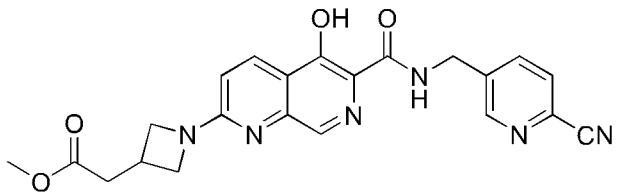
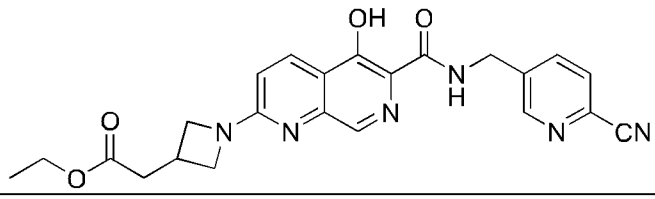
146	
147	
148	
149	
150	
151	
152	
153	

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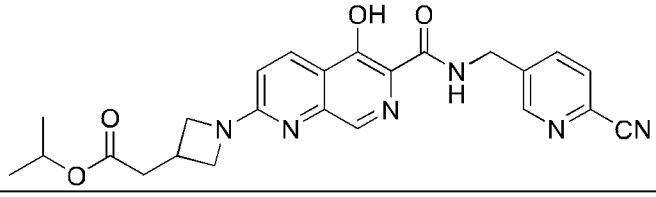
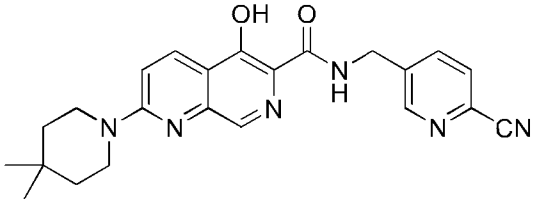
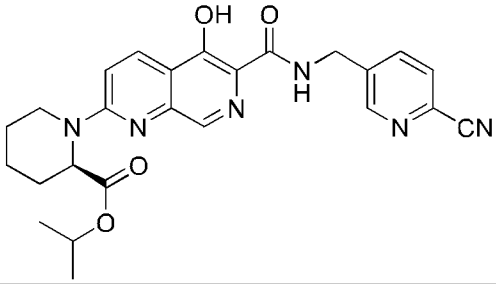
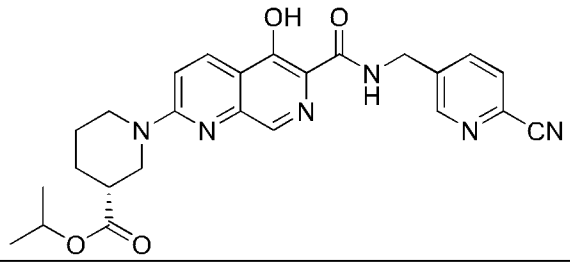
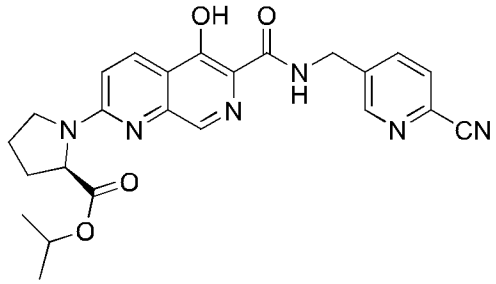
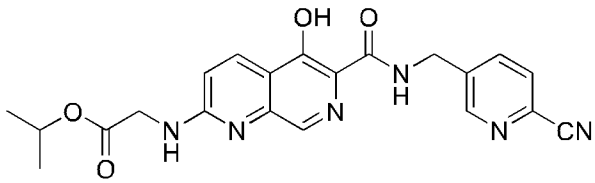
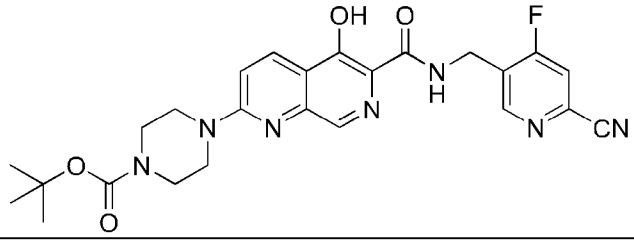
154	
155	
156	
157	
158	
159	
160	

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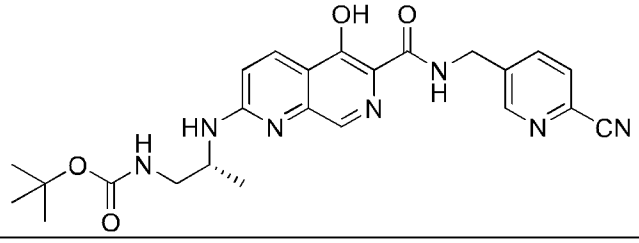
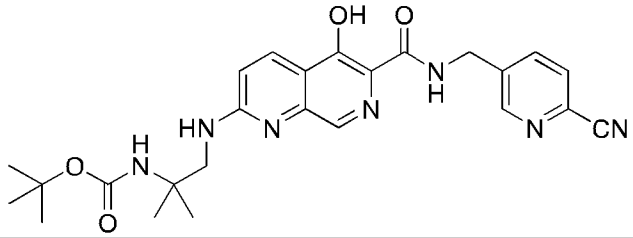
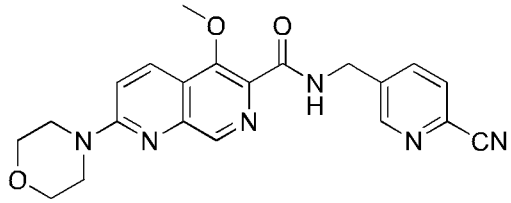
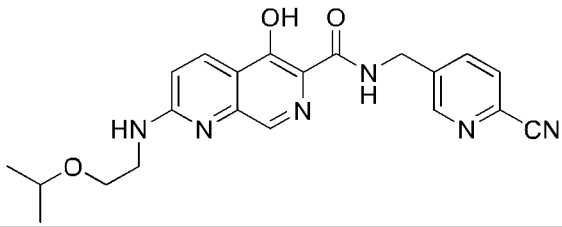
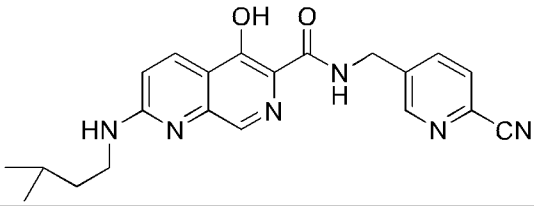
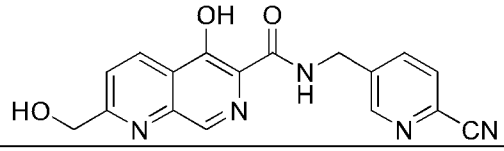
161	
162	
163	
164	
165	
167	

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00107] 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.

Labeled compounds

[00108] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^{2}H (D), ^{3}H (T), ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability.

[00109] In some embodiments, the abundance of deuterium in each of the substituents disclosed herein 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% of a total number of hydrogen and deuterium. In some embodiments, one or more of the substituents disclosed herein comprise deuterium at a percentage higher than the natural abundance of deuterium. In some embodiments, one or more hydrogens are replaced with one or more deuteriums in one or more of the substituents disclosed herein.

[00110] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00111] 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.

[00112] 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 a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00113] 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.

[00114] 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, solvate, or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[00115] 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.

[00116] 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

[00117] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00118] 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 such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Tautomers

[00119] 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

[00120] Disclosed herein is a method of treating a disease in which inhibition of PHD is beneficial, the method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the method comprises administering a

pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00121] Disclosed herein is a method of treating a disease or disorder associated with PHD, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00122] Disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the disease or disorder is cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, or cancer. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00123] Disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the disease or disorder is stroke, myocardial infarction, congestive heart failure, atherosclerosis, chronic venous insufficiency, cardiac cirrhosis, acute decompensated heart failure, heart failure following a heart attack, peripheral artery disease, occlusive artery disease, diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, impaired glucose tolerance, non-alcoholic liver steatosis, chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension, mountain sickness, acute respiratory failure, interstitial lung disease, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, acute kidney failure, acute kidney injury, renal ischemia reperfusion injury, hepatic ischemia reperfusion injury, diabetic foot ulcers, pressure ulcers, venous ulcers, arterial ulcers, epidermolysis bullosa, pemphigus, Sjogren's syndrome, anemia, inflammatory bowel disease (IBD), chronic kidney disease (CKD), Parkinson's disease (PD), or Alzheimer's disease (AD). In some embodiments, the disease or disorder is Parkinson's disease (PD). In some embodiments, the disease or disorder is Alzheimer's disease (AD).

[00124] In some embodiments, the disease or disorder is anemia, inflammatory bowel disease (IBD), or chronic kidney disease (CKD). In some embodiments, the disease or disorder is anemia. In some embodiments, the disease or disorder is inflammatory bowel disease (IBD). In some embodiments, the disease or disorder is chronic kidney disease (CKD). In some embodiments, the disease or disorder is ulcerative colitis ("UC") or Crohn's disease ("CD"). In some embodiments, the disease or disorder is ulcerative colitis ("UC"). In some embodiments, the disease or disorder is Crohn's disease ("CD").

[00125] Disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the disease or disorder is cancer, including leukemia (e.g., chronic myelogenous leukemia and chronic lymphocytic leukemia); breast cancer; genitourinary cancer; skin cancer; bone cancer; prostate cancer; liver cancer; brain cancer; cancer of the larynx, gall bladder, rectum, parathyroid, thyroid, adrenal, neural tissue, bladder, head, neck, stomach, bronchi, and kidneys; basal cell carcinoma, squamous cell carcinoma, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, reticulum cell sarcoma, and Kaposi's sarcoma; myeloma, giant cell tumor, islet cell tumor, acute and chronic lymphocytic and granulocytic tumors; hairy-cell tumor, adenoma, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilms' tumor, seminoma, ovarian tumor, leiomyomatous tumor, cervical dysplasia, neuroblastoma, retinoblastoma, myelodysplastic syndrome, rhabdomyosarcoma, astrocytoma, non-Hodgkin's lymphoma, malignant hypercalcemia, polycythemia vera, adenocarcinoma, glioblastoma multiforma, glioma, lymphomas, and malignant melanomas. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00126] In one aspect, disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition comprising the same. In one aspect, disclosed herein is a method of modulating PHD in a subject in need thereof. In one aspect, disclosed herein is a method of inhibiting PHD in a subject in need thereof. In one aspect, disclosed herein is a method of stabilizing hypoxia inducible factor (HIF) in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition comprising the same. In some embodiments, the HIF is HIF-1α. In some embodiments, the method comprises administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the subject has a disease or disorder that is cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, or cancer. In some embodiments, the subject has a disease or disorder that is stroke, myocardial infarction, congestive heart failure, atherosclerosis, chronic venous insufficiency, cardiac cirrhosis, acute decompensated heart failure, heart failure following a heart attack, peripheral artery disease, occlusive artery disease, diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, impaired glucose tolerance, non-alcoholic liver steatosis, chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension, mountain sickness, acute respiratory failure, interstitial lung disease, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis-associated interstitial lung

disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, acute kidney failure, acute kidney injury, renal ischemia reperfusion injury, hepatic ischemia reperfusion injury, diabetic foot ulcers, pressure ulcers, venous ulcers, arterial ulcers, epidermolysis bullosa, pemphigus, Sjogren's syndrome, anemia, inflammatory bowel disease (IBD), chronic kidney disease (CKD), Parkinson's disease (PD), or Alzheimer's disease (AD). In some embodiments, the disease or disorder is Parkinson's disease (PD). In some embodiments, the disease or disorder is Alzheimer's disease (AD). In some embodiments, the disease or disorder is anemia, inflammatory bowel disease (IBD), or chronic kidney disease (CKD). In some embodiments, the disease or disorder is anemia. In some embodiments, the disease or disorder is anemia resulting from chronic kidney diseases. In some embodiments, the disease or disorder is inflammatory bowel disease (IBD). In some embodiments, the disease or disorder is chronic inflammation of the digestive tract. In some embodiments, the disease or disorder is ulcerative colitis (UC). In some embodiments, the disease or disorder is Crohn's disease (CD). In some embodiments, the disease or disorder is chronic kidney disease (CKD). In some embodiments, the disease or disorder is cancer, including leukemia (e.g., chronic myelogenous leukemia and chronic lymphocytic leukemia); breast cancer; genitourinary cancer; skin cancer; bone cancer; prostate cancer; liver cancer; brain cancer; cancer of the larynx, gall bladder, rectum, parathyroid, thyroid, adrenal, neural tissue, bladder, head, neck, stomach, bronchi, and kidneys; basal cell carcinoma, squamous cell carcinoma, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, reticulum cell sarcoma, and Kaposi's sarcoma; myeloma, giant cell tumor, islet cell tumor, acute and chronic lymphocytic and granulocytic tumors; hairy-cell tumor, adenoma, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilms' tumor, seminoma, ovarian tumor, leiomyomatous tumor, cervical dysplasia, neuroblastoma, retinoblastoma, myelodysplastic syndrome, rhabdomyosarcoma, astrocytoma, non-Hodgkin's lymphoma, malignant hypercalcemia, polycythemia vera, adenocarcinoma, glioblastoma multiforma, glioma, lymphomas, and malignant melanomas.

Anemia

[00127] Anemia is a frequent and serious complication of chronic kidney diseases with a relative deficiency in EPO production and a decrease in iron availability for hemoglobin ("Hb") synthesis. According to Informa, in 2020, there were 168 million prevalent cases of anemia resulted from chronic kidney diseases around the world. It is estimated that the number will rise to 182 million in 2027, according to the same source.

[00128] Currently, anemia resulting from chronic kidney diseases is managed by iron supplementation and, in more severe cases, by administration of supraphysiologic doses of erythropoiesis stimulating agents ("ESAs") in combination with adjuvant iron therapy. High doses of ESAs increase the risk of serious adverse events, including myocardial infarction, congestive heart failure, stroke, and death. Several inhibitors of PHDs have been launched and may serve as effective treatments for patients with anemia resulted from chronic kidney disease. However, the cardiovascular side effects caused by erythropoietin induction and potential off-target toxicities may raise safety concerns for long-term

treatment. New therapies are needed to address both impaired EPO production and functional iron deficiency.

Inflammatory Bowel Disease (IBD)

[00129] IBD is an umbrella term used to describe disorders that involve chronic inflammation of the digestive tract. Types of IBD include ulcerative colitis ("UC") and Crohn's disease ("CD"). IBD symptoms vary and depend on the severity of inflammation and the location it occurs. According to GlobalData, in 2019, there were 1.7 million diagnosed UC patients in 8 major markets (US, 5EU, Japan and Canada) and the market sales reached $6.8 billion in that year. [In addition, there were 1.3 million UC diagnosed prevalent population in 8 major markets (US, 5EU, Japan and Canada) and the market sales reach $7.4 billion.]

[00130] Inflammatory bowel diseases are characterized by repeated inflammation and wounding of the mucosa and loss of the intestinal epithelial barrier function, which lead to the passage of bacteria or bacterial products from the gut lumen to the serosa and into the blood, resulting in systemic bacteremia and endotoxemia. PHD inhibition has been shown to reduce disease severity in murine models of colitis on several levels of clinical scoring. The proposed mechanism for the therapeutic activity of PHD inhibitors is through HIF-1α stabilization, which drives epithelial barrier augmentation and healing.

[00131] Despite the efficacy of current treatment with anti-inflammation agents or immune-suppressive agents, a large fraction of IBD patients do not respond adequately to currently available therapies and do not achieve long-term remission. Inhibitors of PHDs may provide a new therapeutic option for IBD and may be combined with available anti-inflammatory drugs to achieve an enhanced efficacy.

Dosing

[00132] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or 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. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00133] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder, or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of or risk factor for the disease being treated and is currently in

remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00134] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00135] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00136] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage, or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent or daily treatment on a long-term basis upon any recurrence of symptoms.

[00137] 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.

[00138] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00139] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage, or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00140] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the

determination of the LD_{10} and the ED_{90}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00141] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00142] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00143] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the subject every 12 hours; (v) the compound is administered to the subject every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Routes of Administration

[00144] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00145] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular

injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00146] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, and topical routes of administration.

[00147] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00148] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

[00149] The pharmaceutical compositions described herein are administered to a subject by appropriate administration routes, including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent

formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00150] Pharmaceutical compositions including compounds described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes.

[00151] Pharmaceutical compositions for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00152] Pharmaceutical compositions that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00153] Pharmaceutical compositions for parental use are formulated as infusions or injections. In some embodiments, the pharmaceutical composition suitable for injection or infusion includes sterile aqueous solutions, or dispersions, or sterile powders comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the pharmaceutical composition comprises a liquid carrier. In some embodiments, the liquid carrier is a solvent or liquid dispersion medium comprising, for example, water, saline, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and any combinations thereof. In some embodiments, the pharmaceutical compositions further comprise a preservative to prevent growth of microorganisms.

Combination

[00154] Disclosed herein are methods of treating a disease or disorder associated with PHD using a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in combination with an additional therapeutic agent.

[00155] In some embodiments, the additional therapeutic agent is administered at the same time as the compound disclosed herein. In some embodiments, the additional therapeutic agent and the compound disclosed herein are administered sequentially. In some embodiments, the additional therapeutic agent is administered less frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered more frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered prior than the administration of the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered after the administration of the compound disclosed herein.

[00156] In some embodiments, the additional therapeutic agent is a compound or therapy for cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, and cancer, among others.

[00157] In some embodiments, the additional therapeutic agent is a cardiovascular agent such as calcium channel blockers, including amlodipine, clevidipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil; statins, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin; a fibrate, including gemfibrozil and fenofibrate; beta-blockers, including acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalo metoprolol, nadolol, nebivolol, penbutolol, propranolol, sotalol, and timolol; an ACE inhibitor, including benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril; and platelet aggregation inhibitors, including aspirin, cangrelor, clopidogrel, cilostazol, dipyridamole, prasugrel, and ticagrelor.

[00158] In some embodiments, the additional therapeutic agent is an agent for treating metabolic disorders. These agents include pancreatic lipase inhibitors (e.g., orlistat); insulin; insulin sensitizers, including biguanides (e.g., buformin, metformin, and phenformin) and glitazones (e.g., pioglitazone and rosiglitazone); insulin secretagogues, including sulfonylureas (e.g., acetohexamide, chlorpropamide, tolazamide, tolbutamide, gliclazide, glimepiride, glipizide, and glyburide), and meglitinides (e.g., nateglinide and repaglinide); alpha-glucosidase inhibitors (e.g., acarbose and miglitol); glucagon-like peptide analogs and agonists (e.g., exenatide, liraglutide, and taspoglutide); dipeptidyl peptidase-4 inhibitors (e.g., alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin); and amylin analogs (e.g., pramlinitide).

[00159] In some embodiments, the additional therapeutic agent is an agent for treating wound healing disorders. In some embodiments, the additional therapeutic agent is an anti-inflammatory agent, analgesics, an antipruritic, or an anti-infective.

[00160] Examples of anti-inflammatory agents include nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Representative NSAIDs include apazone, aspirin, celecoxib, diclofenac (with and without misoprostol), diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, choline and magnesium salicylates, salsalate, and sulindac. Representative corticosteroids include betamethasone, cortisone acetate, dexamethasone, hydrocortisone, methylprednisolone,

prednisolone, and prednisone. Representative analgesics include acetaminophen and morphine sulfate, as well as codeine, hydrocodone, oxycodone, propoxyphene, and tramadol, all with or without acetaminophen. Representative antipruritics for systemic use include cyproheptadine, diphenhydramine, gabapentin, hydroxyzine, and ondansetron.

[00161] Representative antipruritics for topical use include ammonium lactate, benzocaine, calamine, capsaicin, clioquinol, crotamiton, diphenhydramine, doxepin, hydrocortisone, lidocaine, menthol, methyl salicylate, and pramoxine.

[00162] Example anti-infective agents may include antibacterials, antifungals, and antivirals.

[00163] Representative antibacterials include aminoglycosides, such as amikacin, gentamicin, kanamycin, neomycin, paromomycin, and tobramycin; carbapenems, such as doripenem, ertapenem, imipenem, and meropenem; cephalosporins, including combinations with beta- lactamase inhibitors such as ceftazidime/avibactam and ceftolozane/tazobactam; first- generation cephalosporins, such as cefadroxil, cefazolin, cephalexin, and cephradine; second- generation cephalosporins, such as cefotetan, cefprozil, cefuroxime, efoxitin, and loracarbef; third-generation cephalosporins, such as cefdinir, cefditoren, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, and ceftriaxone; and fourth- and next-generation cephalosporins, such as cefepime and ceftaroline; glycopeptide antibiotics, such as dalbavancin, oritavancin, telavancin, and vancomycin; glycylcyclines, such as tigecycline; lincomycin and its derivatives, such as clindamycin; macrolides, such as azithromycin, clarithromycin, erythromycin, and fidaxomicin, and macrolide derivatives, including ketolides such as telithromycin; oxazolidinone antibiotics, such as linezolid and tedizolid; penicillins, including aminopenicillins, such as amoxicillin and ampicillin; antipseudomonal penicillins, such as carbenicillin, piperacillin, and ticarcillin; penicillins with beta-lactamase inhibitors such as amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, and ticarcillin/clavulanate; natural penicillins, such as penicillin G benzathine, penicillin V potassium, and procaine penicillin; penicillinase resistant penicillins, such as dicloxacillin, nafcillin, and oxacillin; quinolones, such as cinoxacin, ciprofloxacin, delafloxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, and trovafloxacin; sulfonamides, such as sulfamethoxazole/trimethoprim and sulfisoxazole; tetracycline and its derivatives, such as demeclocycline, doxycycline, doxycycline/omega-3 polyunsaturated fatty acids, doxycycline/salicylic acid, minocycline, and oxytetracycline. Other representative antibacterials include atovaquone, aztreonam, bacitracin, chloramphenicol, colistimethate, dalfopristin/quinupristin, daptomycin, erythromycin/sulfisoxazole, fosfomycin, metronidazole, pentamidine, rifaximin, spectinomycin, and trimetrexate.

[00164] Representative antifungals include azole antifungals, such as clotrimazole, fluconazole, isavuconazonium, itraconazole, ketoconazole, miconazole, posaconazole, and voriconazole; echinocandins, such as anidulafungin, caspofungin, and micafungin; and polyenes, such as amphotericin B, amphotericin B cholesteryl sulfate, amphotericin B lipid complex, and nystatin. Other representative antifungals include flucytosine, griseofulvin, and terbinafine.

[00165] Representative antiviral agents include purine nucleosides, such as acyclovir, cidofovir, famciclovir, ganciclovir, ribavirin, valacyclovir, and valganciclovir.

[00166] In some embodiments, the additional therapeutic agent is an anti-cancer agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent (i.e., cytotoxic, or antineoplastic agents) such as alkylating agents, antibiotics, antimetabolic agents, plant- derived agents, and topoisomerase inhibitors, as well as molecularly targeted drugs which block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Molecularly targeted drugs include both small molecules and biologics.

[00167] Representative alkylating agents include bischloroethylamines (nitrogen mustards) including chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and uracil mustard); aziridines, including thiotepa; alkyl alkone sulfonates, including busulfan; nitrosoureas, including carmustine, lomustine, and streptozocin; nonclassical alkylating agents, including altretamine, dacarbazine, and procarbazine; and platinum compounds, including carboplatin, cisplatin, nedaplatin, oxaliplatin, satraplatin, and triplatin tetranitrate.

[00168] Representative antibiotic agents include anthracyclines, including aclarubicin, amrubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin, valrubicin, and zorubicin; anthracenediones, including mitoxantrone and pixantrone; and Streptomyces, including actinomycin, bleomycin, dactinomycin, mitomycin C, and plicamycin.

[00169] Representative antimetabolic agents include dihydrofolate reductase inhibitors, including aminopterin, methotrexate, and pemetrexed; hymidylate synthase inhibitors, including raltitrexed and pemetrexed; folinic acid, including leucovorin; adenosine deaminase inhibitors, including pentostatin; halogenated/ribonucleotide reductase inhibitors, including cladribine, clofarabine, and fludarabine; thiopurines, including thioguanine and mercaptopurine; thymidylate synthase inhibitors, including fluorouracil, capecitabine, tegafur, carmofur, and floxuridine; DNA polymerase inhibitors, including cytarabine; ribonucleotide reductase inhibitors, including gemcitabine; hypomethylating agent, including azacitidine and decitabine; ribonucleotide reductase inhibitor, including hydroxyurea; and an asparagine deplete, including asparaginase.

[00170] Representative plant-derived agents include vinca alkaloids, including vincristine, vinblastine, vindesine, vinzolidine, and vinorelbine; podophyllotoxins, including etoposide and teniposide; and taxanes, including docetaxel, larotaxel, ortataxel, paclitaxel, and tesetaxel.

[00171] Representative type I topoisomerase inhibitors include camptothecins, including belotecan, irinotecan, rubitecan, and topotecan. Representative type II topoisomerase inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide, which are derivatives of epipodophyllotoxins.

[00172] Molecularly targeted therapies include biologic agents such as cytokines and other immune-regulating agents. Useful cytokines include interleukin-2 (IL-2, aldesleukin), interleukin 4 (IL-4), interleukin 12 (IL-12), and interferon, which includes more than 23 related subtypes. Other cytokines include granulocyte colony stimulating factor (CSF) (filgrastim) and granulocyte macrophage CSF (sargramostim). Other immuno-modulating agents include bacillus Calmette-Guerin, levamisole, and

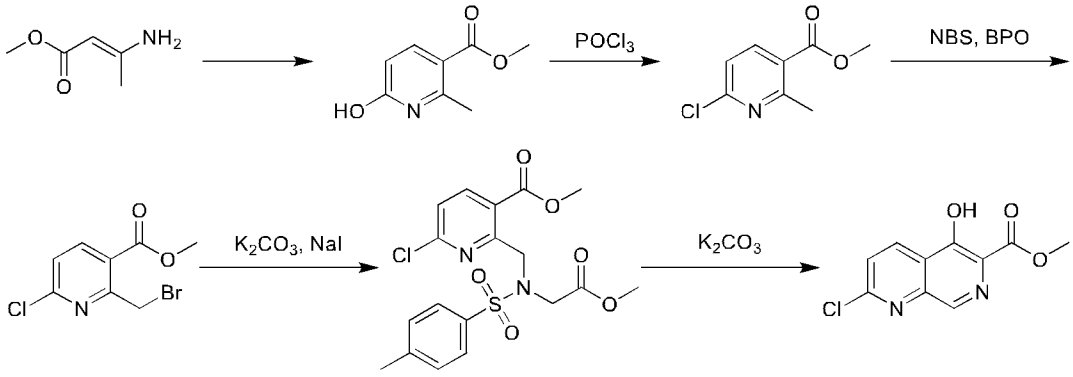
octreotide; monoclonal antibodies against tumor antigens, such as trastruzumab and rituximab; and cancer vaccines, which induce an immune response to tumors.

[00173] In addition, molecularly targeted drugs that interfere with specific molecules involved in tumor growth and progression include inhibitors of epidermal growth factor (EGF), transforming growth factor-alpha (TGF_a), TGFp, heregulin, insulin-like growth factor (IGF), fibroblast growth factor (FGF), keratinocyte growth factor (KGF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin-2 (IL-2), nerve growth factor (NGF), platelet- derived growth factor (PDGF), hetaptocyte growth factor (HGF), vascular endothelial growth factor (VEGF), angiopoietin, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), HER4, insulin-like growth factor 1 receptor (IGF1R), IGF2R, fibroblast growth factor 1 receptor (FGF1R), FGF2R, FGF3R, FGF4R, vascular endothelial growth factor receptor (VEGFR), tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 (Tie-2), platelet-derived growth factor receptor (PDGFR), Abl, Bcr-Abl, Raf, FMS-like tyrosine kinase 3 (FLT3), c-Kit, Src, protein kinase c (PKC), tropomyosin receptor kinase (Trk), Ret, mammalian target of rapamycin (mTOR), Aurora kinase, polo-like kinase (PLK), mitogen activated protein kinase (MEK), mesenchymal-epithelial transition factor (c-MET), cyclin-dependant kinase (CDK), Akt, extracellular signal-regulated kinases (ERK), poly(ADP) ribose polymerase (PARP), and the like.

[00174] Specific molecularly targeted drugs include selective estrogen receptor modulators, such as tamoxifen, toremifene, fulvestrant, and raloxifene; antiandrogens, such as bicalutamide, nilutamide, megestrol, and flutamide; and aromatase inhibitors, such as exemestane, anastrozole, and letrozole. Other specific molecularly targeted drugs include agents which inhibit signal transduction, such as imatinib, dasatinib, nilotinib, trastuzumab, gefitinib, erlotinib, cetuximab, lapatinib, panitumumab, and temsirolimus; agents that induce apoptosis, such as bortezomib; agents that block angiogenesis, such as bevacizumab, sorafenib, and sunitinib; agents that help the immune system destroy cancel cells, such as rituximab and alemtuzumab; and monoclonal antibodies which deliver toxic molecules to cancer cells, such as gemtuzumab ozogamicin, tositumomab, 1311-tositumoab, and ibritumomab tiuxetan.

Examples

Intermediate A: Synthesis of methyl 2-chloro-5-hydroxy-1,7-naphthyridine-6-carboxylate



Step 1:

[00175] To a mixture of methyl (*E*)-3-aminobut-2-enoate (10 g, 87 mmol) in MeOH (100 mL) was added methyl prop-2-ynoate (7.78 g, 92.6 mmol). The mixture was stirred at 70 °C for 12 h. The mixture was cooled to 5 °C. The precipitatie was filtered triturated with MTBE (50 mL × 3). Methyl 6-hydroxy-2-methylnicotinate (5 g, 34% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H), 8.02 (d, J = 8 Hz, 1H), 6.42 (d, J = 12 Hz, 1H), 3.84 (s, 3H), 2.72 (s, 3H).

Step 2:

[00176] A solution of mixture of methyl 6-hydroxy-2-methylnicotinate (5 g, 29.8 mmol) in $POCl_3$ (17.7 g, 115 mmol) was stirred at 100 °C for 4 h. The reaction was slowly poured into ice water (100 mL) and then extracted with ethyl acetate (100 mL × 2). The combined organic layers were washed with $NaHCO_3$ (50 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude was used directly for the next step.

Step 3:

[00177] To a solution of methyl 6-chloro-2-methylnicotinate (6 g, 32.4 mmol) in CCl_4 (60 mL) was added NBS (6.9 g, 38.7 mmol) and BPO (1.56 g, 6.45 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with DCM (60 mL) and washed with H_2O (60 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatograph to afford Methyl 2-(bromomethyl)-6-chloronicotinate as a yellow solid (11 g, crude). LCMS: RT = 0. 981 min; MS m/z (ESI) $[M+H]^+$ = 264.1.

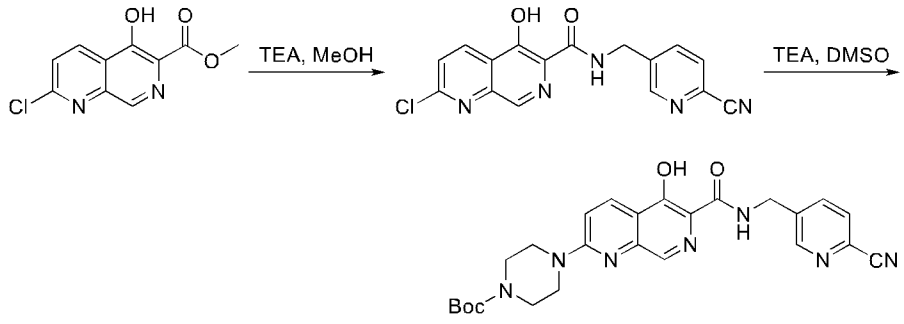
Step 4:

[00178] To a solution of methyl 2-(bromomethyl)-6-chloronicotinate (5 g, 18.9 mmol) and methyl 2-(*p*-tolylsulfonylamino) acetate (4.6 g, 18.9 mmol) in DMF (50 mL) was added K_2CO_3 (5.02 g, 47.4 mmol) and NaI (0.28 g, 1.86 mmol). The mixture was stirred at 50 °C for 12 h under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with H_2O (80 mL × 3). The organic layer was washed with brine (80 mL × 3), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatograph to afford methyl 6-chloro-2-(((*N*-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)nicotinate (6 g, crude) as a yellow solid.

Step 5:

[00179] To a solution of methyl 6-chloro-2-(((*N*-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)nicotinate (6 g, 14 mmol) in DMSO (60 mL) was added K_2CO_3 (11.6 g, 84.3 mmol). The mixture was stirred at 50 °C for 4 h under N_2 atmosphere. The mixture was diluted with H_2O (60 mL) and the aqueous was adjusted pH to 6 with 1 M HCl. The precipitated solid was filtered and dried to afford Intermediate A (1.5 g, 45% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.72 (d, J = 0.9 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H).

General procedure A: The synthesis of *tert*-butyl 4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-1-carboxylate (Example 29)



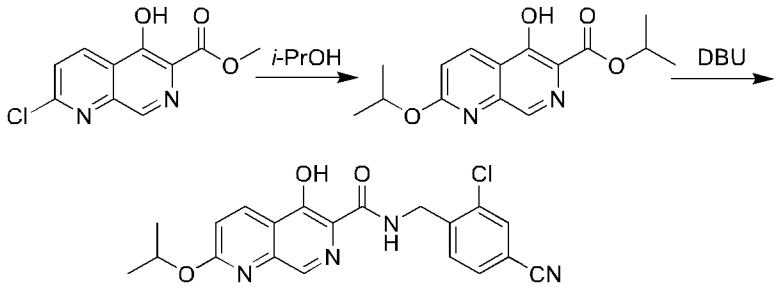
Step 1:

[00180] To a solution of Intermediate A (1 g, 4.19 mmol) in MeOH (30 mL) were added 5-(aminomethyl)pyridine-2-carbonitrile (0.84 g, 6.29 mmol), TEA (2.91 mL, 20.95 mmol), and the reaction was stirred at 75 °C overnight. The reaction mixture was filtered through normal funnel and the filter cake was washed with 10 mL MeOH, dried in vacuum to afford 2-chloro-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide, Intermediate B (1.1 g, 3.24 mmol, 77% yield) as a yellow solid.

Step 2:

[00181] To a solution of Intermediate B (1.1 g, 3.24 mmol) in DMSO (15 mL) were added TEA (1.35 mL, 9.71 mmol), *tert*-butyl piperazine-1-carboxylate (904 mg, 4.86 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. The reaction was cooled and poured into water H_2O (200 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with saturated NaCl solution (30 mL × 3), and concentrated in vacuo. The residue was triturated with CH_3CN (20 mL) and CH_2Cl_2 (5 mL) and filtered to afford Example 29 (500 mg, 1.02 mmol, 32% yield) as a white solid. LCMS: RT = 1.838 min; MS m/z (ESI) $[M+H]^+$ = 490.1. ^1H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 9.77 (t, J = 6.3 Hz, 1H), 8.76 (s, 1H), 8.44 (s, 1H), 8.29 (d, J = 9.4 Hz, 1H), 8.00 (s, 2H), 7.48 (d, J = 9.5 Hz, 1H), 4.63 (d, J = 6.3 Hz, 2H), 3.82 - 3.79 (m, 4H), 3.50 - 3.48 (m, 4H), 1.46 (s, 9H).

General procedure B: The synthesis of *N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-isopropoxy-1,7-naphthyridine-6-carboxamide (Example 1)



Step 1:

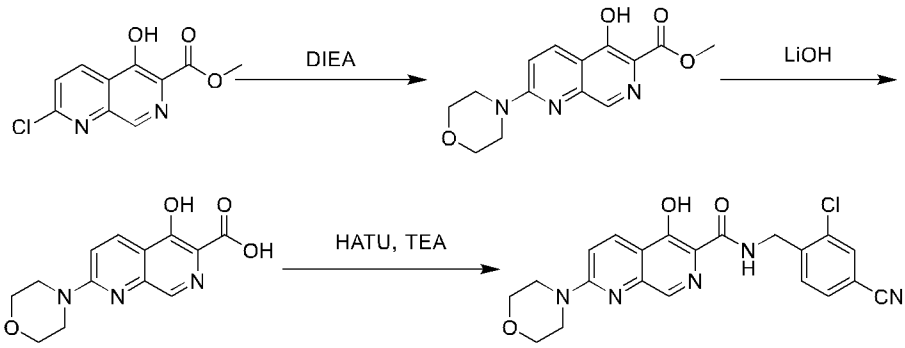
[00182] To a solution of Intermediate A (200 mg, 838.13 μmol) in *i*-PrOH (3 mL) was added TBAB (270.18 mg, 838.13 μmol) and *t*-BuOK (282.14 mg, 2.51 mmol). The mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to 20 °C, diluted with MeOH (15 mL), filtered and the filtrate was concentrated under reduce pressure. The residue was purified by reverse-phase HPLC. Isopropyl 5-

hydroxy-2-isopropoxy-1,7-naphthyridine-6-carboxylate (100 mg, crude) was obtained as a light gray solid. LCMS: RT = 0.809 min; MS m/z (ESI) $[M+H]^+$ = 304.7.

Step 2:

To a solution of above material (100 mg, 344.45 μmol), 4-(aminomethyl)-3-chlorobenzonitrile (114.78 mg, 688.91 μmol) and DBU (52.44 mg, 344.45 μmol, 51.92 μL) in MeOH (5 mL) was stirred at 75 °C for 16 h. 4-(aminomethyl)-3-chlorobenzonitrile (114.78 mg, 688.91 μmol) and DBU (52.44 mg, 344.45 μmol, 51.92 μL) were added. The mixture was stirred at 75 °C for 40 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC. Example 1 (7 mg, 17.64 μmol, 5% yield) was obtained as a white solid. LCMS: RT = 0.994 min; MS m/z (ESI) $[M+H]^+$ = 397.1. ^{1}H NMR (400 MHz, DMSO-d_6) 13.42 (brs, 1H), 9.89 (brs, 1H), 8.66 (brs, 1H), 8.48 (d, J = 9.2 Hz, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.85 - 7.77 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 5.62 - 5.43 (m, 1H), 4.66 (d, J = 6.4 Hz, 2H), 1.40 (d, J = 6.4 Hz, 6H).

General procedure C: The synthesis of *N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxamide (Example 3)



Step 1:

[00183] To a mixture of Intermediate A (300 mg, 1.26 mmol) and morpholine (76.67 mg, 880.03 μmol, 77.44 μL) in THF (10 mL) was added DIEA (324.96 mg, 2.51 mmol, 437.95 μL) at 25 °C. The mixture was stirred at 50 °C for 17 h. Morpholine (76.67 mg, 880.03 μmol, 77.44 μL) was added and the mixture was stirred at 65 °C for 4.5 h. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford methyl 5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxylate (128 mg, 383.84 μmol, 31% yield) as a white solid. LCMS: RT = 0.637 min; MS m/z (ESI) $[M+H]^+$ = 290.1.

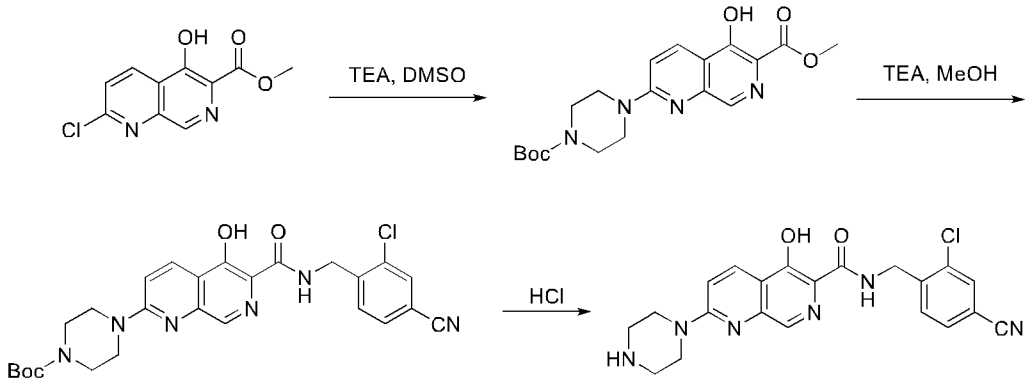
Step 2:

[00184] To a solution of methyl 5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxylate (128 mg, 442.47 μmol) in THF (1.5 mL) and H_2O (1.5 mL) was added $LiOH{\cdot}H_2O$ (37.14 mg, 884.94 μmol) at 25 °C. The mixture was stirred at 25 °C for 16 h and at 50 °C for another 3 h. The reaction mixture was concentrated and adjusted with HCl (1 M) to pH = 6. Water (20 mL) was added, and the mixture was extracted with EtOAc (20 mL × 3). The aqueous was lyophilized to afford 5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxylic acid (130 mg, crude) as a yellow solid. LCMS: RT = 0.525 min; MS m/z (ESI) $[M+H]^+$ = 276.1.

Step 3:

[00185] To a mixture of carboxylic acid (45 mg, 163.48 μmol) and TEA (49.63 mg, 490.45 μmol, 68.26 μL) in DMF (1 mL) was added HATU (68.38 mg, 179.83 μmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. Then amine (32.68 mg, 196.18 μmol) was added and the mixture was stirred at 25 °C for 2 h. Two drops of water were added. The mixture was filtered. The filtrate was purified by prep-HPLC and lyophilized to afford the product, which was combined with another batch of the product (6.0 mg) and lyophilized to afford Example 3 (10.78 mg, 25.15 μmol, 6% yield) as a white solid. LCMS: RT = 0.831 min; MS m/z (ESI) $[M+H]^+$ = 424.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.31 (s, 1H), 9.76 - 9.68 (m, 1H), 8.47 (s, 1H), 8.29 (d, *J* = 9.6 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.85 - 7.76 (m, 1H), 7.55 - 7.46 (m, 2H), 4.63 (d, *J* = 6.4 Hz, 2H), 3.80 - 3.70 (m, 8H).

General procedure D: The synthesis of *N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (Example 5)



Step 1:

[00186] To a solution of Intermediate A (500 mg, 2.10 mmol) and *tert*-butyl piperazine-1-carboxylate (467.5 mg, 2.52 mmol) in anhydrous DMSO (5 mL) was added TEA (525 mg, 5.25 mmol). The solution was stirred at 100 °C for 16 h under N_2. The reaction mixture was poured into H_2O (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography. Methyl 2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-hydroxy-1,7-naphthyridine-6-carboxylate (200 mg, 25% yield) was obtained as a yellow solid. LCMS: RT = 1.002 min; MS m/z (ESI) $[M+H]^+$ = 389.0.

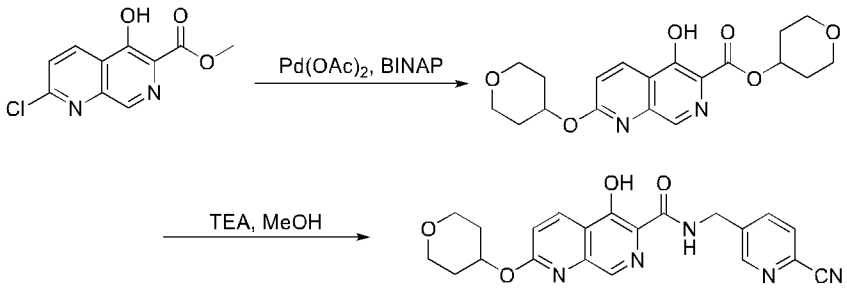
Step 2:

[00187] To a solution of methyl 2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-hydroxy-1,7-naphthyridine-6-carboxylate (100 mg, 0.295 mmol) and 4-(aminomethyl)-3-chlorobenzonitrile (60 mg, 0.359 mmol) in anhydrous MeOH (1.5 mL) was added TEA (60 mg, 0.594 mmol). The solution was stirred at 75 °C for 20 h under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product (150 mg, crude, yellow oil) was directly put into the next step without further purification. LCMS: RT = 1.097 min; MS m/z (ESI) $[M+H]^+$ = 523.4.

Step 3:

[00188] To a solution of the crude (150.0 mg, 0.287 mmol) in ethyl acetate (1.5 mL) was added a solution of 4N HCl/EtOAc (0.4 mL, 1.435 mmol). The solution was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove the solvent. The crude product was purified by prep-HPLC to afford Example 5 (25.4 mg, 21% yield) as a white solid. LCMS: RT = 2.217 min; MS m/z (ESI) $[M+H]^+$ = 423.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.41 (s, 1H), 8.41 - 8.23 (m, 2H), 8.07 - 8.06 (m, 1H), 7.81 - 7.79 (m, 1H), 7.51 - 7.49 (m, 2H), 4.63 - 4.62 (m, 2H), 3.75 - 3.72 (m, 4H), 2.83 - 2.80 (m, 4H).

General procedure E: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-((tetrahydro-2*H*-pyran-4-yl)oxy)-1,7-naphthyridine-6-carboxamide (Example 13)



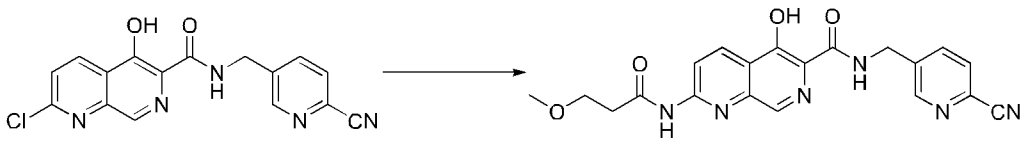
Step 1:

[00189] To a solution of Intermediate A (300 mg, 1.26 mmol) in dioxane (5 mL) were added oxan-4-ol (385.19 mg, 3.77 mmol), $Pd(OAc)_2$ (28.22 mg, 0.13 mmol), BINAP (156.56 mg, 0.25 mmol) and Cs_2CO_3 (1228.84 mg, 3.77 mmol), and the reaction was stirred at 115 °C for 16 h. The mixture was purified using silica gel column chromatography to afford tetrahydro-2*H*-pyran-4-yl 5-hydroxy-2-((tetrahydro-2*H*-pyran-4-yl)oxy)-1,7-naphthyridine-6-carboxylate (70 mg, 0.23 mmol, 18% yield) as a yellow solid. LCMS: RT = 1.200 min; MS m/z (ESI) $[M+H]^+$ = 375.1.

Step 2:

[00190] To a solution of tetrahydro-2*H*-pyran-4-yl 5-hydroxy-2-((tetrahydro-2*H*-pyran-4-yl)oxy)-1,7-naphthyridine-6-carboxylate (70 mg, 0.19 mmol) in MeOH (3 mL) were added 5-(aminomethyl)pyridine-2-carbonitrile (74.69 mg, 0.56 mmol), TEA (0.260 mL, 1.87 mmol), and the reaction was stirred at 75 °C for 24 h. The reaction mixture was poured into saturated $NaHCO_3$ (70 mL) and extracted with EtOAc (40 mL × 3), the organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was triturated with MeOH (3 mL) and filtered to afford Example 13 (6.78 mg, 0.02 mmol, 9% yield) as a white solid. LCMS: RT = 1.868 min; MS m/z (ESI) $[M+H]^+$ = 406.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.50 (s, 1H), 9.94 (t, J = 6.2 Hz, 1H), 8.77 (s, 1H), 8.65 (s, 1H), 8.50 (d, J = 9.0 Hz, 1H), 8.01 (s, 2H), 7.29 (d, J = 9.0 Hz, 1H), 5.51 - 5.41 (m, 1H), 4.65 (d, J = 6.3 Hz, 2H), 3.96 - 3.82 (m, 2H), 3.57 - 3.55 (m, 2H), 2.16 - 2.04 (m, 2H), 1.75 - 1.72 (m, 2H).

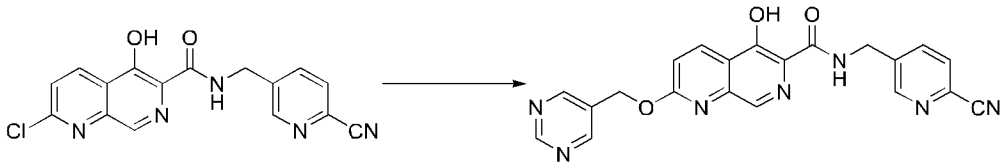
General procedure F: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-methoxypropanamido)-1,7-naphthyridine-6-carboxamide (example 77)



Intermediate B

To a solution of **Intermediate B** (80 mg, 0.24 mmol) in NMP (2 mL) were added 3-methoxypropanamide (48.56 mg, 0.47 mmol), Xantphos (27.25 mg, 0.05 mmol), $Pd_2(dba)_3$ (21.56 mg, 0.02 mmol), and K_3PO_4 (149.95 mg, 0.71 mmol), and the reaction was stirred at 150 °C for 1 h in a microwave reactor under N_2. The reaction mixture was poured into saturated NaCl (100 mL), and extracted with EA (40 mL × 3). The organic layer was dried over Na_2SO_4, filtered and the organic layer was separated, and concentrated in vacuo. The residue was purified using prep-HPLC eluting with MeCN in water (0.1% FA) to afford **example 77** (36.81 mg, 39%). **LCMS:** 407.4 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.55 (s, 1H), 11.13 (s, 1H), 9.87 (s, 1H), 8.78 (s, 1H), 8.64 - 8.60 (m, 3H), 8.01 (d, J = 1.3 Hz, 2H), 4.68 (d, J = 6.3 Hz, 2H), 3.66 (t, J = 6.1 Hz, 2H), 3.26 (s, 3H), 2.75 (t, J = 6.1 Hz, 2H).

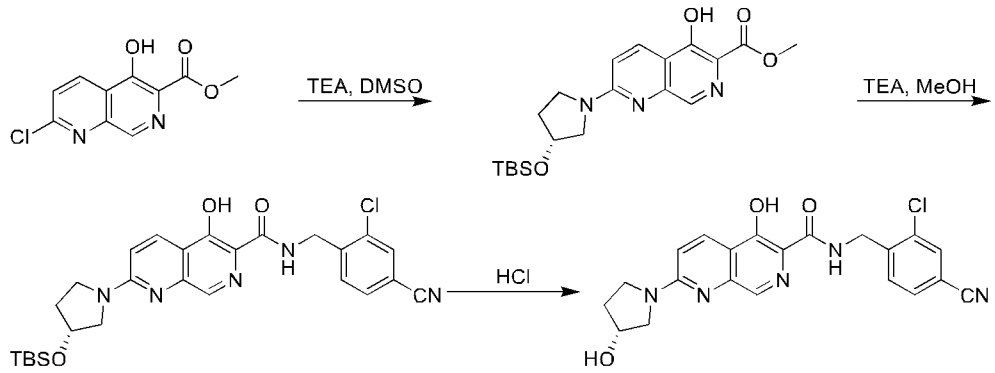
General procedure G: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(pyrimidin-5-ylmethoxy)-1,7-naphthyridine-6-carboxamide (example 108)



Intermediate B

To a solution of **Intermediate B** (200 mg, 0.64 mmol) in dioxane (3 mL) were added (pyrimidin-5-yl)methanol (210.59 mg, 1.91 mmol), Cs_2CO_3 (623.08 mg, 1.91 mmol), BINAP (79.38 mg, 0.13 mmol) and $Pd(OAc)_2$ (14.31 mg, 0.06 mmol) and the reaction was stirred at 110 °C for 18 h. The reaction was poured into water (50 mL), extracted with EA (30 mL × 3). The organic layer was washed with aq. NaCl (30 mL × 3), dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by pre-HPLC to afford **example 108** (16.59 mg, 6%). **LCMS:** 414.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.53 (s, 1H), 9.95 (s, 1H), 9.19 (s, 1H), 9.05 (s, 2H), 8.78 (s, 1H), 8.76 (s, 1H), 8.55 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 1.1 Hz, 2H), 7.40 (d, J = 8.9 Hz, 1H), 5.64 (s, 2H), 4.67 (d, J = 6.2 Hz, 2H).

Example 6: Synthesis of (*R*)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(3-hydroxypyrrolidin-1-yl)-1,7-naphthyridine-6-carboxamide

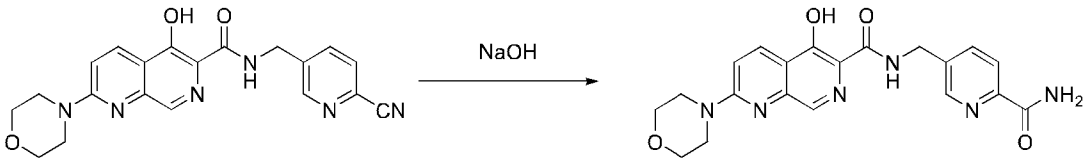


[00191] To a solution of Intermediate A (100 mg, 0.42 mmol) and (*R*)-3-((*tert*-butyldimethylsilyl)oxy)pyrrolidine (126 mg, 0.63 mmol) in anhydrous DMSO (30 mL) was added TEA (106 mg, 1.06 mmol). The solution was stirred at 100 °C for 16 h. The reaction mixture was poured into H_2O (30 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography. Methyl (*R*)-2-(3-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-5-hydroxy-1,7-naphthyridine-6-carboxylate (110 mg, 65% yield) was obtained as a yellow solid. LCMS: RT = 1.179 min; MS m/z (ESI) $[M+H]^+$ = 404.3.

[00192] To a solution of methyl (*R*)-2-(3-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-5-hydroxy-1,7-naphthyridine-6-carboxylate (100 mg, 0.25 mmol) and 4-(aminomethyl)-3-chlorobenzonitrile (50.0 mg, 0.30 mmol) in anhydrous MeOH (1.5 mL) was added TEA (50 mg, 0.50 mmol). The solution was stirred at 75 °C for 20 h under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product (140 mg, yellow oil) was directly put into the next step without further purification. LCMS: RT = 1.099 min; MS m/z (ESI) $[M+H]^+$ = 538.4.

[00193] To a solution of (*R*)-2-(3-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide (140 mg, 0.26 mmol) in ethyl acetate (1.5 mL) was added a solution of 4N HCl in ethyl acetate (0.35 mL, 1.30 mmol). The solution was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by prep-HPLC to afford Example 6 (13.3 mg, 12% yield) as a white solid. LCMS: RT = 2.472 min; MS m/z (ESI) $[M+H]^+$ = 424.2. ^1H NMR (400 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.47 (s, 1H), 8.46 - 8.31 (m, 2H), 7.70 - 7.69 (m, 1H), 7.58 - 7.56 (m, 2H), 6.99 (s, 1H), 4.80 - 4.70 (m, 3H), 3.74 (s, 4H), 2.21 - 2.18 (m, 2H).

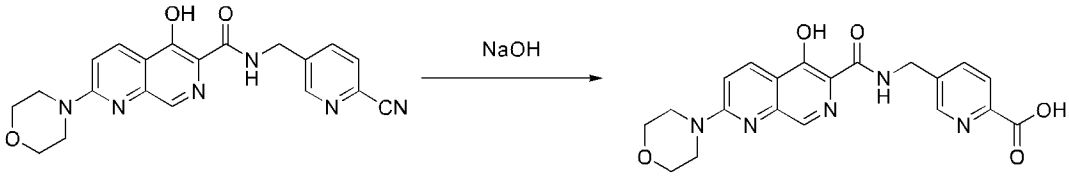
Example 22: The synthesis of *N*-((6-carbamoylpyridin-3-yl)methyl)-5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxamide



[00194] To a solution of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxamide (120 mg, 0.31 mmol) in anhydrous MeOH (2 mL) was added 3M NaOH solution (3 mL). The mixture was stirred at room temperature for 12 h under N_2. The reaction mixture was concentrated

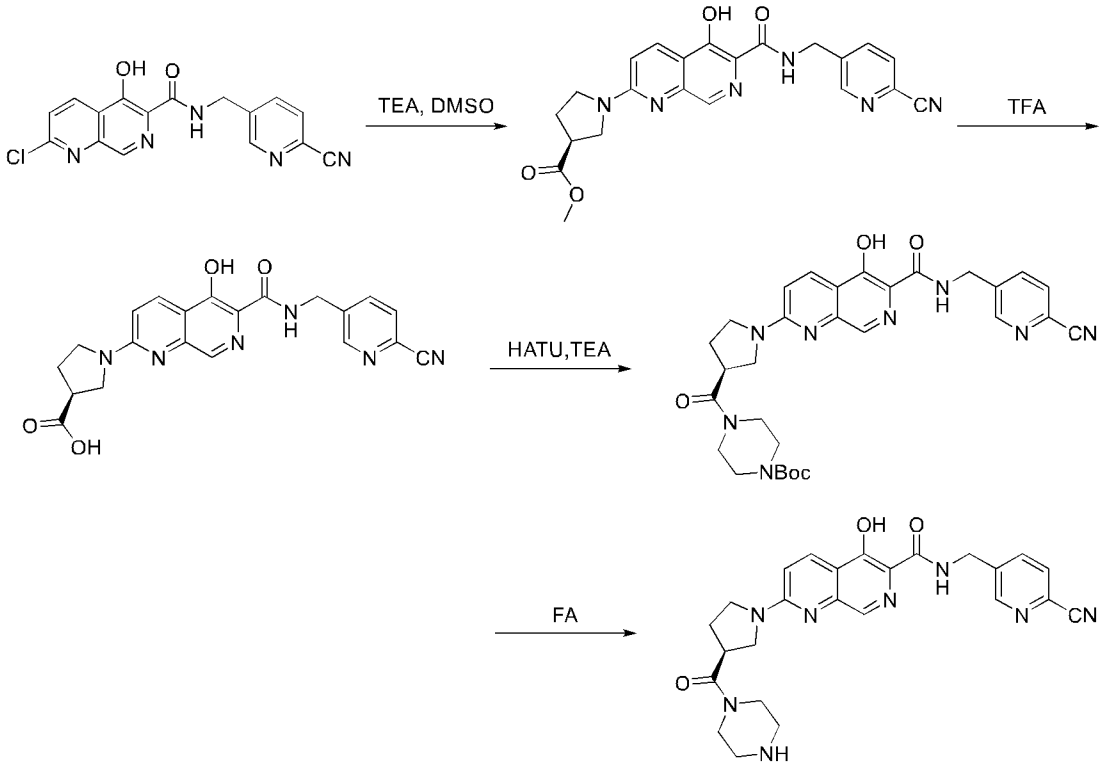
under reduced pressure. The residue was purified by prep-HPLC afford Example 22 (8.5 mg, 7% yield) as a white solid. LCMS: RT = 0.890 min; MS m/z (ESI) $[M+H]^+$ = 409.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (s, 1H), 9.74 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.38 (s, 1H), 8.25 (d, J = 9.4 Hz, 1H), 8.05 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.89 (dd, J = 8.1, 2.0 Hz, 1H), 7.56 (s, 1H), 7.43 (d, J = 10.0 Hz, 1H), 4.57 (d, J = 6.3 Hz, 2H), 3.70 (d, J = 5.5 Hz, 8H).

Example 24: The synthesis of 5-((5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxamido)methyl)picolinic acid



[00195] To a solution of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-morpholino-1,7-naphthyridine-6-carboxamide (120 mg, 0.3 mmol) in anhydrous MeOH (2 mL) was added 3M aqueous NaOH (3 ml). The solution was stirred at 70 °C for 20 h under N_2. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford Example 24 (37 mg, 30% yield) as a yellow solid. LCMS: RT = 1.962 min; MS m/z (ESI) $[M+H]^+$ = 410.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.45 (s, 1H), 9.73 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 8.25 (d, J = 9.4 Hz, 1H), 7.93 (dd, J = 38.0, 7.9 Hz, 2H), 7.44 (d, J = 9.4 Hz, 1H), 4.58 (s, 2H), 3.70 (d, J = 6.7 Hz, 8H).

Example 41: The synthesis of (*S*)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-(piperazine-1-carbonyl)pyrrolidin-1-yl)-1,7-naphthyridine-6-carboxamide



[00196] To a solution of Intermediate B (150 mg, 0.44 mmol) in DMSO (2 mL) were added TEA (0.245 mL, 1.77 mmol), methyl (3*S*)-pyrrolidine-3-carboxylate hydrochloride (95 mg, 0.57 mmol), and

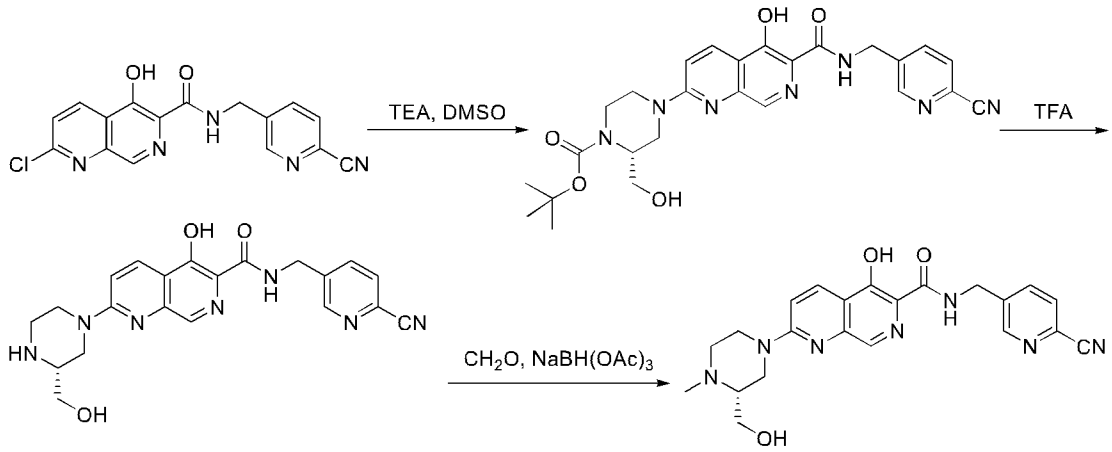
the reaction was stirred at 100 °C for 3 h. The reaction was purified prep-HPLC to afford methyl (*S*)-1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carboxylate (120 mg, 0.28 mmol, 63% yield) as a white solid. LCMS: RT = 1.102 min; MS m/z (ESI) $[M+H]^+$ = 433.3.

[00197] To a solution of methyl (*S*)-1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carboxylate (100 mg, 0.23 mmol) in THF (0.5 mL) were added TFA (2 mL), and the reaction was stirred at room temperature for 48 h. The reaction was diluted with water (10 mL) and extracted with DCM (10 mL × 3). The organic layer was separated, washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with methanol (0 ~ 10 %) in chloroform (0 ~ 10 %) to afford (*S*)-1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carboxylic acid (85 mg, 0.20 mmol, 88% yield) as a white solid. LCMS: RT = 0.912 min; MS m/z (ESI) $[M+H]^+$ = 419.1.

[00198] To a solution of (*S*)-1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carboxylic acid (80 mg, 0.19 mmol) in DMF (2 mL) were added *tert*-butyl piperazine-1-carboxylate (46 mg, 0.25 mmol), HATU (109 mg, 0.29 mmol), TEA (0.080 mL, 0.57 mmol), and the reaction was stirred at room temperature for 3 h. The mixture was added H_2O (15 mL) and extracted with *tert*-butyl methyl ether (10 mL × 3). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give *tert*-butyl (*S*)-4-(1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carbonyl)piperazine-1-carboxylate (80 mg, 0.14 mmol, 71% yield) as a white solid. LCMS: RT = 1.009 min; MS m/z (ESI) $[M+H]^+$ = 587.2.

[00199] To a solution of *tert*-butyl (*S*)-4-(1-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)pyrrolidine-3-carbonyl)piperazine-1-carboxylate (75 mg, 0.13 mmol) in FA (4 mL), the reaction was stirred at room temperature for 2 h. The reaction was concentrated in vacuo. The residue was purified by pre-HPLC to afford Example 41 (6.86 mg, 0.01 mmol, 11% yield) as a white solid. LCMS: RT = 1.296 min; MS m/z (ESI) $[M+H]^+$ = 487.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.42 (s, 1H), 8.26 (d, J = 9.1 Hz, 2H), 8.00 (d, J = 1.2 Hz, 2H), 7.14 (d, J = 9.3 Hz, 1H), 4.63 (s, 2H), 3.85 - 3.54 (m, 9H), 2.82 - 2.80 (m, 2H), 2.75-2.73 (m, 2H), 2.20-2.15 (m, 2H).

Example 45: The synthesis of (*R*)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)-1,7-naphthyridine-6-carboxamide

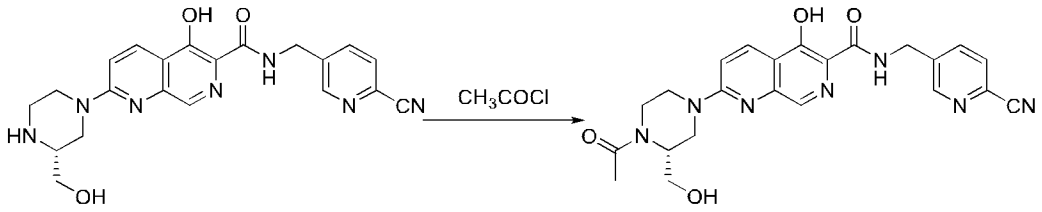


[00200] To a solution of Intermediate B (200 mg, 0.59 mmol) in DMSO (2 mL) were added TEA (0.41 mL, 2.95 mmol) and *tert*-butyl (2*R*)-2-(hydroxymethyl)piperazine-1-carboxylate (191.41 mg, 0.89 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. The reaction was cooled and poured into water H_2O (200 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, and concentrated. The crude was purified by silica gel chromatograph (0 ~ 50% Ethyl acetate in Petroleum) to afford *tert*-butyl (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (206 mg, 0.40 mmol, 67% yield) as off-white solid. LCMS: RT = 0.888 min; MS m/z (ESI) $[M+H]^+$ = 520.0.

[00201] To a solution of *tert*-butyl (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (50 mg, 0.10 mmol) in DCM (0.5 mL) were added TFA (0.5 mL, 6.73 mmol), and the reaction was stirred at room temperature for 1 h. The reaction concentrated in vacuo and dried to afford (*R*)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (50 mg, 0.09 mmol, 94% yield) as yellow oil. LCMS: RT = 0.695 min; MS m/z (ESI) $[M+H]^+$ = 420.0.

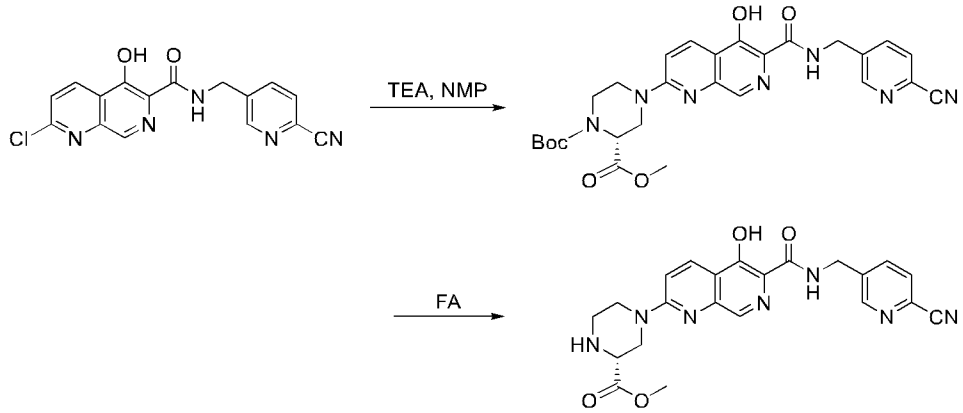
[00202] To a solution of (*R*)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (40 mg, 0.1 mmol) in DCE (5 mL) were added sodium bis(acetyloxy)boranyl acetate (80.5 mg, 0.4 mmol) and formaldehyde (4.3 mg, 0.1 mmol), and the reaction was stirred at room temperature for 16 h. The reaction was concentrated in vacuo and purified by pre-HPLC to afford Example 45 (5.37 mg, 0.012 mmol, 13% yield) as a red solid. LCMS: RT = 0.870 min; MS m/z (ESI) $[M+H]^+$ = 434.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 9.78 - 9.76 (m, 1H), 8.76 (s, 1H), 8.43 (s, 1H), 8.28 (d, J = 9.2 Hz, 1H), 8.14 (s, 1H), 8.00 (s, 2H), 7.48 (d, J = 9.5 Hz, 1H), 4.85 - 4.84 (m, 1H), 4.65 - 4.63 (m, 2H), 4.59 - 4.24 (m, 4H), 3.72 - 3.70 (m, 3H), 3.00 - 2.92 (m, 3H), 2.35 (s, 3H).

Example 46: The synthesis of (*R*)-2-(4-acetyl-3-(hydroxymethyl)piperazin-1-yl)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



[00203] To a solution of (*R*)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (20 mg, 0.05 mmol) in DCM (1 mL) were added TEA (0.066 mL, 0.48 mmol) and acetyl chloride (0.003 mL, 0.04 mmol), and the reaction was stirred at room temperature for 3 h. The reaction was concentrated in vacuo and purified by pre-HPLC to afford Example 46 (6.60 mg, 0.014 mmol, 30% yield) as a white solid. LCMS: RT = 0.964 min; MS m/z (ESI) $[M+H]^+$ = 462.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 9.85 - 9.82 (m, 1H), 8.76 (s, 1H), 8.41 (s, 1H), 8.29 (d, J = 9.5 Hz, 1H), 8.01 - 7.99 (m, 2H), 7.47 - 7.45 (m, 1H), 4.95 - 4.92 (m, 1H), 4.67 - 4.62 (m, 2H), 4.61 - 4.22 (m, 4H), 4.07 - 3.75 (m, 1H), 3.51 - 3.49 (m, 2H), 3.16 - 2.82 (m, 2H), 2.08 (d, J = 15.3 Hz, 3H).

Example 50: The synthesis of methyl (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-2-carboxylate

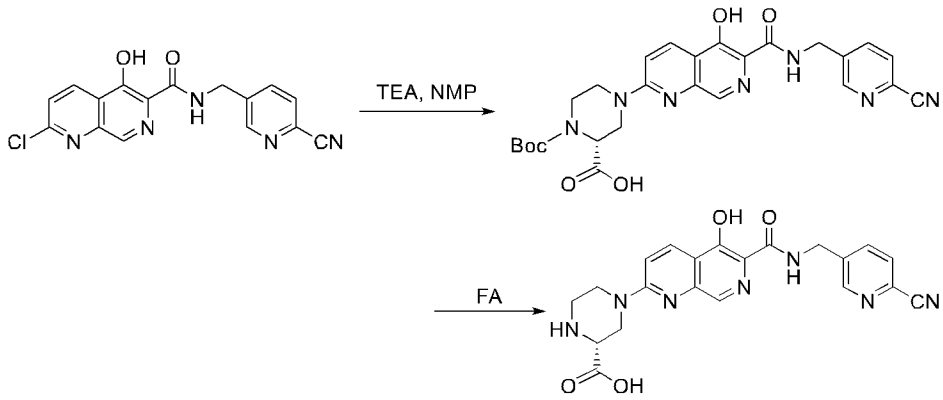


[00204] To a solution of Intermediate B (100 mg, 0.29 mmol) in NMP (2 mL) were added 1-*tert*-butyl 2-methyl (2*R*)-piperazine-1,2-dicarboxylate (107.86 mg, 0.44 mmol), TEA (0.12 mL, 0.88 mmol). The sealed vial was irradiated in a microwave reactor at 140 °C for 2.5 h. The reaction was purified using silica gel column chromatography eluting with water/ CH_3CN/HCOOH to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-1,2-dicarboxylate (60 mg, 0.11 mmol, 37% yield) as a white solid. LCMS: RT = 1.871 min; MS m/z (ESI) $[M+H]^+$ = 548.2.

[00205] A solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-1,2-dicarboxylate (55 mg, 0.10 mmol) in formic acid (2 mL) was stirred at room temperature for 2 h. The reaction was purified by pre-HPLC to afford Example 50 (15.66 mg, 0.03 mmol, 35% yield) as a white solid. LCMS: RT = 1.309 min; MS m/z (ESI) $[M+H]^+$ = 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.76 (s, 1H), 8.42 (s, 1H), 8.27 (d, J = 9.4 Hz,1H), 8.18 (s, 1H), 8.00 (d, J = 1.2 Hz, 2H), 7.48 (d, J = 9.5 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H), 4.37 - 4.34 (m,

1H), 3.95 - 3.93 (m, 1H), 3.66 (s, 3H), 3.61 - 3.54 (m, 2H), 3.49 - 3.46 (m, 2H), 3.03 - 3.01 (m, 1H), 2.75 - 2.71 (m, 1H).

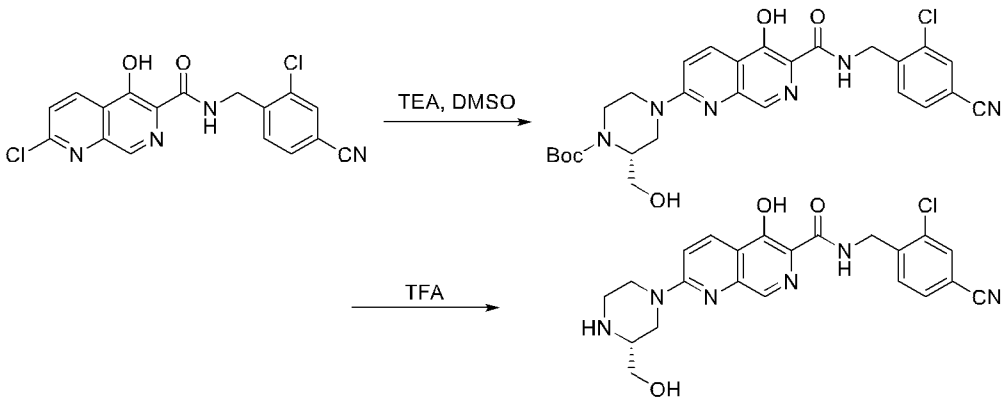
Example 51: The synthesis of (*R*)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-2-carboxylic acid



[00206] To a solution of Intermediate B (100 mg, 0.29 mmol) in NMP (2 mL) were added 1-*tert*-butyl 2-methyl (2*R*)-piperazine-1,2-dicarboxylate (107.86 mg, 0.44 mmol), TEA (0.123 mL, 0.88 mmol). The sealed vial was irradiated in a microwave reactor at 140 °C for 2.5 h. The reaction was purified using silica gel column chromatography eluting with water/CH_3CN/HCOOH to give (*R*)-1-(*tert*-butoxycarbonyl)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-2-carboxylic acid (50 mg, 0.09 mmol, 32% yield) as a white solid. LCMS: RT = 1.094 min; MS m/z (ESI) $[M+H]^+$ = 534.1.

[00207] To a solution of (*R*)-1-(*tert*-butoxycarbonyl)-4-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-2-carboxylic acid (45 mg, 0.08 mmol) in formic acid (2 mL), the reaction was stirred at room temperature for 2 h. The reaction was purified by pre-HPLC to give Example 51 (11.18 mg, 0.03 mmol, 31% yield) as a white solid. LCMS: RT = 1.249 min; MS m/z (ESI) $[M+H]^+$ = 434.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 9.83 (s, 1H), 8.76 (s, 1H), 8.47 (s, 1H), 8.32 (d, J = 9.3 Hz, 1H), 8.01 (s, 2H), 7.51 (d, J = 9.3 Hz, 1H), 4.75 - 4.73 (m, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.37 - 4.34 (m, 1H), 3.44 - 2.99 (m, 6H).

Example 60: The synthesis of (*R*)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide

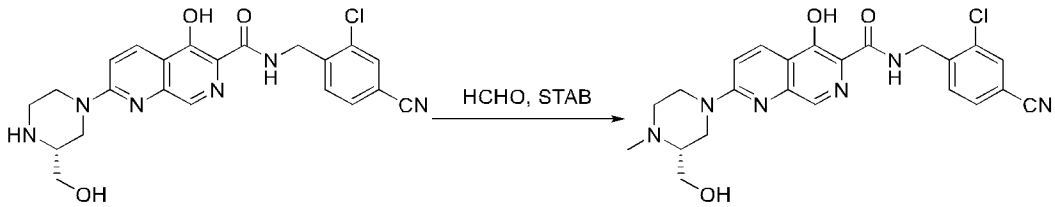


[00208] To a solution of 2-chloro-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide (250 mg, 0.67 mmol) in DMSO (5 mL) were added TEA (0.279 mL, 2.01 mmol), *tert*-butyl

(*R*)-2-(hydroxymethyl)piperazine-1-carboxylate (23 mg, 0.20 mmol), and the reaction was stirred at 100 °C for 2 h under N_2. The reaction was diluted with water (200 mL), extracted with EtOAc (50 mL × 3). The combined organic layer was separated, washed with further saturated NaCl solution (100 mL × 3), and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with methanol (0 ~ 15%) in chloroform. The organic layers were collected, concentrated in vacuo, and dried to afford the title compound *tert*-butyl (*R*)-4-(6-((2-chloro-4-cyanobenzyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (50 mg, 0.12 mmol, 50% yield) as a white solid. LCMS: RT = 1.471 min; MS m/z (ESI) $[M+H]^+$ = 553.3.

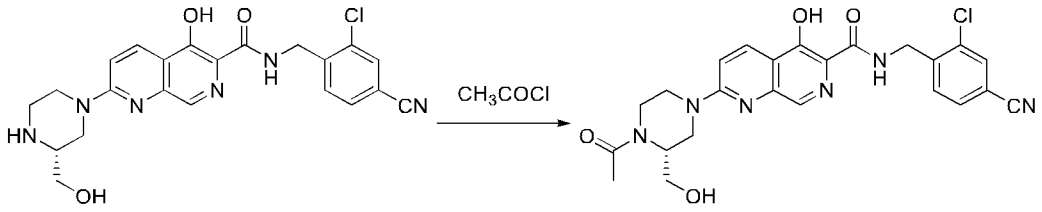
[00209] To a solution of (*R*)-4-(6-((2-chloro-4-cyanobenzyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (270 mg, 0.49 mmol) was added TFA (2 mL, 26.93 mmol), and the reaction was stirred at room temperature for 1 h. The reaction mixture was poured into saturated Na_2CO_3 (100 mL), and extracted with EtOAc (40 mL × 3), the organic layer was dried over Na_2SO_4, filtered, and evaporated to afford Example 60 (200 mg, 0.44 mmol, 90% yield) as a yellow oil. LCMS: RT = 0.740 min; MS m/z (ESI) $[M+H]^+$ = 453.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.82 (s, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 5.08 - 5.06 (m, 1H), 4.66 - 4.52 (m, 4H), 3.59 - 3.51 (m, 2H), 3.21 - 3.18 (m, 2H), 2.98 - 2.88 (m, 4H).

Example 59: The synthesis of (*R*)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)-1,7-naphthyridine-6-carboxamide



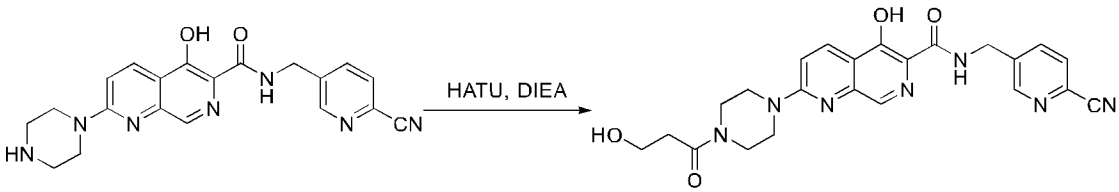
[00210] To a solution of (*R*)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (50 mg, 0.11 mmol) in DCM (1 mL) were added sodium bis(acetyloxy)boranyl acetate (69.86 mg, 0.33 mmol), formaldehyde (18.42 mg, 0.22 mmol), and the reaction was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (30 mL) and water (50 mL). The organic layer was separated, and concentrated in vacuo. The residue was purified using prep-HPLC to afford Example 59 (13.39 mg, 0.03 mmol, 26% yield) as a pale yellow solid. LCMS: RT = 1.376 min; MS m/z (ESI) $[M+H]^+$ = 467.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.42 (s, 1H), 8.28 (d, J = 9.4 Hz, 1H), 8.21 (s, 1H), 8.07 (d, J = 1.5 Hz, 1H), 7.81 (dd, J = 8.0, 1.4 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 9.4 Hz, 1H), 4.64 (d, J = 6.1 Hz, 2H), 4.55 - 4.44 (m, 1H), 4.37 - 4.35 (m, 1H), 3.72 - 3.70 (m, 2H), 3.42 - 3.40 (m, 1H), 3.21 - 3.13 (m, 1H), 2.98 - 2.83 (m, 2H), 2.28 (s, 3H), 2.24 - 2.20 (m, 1H), 2.11 - 2.04 (m, 1H).

Example 63: The synthesis of (*R*)-2-(4-acetyl-3-(hydroxymethyl)piperazin-1-yl)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



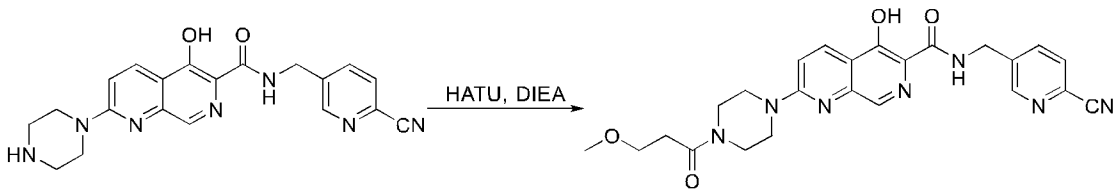
[00211] To a solution of (*R*)-*N*-(2-chloro-4-cyanobenzyl)-5-hydroxy-2-(3-(hydroxymethyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (70 mg, 0.15 mmol) in DCM (3 mL) were added acetyl chloride (0.105 mL, 0.10 mmol), and the reaction was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (30 mL) and water (50 mL). The organic layer was separated, and concentrated in vacuo. The residue was purified using prep-HPLC to afford Example 63 (6.75 mg, 0.01 mmol, 9% yield) as a pale yellow solid. LCMS: RT = 1.620 min; MS m/z (ESI) $[M+H]^+$ = 495.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.40 - 8.38 (m, 1H), 8.30 (d, J = 8.9 Hz, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.46 - 7.44 (m, 1H), 4.86 - 4.84 (m, 1H), 4.65 - 4.63 (m, 2H), 4.55 - 4.47 (m, 2H), 4.35 - 4.33 (m, 2H), 4.07 - 4.05 (m, 1H), 3.30 - 3.78 (m, 1H), 3.50 (d, J = 7.1 Hz, 2H), 3.00 - 2.96 (m, 1H), 2.09 (d, J = 14.9 Hz, 3H).

Example 72: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(4-(3-hydroxypropanoyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide



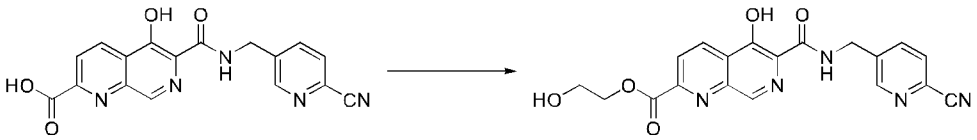
[00212] To a solution of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (50 mg, 0.13 mmol) in DCM (4 mL) were added 3-hydroxypropanoic acid (0.011 mL, 0.13 mmol), HATU (73.23 mg, 0.19 mmol), and DIEA (0.064 mL, 0.39 mmol), and the reaction was stirred at room temperature for 16 h. The reaction mixture was poured into saturated NaCl (100 mL), and extracted with ethyl acetate (40 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by prep-HPLC to afford Example 72 (7.07 mg, 0.02 mmol, 12% yield) as a pale yellow solid. LCMS: RT = 1.420 min; MS m/z (ESI) $[M+H]^+$ = 462.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 9.77 (t, J = 6.1 Hz, 1H), 8.76 (s, 1H), 8.45 (s, 1H), 8.29 (d, J = 9.4 Hz, 1H), 8.00 (s, 2H), 7.50 (d, J = 9.5 Hz, 1H), 4.63 (d, J = 6.2 Hz, 2H), 4.55 (d, J = 5.3 Hz, 1H), 3.84 - 3.81 (m, 4H), 3.69 - 3.66 (m, 6H), 2.57 - 2.55 (m, 2H).

Example 73: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(4-(3-methoxypropanoyl)piperazin-1-yl)-1,7-naphthyridine-6-carboxamide



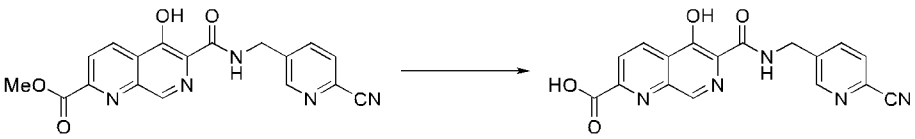
[00213] To a solution of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(piperazin-1-yl)-1,7-naphthyridine-6-carboxamide (50 mg, 0.13 mmol) in DCM (4 mL) were added 3-hydroxypropanoic acid (0.011 mL, 0.13 mmol), HATU (73.23 mg, 0.19 mmol), and DIEA (0.064 mL, 0.39 mmol), and the reaction was stirred at room temperature for 16 h. The reaction mixture was poured into saturated NaCl (100 mL), and extracted with ethyl acetate (40 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified using prep-HPLC to afford Example 73 (6.18 mg, 0.01 mmol, 6% yield) as a white solid. LCMS: RT = 1.505 min; MS m/z (ESI) $[M+H]^+$ = 476.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 9.77 (t, J = 6.3 Hz, 1H), 8.76 (s, 1H), 8.45 (s, 1H), 8.29 (d, J = 9.4 Hz, 1H), 8.00 (d, J = 1.2 Hz, 2H), 7.50 (d, J = 9.5 Hz, 1H), 4.63 (d, J = 6.3 Hz, 2H), 3.83 - 3.81 (m, 4H), 3.65 - 3.56 (m, 6H), 3.24 (s, 3H), 2.64 (t, J = 6.6 Hz, 2H).

Example 93: The synthesis of 2-hydroxyethyl 6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridine-2-carboxylate



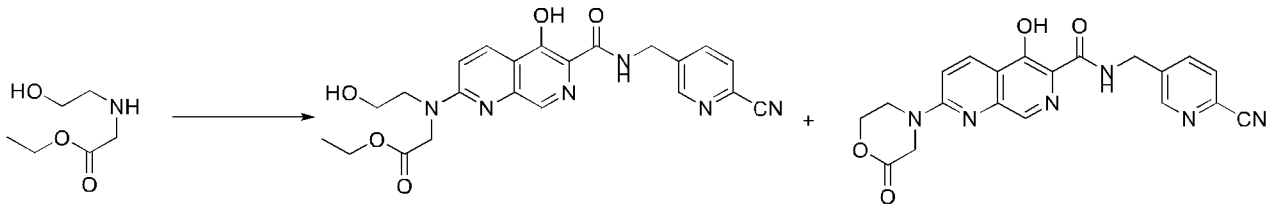
[00214] To a solution of **example 99** (100 mg, 0.29 mmol) in ethane-1,2-diol (3 mL) was added $SOCl_2$ (0.031 mL, 0.43 mmol) at 0 °C, and the reaction was stirred at room temperature overnight. The reaction was concentrated in vacuo. The residue was purified by pre-HPLC to give **example 93** (14.39 mg, 13%). **LCMS:** 394.1 $[M+H]^+$; **^{1}H NMR:** (400 MHz, DMSO-d_6) δ 13.72 (s, 1H), 10.11 (s, 1H), 9.11 (s, 1H), 8.88 (d, J = 8.7 Hz, 1H), 8.79 (s, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.09 - 7.95 (m, 2H), 4.99 (t, J = 5.6 Hz, 1H), 4.69 (d, J = 6.3 Hz, 2H), 4.48 - 4.35 (m, 2H), 3.79 - 3.75 (m, 2H).

Example 99: The synthesis of 6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridine-2-carboxylic acid



[00215] To a solution of **example 90** (200 mg, 0.55 mmol) in THF (2 mL) and H_2O (2 mL) was added LiOH (69 mg, 1.65 mmol), and the reaction was stirred at room temperature for 1 h. The reaction was diluted with water (20 mL), adjusted to pH = 4 by 1 M HCl. The reaction was extracted with EA (25 mL × 3). The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo. The residue was washed by MeOH (10 mL × 3) and purified by pre-HPLC to afford **example 99** (4.81 mg, 3%). **LCMS:** 350.1 $[M+H]^+$; **^{1}H NMR:** (400 MHz, DMSO-d_6) δ 13.71 (s, 2H), 10.13 (s, 1H), 9.02 (s, 1H), 8.80 (d, J = 7.9 Hz, 2H), 8.34 (d, J = 8.7 Hz, 1H), 8.02 (s, 2H), 4.69 (d, J = 6.3 Hz, 2H).

Example 85: The sytnhesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(2-oxomorpholino)-1,7-naphthyridine-6-carboxamide and example 115: The sytnhesis of ethyl *N*-(6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)-*N*-(2-hydroxyethyl)glycinate

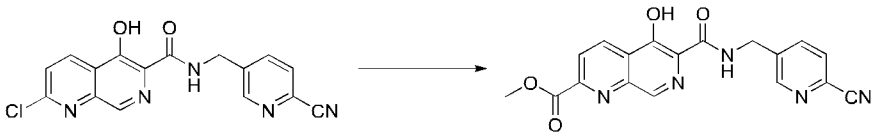


[00216] To a solution of **Intermediate B** (150 mg, 0.44 mmol) in DMSO (5 mL) were added ethyl (2-hydroxyethyl)glycinate (195 mg, 1.32 mmol) and TEA (222 mg, 2.2 mmol) , and the reaction was stirred at 100 °C for 16 h. The mixture concentrated and purified by pre-TLC to afford **example 85** (19.20 mg, 11%) and **example 115** (23.79 mg, 12%).

[00217] **Example 85: LCMS:** 405.1 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 9.79 (s, 1H), 8.76 (s, 1H), 8.52 (s, 1H), 8.36 (d, J = 9.3 Hz, 1H), 8.00 (d, J = 1.4 Hz, 2H), 7.39 (d, J = 9.4 Hz, 1H), 4.70 - 4.54 (m, 6H), 4.00 - 3.88 (m, 2H).

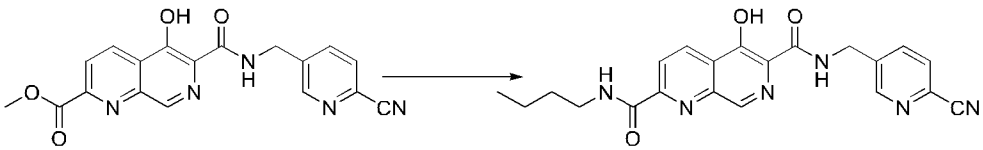
[00218] **Example 115: LCMS:** 451.3 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 9.75 (t, J = 6.1 Hz, 1H), 8.76 (s, 1H), 8.36 (s, 1H), 8.27 (d, J = 9.3 Hz, 1H), 8.00 (s, 2H), 7.43 (s, 1H), 4.79 (s, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.49 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.68 (dd, J = 19.2, 14.3 Hz, 4H), 1.19 (t, J = 7.1 Hz, 3H).

Example 90: The synthesis of methyl 6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridine-2-carboxylate



[00219] To a solution of **Intermediate B** (500 mg, 1.47 mmol) in MeOH (30 mL) were added Pd(dppf)Cl_2 (107.69 mg, 0.15 mmol), TEA (0.614 mL, 4.42 mmol) under CO (20 atm), and the reaction was stirred at 80 °C overnight. The reaction was diluted with water (50 mL) and extracted with EA (30 mL × 3). The organic layer was washed with aq.NaCl (3 × 20 mL), concentrated in vacuo. The residue was purified by pre-HPLC to afford **example 90** (9.43 mg, 2%). **LCMS:** 364.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.69 (s, 1H), 10.13 (s, 1H), 9.06 (s, 1H), 8.86 (d, J = 8.5 Hz, 1H), 8.79 (s, 1H), 8.38 (d, J = 7.4 Hz, 1H), 8.02 (s, 2H), 4.69 (d, J = 6.2 Hz, 2H), 3.99 (s, 3H).

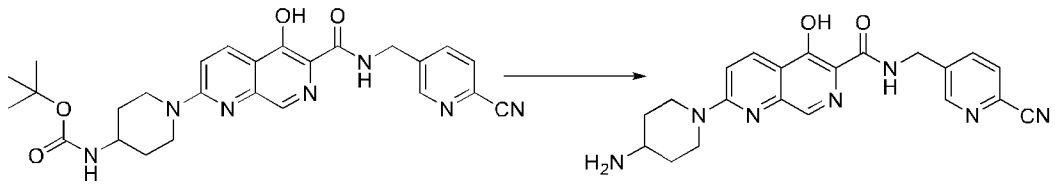
Example 110: The syntheis of N^2-butyl-N^6-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-2,6-dicarboxamide



[00220] To a solution of **example 90** (114 mg, 0.31 mmol) in THF (3 mL) were added butan-1-amine (0.153 mL, 1.55 mmol), and $MgCl_2$ (30 mg), and the reaction was stirred at room temperature overnight. The reaction was poured into water (50 mL), extrated with EA (30 mL × 3). The organic layer was

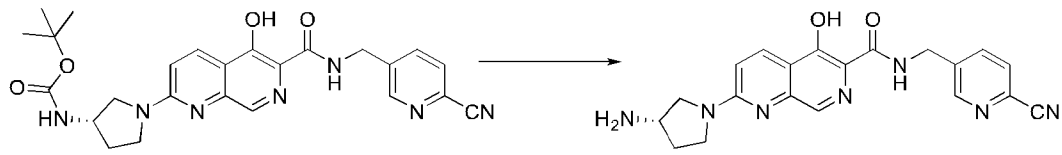
washed with aq. NaCl (30 mL × 3), dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by prep-HPLC to afford **example 110** (16.02 mg, 13%). **LCMS:** 405.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.70 (s, 1H), 10.07 (s, 1H), 9.06 - 9.04 (m, 2H), 8.90 - 8.72 (m, 2H), 8.41 (d, J = 8.6 Hz, 1H), 8.02 (s, 2H), 4.69 (d, J = 6.3 Hz, 2H), 3.38 - 3.31 (m 3H), 1.79 - 1.51 (m, 2H), 1.45 - 1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

Example 124: The synthesis of 2-(4-aminopiperidin-1-yl)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



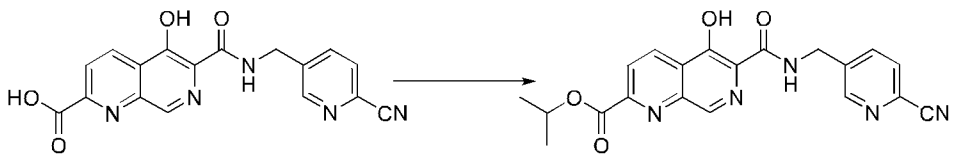
[00221] To a solution of **example 123** (100 mg, 0.198 mmol) was added formic acid (3 mL, 0.225 mmol), and the reaction was stirred at 25 °C for 3 h. The reaction was concentrated in vacuo. The residue was purified by prep-HPLC to afford **example 124** (34.39 mg, 43%). **LCMS:** 404.3 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.76 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.25 (s, 1H), 8.01 - 7.97 (m, 2H), 7.47 (d, J = 9.5 Hz, 1H), 4.63 (d, J = 5.4 Hz, 2H), 4.57 (d, J = 13.5 Hz, 2H), 3.25 - 3.17 (m, 1H), 3.10 (t, J = 11.9 Hz, 2H), 1.96 (d, J = 12.5 Hz, 2H), 1.45 - 1.42 (m, 2H).

Example 126: The synthesis of (*S*)-2-(3-aminopyrrolidin-1-yl)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



[00222] To a solution of **example 125** (110 mg, 0.225 mmol) was added formic acid (3 mL, 0.225 mmol), and the reaction was stirred at 25 °C for 3 h. The reaction was concentrated in vacuo. The residue was purified by prep-HPLC to afford **example 126** (22.01 mg, 24%). **LCMS:** 390.5 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.76 (s, 1H), 8.37 (d, J = 18.9 Hz, 2H), 8.25 (d, J = 9.2 Hz, 1H), 8.00 (s, 2H), 7.08 (d, J = 9.1 Hz, 1H), 4.64 (d, J = 4.8 Hz, 2H), 3.81 - 3.69 (m, 4H), 3.65 - 3.62 (m, 1H), 2.23 - 2.21 (m, 1H), 1.99 - 1.97 (m, 1H).

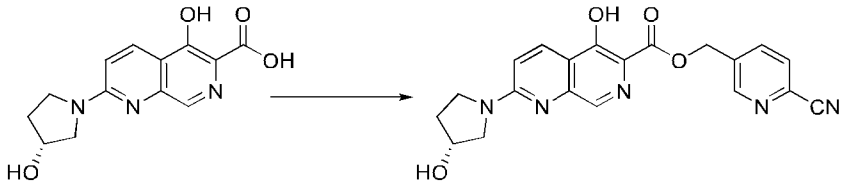
Example 130: The synthesis of isopropyl 6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridine-2-carboxylate



[00223] To a solution of **example 99** (100 mg, 0.286 mmol) in *i*-PrOH (5 mL) were added $SOCl_2$ (0.062 mL, 0.859 mmol), and the reaction was stirred at 70 °C for 3 h. The reaction was concentrated in

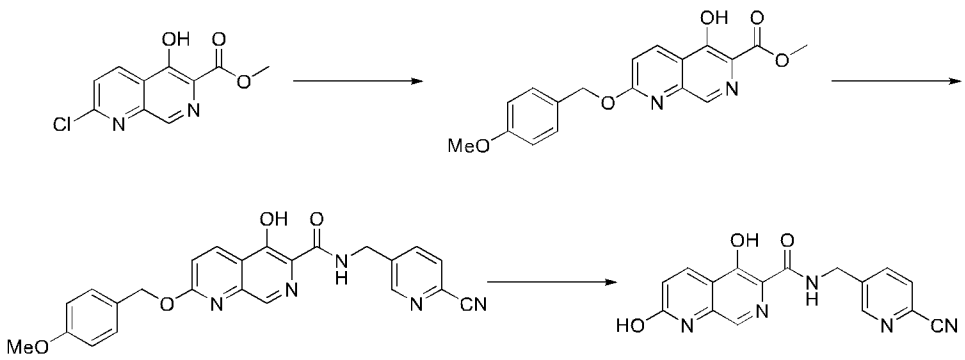
vacuo. The residue was purified by prep-HPLC to afford **example 130** (23.24 mg, 21%). **LCMS:** 392.2 $[M+H]^+$; **^{1}H NMR:** (400 MHz, DMSO-d_6) δ 13.70 (s, 1H), 10.12 (s, 1H), 9.09 (s, 1H), 8.86 (d, J = 8.7 Hz, 1H), 8.79 (s, 1H), 8.38 (d, J = 8.7 Hz, 1H), 8.07 - 7.92 (m, 2H), 5.36 - 5.17 (m, 1H), 4.69 (d, J = 6.3 Hz, 2H), 1.40 (d, J = 6.3 Hz, 6H).

Example 15: The synthesis of (6-cyanopyridin-3-yl)methyl (*R*)-5-hydroxy-2-(3-hydroxypyrrolidin-1-yl)-1,7-naphthyridine-6-carboxylate



[00224] To a solution of 5-(bromomethyl)picolinonitrile (100 mg, 0.51 mmol) in DMF (3 mL) were added carboxylic acid (155.23 mg, 0.56 mmol, which was obtained via a similar procedure as **example 3**), $NaHCO_3$ (94.74 mg, 1.13 mmol), and the reaction was stirred at room temperature for 16 h. The reaction was diluted with H_2O (30 mL) , extracted with EA (30 mL × 3). The combined organic layers were washed with aq. NaCl (30 mL × 3), dried and concentrated in vacuo. The residue was purified by prep-HPL to afford **example 15** (4.1 mg, 2%). **LCMS:** 392.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.32 - 8.08 (m, 5H), 7.14 - 6.91 (m, 1H), 5.52 - 5.50 (m, 2H), 5.03 - 5.01 (m, 1H), 4.45 - 4.43 (m, 1H), 3.63 - 3.61 (m, 4H), 2.03 - 2.01 (m, 3H).

Example 98: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-2,5-dihydroxy-1,7-naphthyridine-6-carboxamide



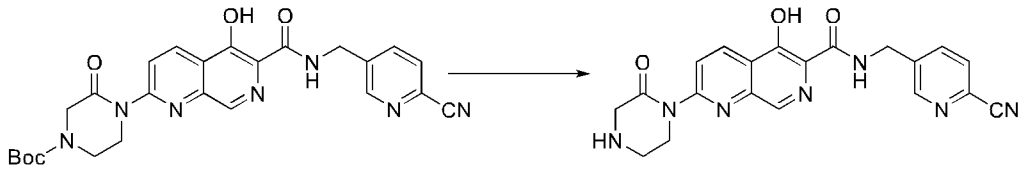
[00225] To a solution of **Intermediate A** (500 mg, 2.10 mmol) in dioxane (10 mL) were added (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (0.151 mL, 1.21 mmol) and $Pd(OAc)_2$ (50 mg, 0.22 mmol), BINAP (260 mg, 0.42 mmol), Cs_2CO_3 (1400 mg, 4.30 mmol), and the reaction was stirred at 110 °C for 16 h. The reaction was filtered, concentrated, the residue was purified by flash silica gel chromatography to afford methyl 5-hydroxy-2-[(4-methoxyphenyl)methoxy]-1,7-naphthyridine-6-carboxylate (330 mg, 46%).

[00226] To a solution of methyl 5-hydroxy-2-[(4-methoxyphenyl)methoxy]-1,7-naphthyridine-6-carboxylate (330 mg, 0.97 mmol) in MeOH (3 mL) were added 5-(aminomethyl)pyridine-2-carbonitrile hydrochloride (330 mg, 1.95 mmol) and TEA (1.2 mL, 8.63 mmol), the reaction was stirred at 70 °C for

18 h. The solution was diluted with EA (10 mL) and water (20 mL), and EA layer was separated, the aqueous layer was extracted with EA (10 mL × 3), combined EA layer was washed with brine .And dried over Na_2SO_4, and concentrated in vacuo to afford *N*-[(6-cyanopyridin-3-yl)methyl]-2,5-dihydroxy-1,7-naphthyridine-6-carboxamide (125mg, 40%).

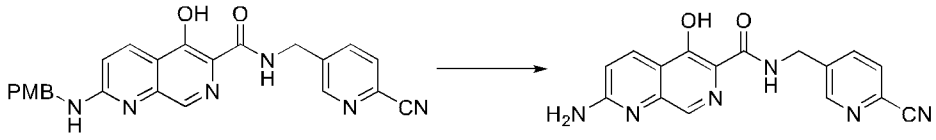
[00227] To TFA (1 mL) was added *N*-[(6-cyanopyridin-3-yl)methyl]-5-hydroxy-2-[(4-methoxyphenyl)methoxy]-1,7-naphthyridine-6-carboxamide (100 mg, 0.23 mmol) and the reaction was stirred at room temperature for 2 h. And the reaction was concentrated and purified by pre-HPLC to afford **example 98** (60 mg, 82%). **LCMS:** 322 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.34 (s, 1H), 12.20 (s, 1H), 9.94 (s, 1H), 8.75 (s, 1H), 8.18 - 7.94 (m, 4H), 6.70 (d, J = 9.1 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H).

Example 102: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(2-oxopiperazin-1-yl)-1,7-naphthyridine-6-carboxamide



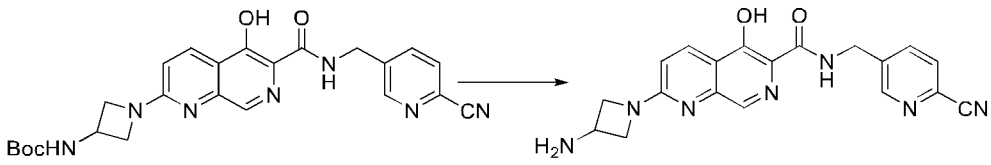
[00228] A solution of example 101 (150 mg, 0.298 mmol) in HCl/EA (3M, 2 mL) was stirred at room temperature for 1 h. The mixture was filtered and concentrated. The crude was purified by pre-HPLC to give **example 102** (24.15 mg, 19%). **LCMS:** 404.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.61 (s, 1H), 10.00 (s, 1H), 9.65 (s, 2H), 8.80 (d, J = 15.4 Hz, 2H), 8.70 (d, J = 9.3 Hz, 1H), 8.36 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 1.4 Hz, 2H), 4.68 (d, J = 6.2 Hz, 2H), 4.43 - 4.23 (m, 2H), 4.05 (s, 2H), 3.67 - 3.50 (m, 2H).

Example 97： The synthesis of 2-amino-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



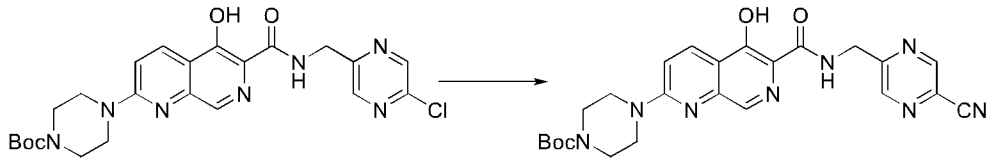
[00229] To a solution of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-((4-methoxybenzyl)amino)-1,7-naphthyridine-6-carboxamide (500 mg, 1.13 mmol, which was obtained via General Procedure A) in TFA (2 mL) and the reaction was stirred at 70 °C for 3 h. The reaction was concentrated in vacuo and purified by pre-HPLC to afford **example 97** (4.43 mg, 1%). **LCMS:** 321.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.34 (s, 1H), 9.74 (s, 1H), 8.76 (s, 1H), 8.35 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.07 - 7.89 (m, 2H), 7.46 (s, 2H), 7.02 (d, J = 9.1 Hz, 1H), 4.63 (d, J = 6.2 Hz, 2H).

Example 128: 2-(3-aminoazetidin-1-yl)-*N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide



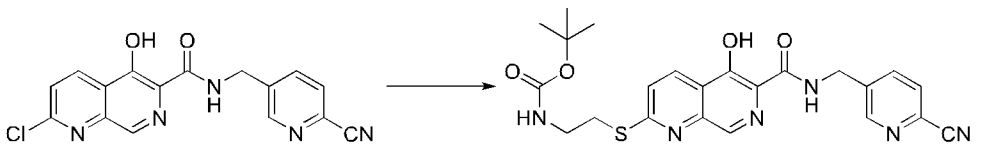
[00230] A mixture of **example 127** (28 mg, 0.059 mmol) in HCl/EA (3 M, 5 mL) was stirred at rt for 1 h, and the reaction was concentrated in vacuo. The residue was purified by pre-HPLC to afford **example 128** (29.91 mg, 38%). **LCMS:** 376 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.76 (s, 1H), 8.41 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.00 (s, 2H), 6.92 (d, J = 9.1 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H), 4.33 (t, J = 8.1 Hz, 2H), 3.93 - 3.85 (m, 1H), 3.82 - 3.73 (m, 2H).

Example 134: The synthesis of *tert-butyl* 4-(6-(((5-cyanopyrazin-2-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-1-carboxylate



[00231] To a solution of *tert*-butyl 4-(6-(((5-chloropyrazin-2-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)piperazine-1-carboxylate (150 mg, 0.300 mmol, which was obtained via General Procedure D) in DMF (2 mL) were added $Zn(CN)_2$ (35.23 mg, 0.300 mmol), $Pd(dppf)Cl_2$ (43.91 mg, 0.060 mmol), and the reaction was stirred at 130 °C for 16 h under N_2. The reaction was poured into water (50 mL), extracted with EA (30 mL × 3). The organic layer was washed with aq. NaCl (30 mL × 3), dried over Na_2SO_4, and concentrated. The crude was purified by pre-HPLC to afford **example 134** (8.28 mg, 5%). **LCMS:** 491.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 9.66-9.65 (m, 1H), 9.18 (d, J = 1.2 Hz, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.30 (d, J = 9.4 Hz, 1H), 7.49 (d, J = 9.4 Hz, 1H), 4.81 (d, J = 6.0 Hz, 2H), 3.83 - 3.81 (m, 4H), 3.49 - 3.46 (m, 4H), 1.44 (s, 9H).

Example 147: The synthesis of *tert*-butyl (2-((6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridin-2-yl)thio)ethyl)carbamate

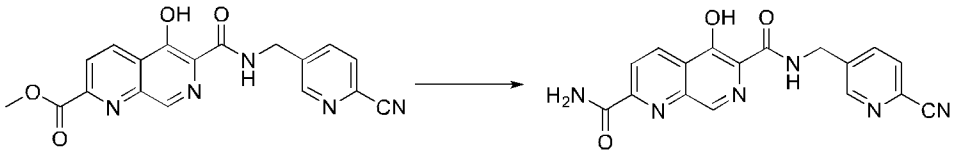


[00232] To a solution of **Intermediate B** (150 mg, 0.444 mmol) in NMP (3 mL) were added *tert*-butyl (2-mercaptoethyl)carbamate (234.79 mg, 1.325 mmol), Cs_2CO_3 (287.71 mg, 0.883 mmol), and $Pd(OAc)_2$ (19.82 mg, 0.088 mmol), BINAP (7.35 mg, 0.012 mmol) and the reaction was stirred at 100 °C for 1 h in Microwave. The reaction was poured into water (50 mL), extracted with EA (30 mL × 3). The organic layer was washed with aq. NaCl (30 mL × 3), dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by pre-HPLC to afford **example 147** (107.23 mg, 50%). **LCMS:** 481.16 $[M+H]^+$; **^{1}H NMR:** (400 MHz, DMSO) δ 13.55 (s, 1H), 9.96 (s, 1H), 8.78 (s, 2H), 8.39 (d, J = 8.8 Hz, 1H), 8.01 (s, 2H), 7.70 (d, J = 8.9 Hz, 1H), 7.11 (s, 1H), 4.67 (d, J = 6.3 Hz, 2H), 3.62 - 3.14 (m, 4H), 1.37 (s, 9H).

Example 129: The synthesis of ethyl 6-(((6-cyanopyridin-3-yl)methyl)carbamoyl)-5-hydroxy-1,7-naphthyridine-2-carboxylate

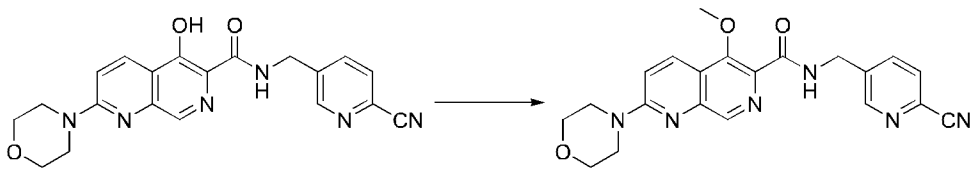
[00233] A solution of **example 99** (80 mg, 0.229 mmol) in EtOH (2 mL) were added $SOCl_2$ (1 mL), and the reaction was stirred at 70 °C for 7 h. The reaction was poured into water (50 mL), extracted with EA (30 mL × 3). The organic layer was washed with aq. NaCl (30 mL × 3), dried over Na_2SO_4, and concentrated in vacuo. The crude product was triturated with MeOH (20 mL) to afford **example 129** (19.82 mg, 23%). **LCMS:** 378.2 $[M+H]^+$; **^{1}H NMR:** (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 10.10 (s, 1H), 9.10 (s, 1H), 8.87 (d, J = 8.5 Hz, 1H), 8.79 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 4.69 (d, J = 5.7 Hz, 2H), 4.49 - 4.47 (m, 2H), 1.40 (t, J = 6.9 Hz, 3H).

Example 131: The synthesis of N^6-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-2,6-dicarboxamide



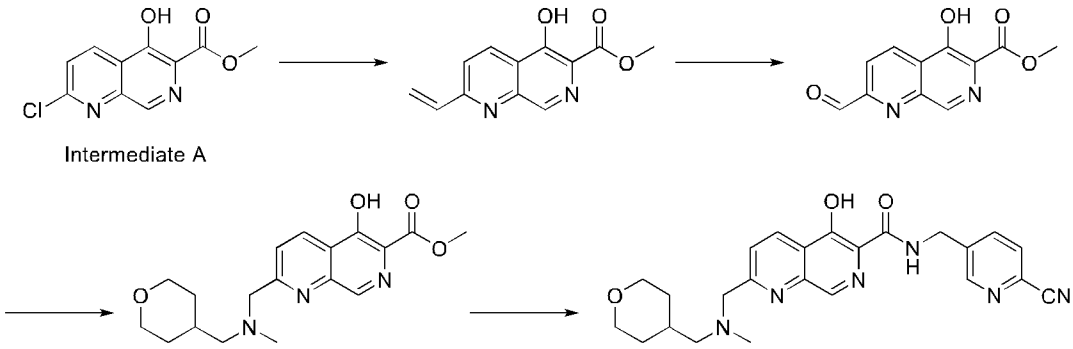
[00234] A solution of **example 90** (100 mg, 0.275 mmol) and NH_3 in MeOH (2 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo. The crude was triturated with MeOH (10 mL) to afford **example 131** (15.61 mg, 16%). **LCMS:** 349.1 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 10.08 (s, 1H), 9.00 (s, 1H), 8.89 - 8.73 (m, 2H), 8.42 (s, 2H), 8.02 - 8.00 (m, 3H), 4.69 (s, 2H).

Example 163: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-methoxy-2-morpholino-1,7-naphthyridine-6-carboxamide



[00235] To a solution of **example 10** (100 mg, 0.256 mmol) in acetone (2 mL) was added MeI (360 mg, 2.536 mmol) and K_2CO_3 (180 mg, 1.302 mmol) , and the reaction was heated to50 °C for 2 h, and the solution was diluted with water (10 mL) and extracted with EA (5 mL × 3), the EA layer was combined and washed with brine (5 mL), and dried over Na_2SO_4 , and concentrated , and the residue was purified by pre-HPLC to afford **example 163** (3.76 mg, 4%). **LCMS:** 405 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.76 (s, 1H), 8.35 (d, J = 9.4 Hz, 1H), 8.13 (s, 1H), 8.01 (s, 2H), 7.42 (d, J = 9.3 Hz, 1H), 4.64 (d, J = 5.9 Hz, 2H), 4.47 (s, 3H), 3.75 - 3.72 (m, 8H).

Example 55: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-((methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)-1,7-naphthyridine-6-carboxamide



Intermediate A

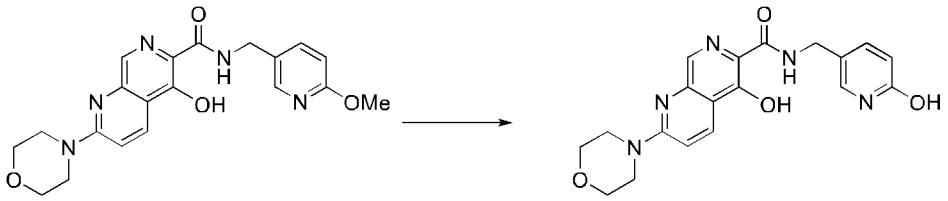
[00236] A mixture of **Intermediate A** (1.00 g, 4.19 mmol), potassium trifluoro(vinyl)boranuide (673.6 mg, 5.03 mmol) and TEA (8.38 mmol, 1.17 mL) in DCM (10 mL) was degassed and purged with N_2 for 3 times, and then $Pd(dppf)Cl_2$ (306.6 mg, 419.1 μmol) was added. The mixture was stirred at 50 °C for 3 h under N_2. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford methyl 5-hydroxy-2-vinyl-1,7-naphthyridine-6-carboxylate (425.0 mg, 44%). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 11.62 (s, 1H), 8.95 (d, J = 0.6 Hz, 1H), 8.57 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 6.97 (dd, J = 10.9, 17.6 Hz, 1H), 6.39 (d, J = 17.6 Hz, 1H), 5.74 (d, J = 10.9 Hz, 1H), 4.04 (s, 3H).

[00237] To a solution of methyl 5-hydroxy-2-vinyl-1,7-naphthyridine-6-carboxylate (350.0 mg, 1.52 mmol) in dioxane (4 mL) and H_2O (4 mL) was added K_2OsO_4 (56.0 mg, 152.0 μmol) and $NaIO_4$ (1.14 g, 5.32 mmol, 294.8 μL), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (3 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford methyl 2-formyl-5-hydroxy-1,7-naphthyridine-6-carboxylate (240.0 mg, 68%). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 10.19 (d, J = 0.6 Hz, 1H), 9.16 (s, 1H), 8.83 (d, J = 8.6 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 4.08 (s, 3H).To a mixture of methyl 2-formyl-5-hydroxy-1,7-naphthyridine-6-carboxylate (210.0 mg, 904.4 μmol) and *N*-methyl-1-(tetrahydro-2H-pyran-4-yl)methanamine (350.6 mg, 2.71 mmol) in THF (4 mL) was added TEA (2.71 mmol, 377.7 μL) and $NaBH_3CN$ (170.5 mg, 2.71 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used directly in the next step without further purification. **LCMS:** 236.1 $[M+H]^+$.

[00238] To a solution of methyl 5-hydroxy-2-((methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)-1,7-naphthyridine-6-carboxylate (300.0 mg, 868.6 μmol) in DMSO (1 mL) was added TEA (2.61 mmol, 362.7 μL) and 5-(aminomethyl)pyridine-2-carbonitrile (173.5 mg, 1.30 mmol), and the mixture was stirred at 120 °C for 15 min under microwave radiation. The reaction mixture was filtered and the filtrated was purified by prep-HPLC to afford Compound **example 55** (7.70 mg, 2%). **LCMS:** 447.3 $[M+H]^+$; **^{1}H NMR:** (400MHz, MeOD) δ 8.78 (s, 1H), 8.74 (d, J = 8.8 Hz, 1H), 8.64 (s,

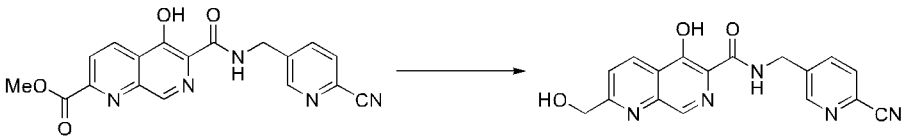
1H), 8.04 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.4, 11.1 Hz, 2H), 4.61 (s, 2H), 3.93 (d, J = 7.5 Hz, 2H), 3.84 (s, 2H), 3.43 (t, J = 11.2 Hz, 2H), 2.35 (d, J = 7.0 Hz, 2H), 2.31 (s, 3H), 1.88 (s, 1H), 1.78 (d, J = 13.8 Hz, 2H), 1.40 - 1.12 (m, 3H).

Example 40: The synthesis of 5-hydroxy-*N*-((6-hydroxypyridin-3-yl)methyl)-2-morpholino-1,7-naphthyridine-6-carboxamide



[00239] To a solution of **example 34** (129 mg, 0.33 mmol) in acetonitrile (5.0 mL) was added iodotrimethylsilane (0.14 mL, 1.00 mmol). The resulting mixture was stirred at 80 °C for 18 h. The residue was purified by prep-HPLC to give **example 40** (50.95 mg, 41%). **LCMS:** 382.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.60 (s, 1H), 11.48 (s, 1H), 9.47 (t, J = 6.1 Hz, 1H), 8.41 (s, 1H), 8.28 (d, J = 9.4 Hz, 1H), 7.51 (dd, J = 9.5, 2.6 Hz, 1H), 7.48 (d, J = 9.5 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 4.24 (d, J = 6.3 Hz, 2H), 3.75 (s, 4H), 3.73 (s, 4H).

Example 167: The synthesis of *N*-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-2-(hydroxymethyl)-1,7-naphthyridine-6-carboxamide



[00240] To a solution of **example 90** (750 mg, 2.06 mmol) in MeOH (5 mL) were added $NaBH_4$ (1.009 mL, 30.90 mmol) at 0 °C, and the reaction was stirred at room temperature for 16 h. The reaction mixture was poured into saturated NH_4Cl (100 mL), and extracted with EA (40 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography. The organic layer was collected, and then purified by prep-HPLC to afford the title compound **example 167** (13.95 mg, 22%). **LCMS:** 336.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.55 (s, 1H), 10.03 (s, 1H), 8.84 (s, 1H), 8.78 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 7.7 Hz, 2H), 7.96 (d, J = 8.5 Hz, 1H), 5.77 - 5.75 (m, 1H), 4.80 (d, J = 5.3 Hz, 2H), 4.68 (d, J = 6.3 Hz, 2H).

[00241] The following compounds were made according to the general procedure as shown in the table 2 below:

[00242] Table 2

Ex.	General procedure
1	B
2	E
3	C
4	C
5	D
6	D

Ex.	General procedure
7	D
8	D
9	D
10	D
12	E
13	E
16	A
17	D
18	D
19	A
20	D
21	C
22	Hydrolyze of example 10
23	C
24	Hydrolyze of example 10
25	D
26	A
27	D
28	deBoc of example 29
29	A
30	D
31	C
32	C
33	C
34	D
35	D
36	D
37	D
38	A
39	D Followed by de-Boc
40	Demethylation of example 34
41	A
42	A
43	D
44	A
45	A Followed by -Boc and +Me
46	A Followed by -Boc and +Ac
47	A
48	D
49	A
50	A Followed by de-Boc
51	A Followed by de-Boc
52	A
53	A
56	A
57	D
58	A
59	methylation of example 60
60	A

Ex.	General procedure
	Followed by deBoc
61	A
62	A
63	Acetylation of example 60
64	A
66	A
67	A
68	A
69	A
70	A
71	A
72	Example 28, then amide cross coupling
73	Example 28, then amide cross coupling
74	A
75	A
76	F
77	F
78	A
79	A
80	A
81	A
83	A
84	A
85	A
86	A
88	A
89	A
91	A
92	A
93	Esterification of example 99
94	A
95	A
96	A
97	A
98	
99	Hydrolyzation of example 99
100	F
101	F
102	De-Boc of example 101
103	F
104	F
106	A
107	A
108	G
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	F BINAP instead of Xantphos
123	A
124	deBoc of example 123

Ex.	General procedure
125	A
126	deBoc of example 125
127	
128	De-Boc of example 127
129	Esterification of example 99
130	Esterification of example 99
131	Amidation of example 90
132	A
133	A
134	Cyanation of a pdt from General Procedure D
135	A
136	C
137	A
138	A
139	A
140	A
141	A
142	A
143	F
144	F
145	A
146	A
148	A
149	A
150	A
151	A
152	A
153	A
154	A
155	A
156	A
157	A
158	A
159	A
160	C
161	A
162	A
163	Methylation of example 10
164	A
165	A
167	Reduce example 90

Biological examples

Example A: PHD2 Enzymatic Assay Procedure

[00243] Compound DMSO stock preparation: All compounds were reconstituted into 20mM stock by DMSO.

[00244] Compound storage: All compounds in DMSO were stored at RT in a desiccator for short-term storage (up to 3 months). Leftover compounds were store at -20 for longer term.

[00245] Working stock preparation:

- Reference Roxadustat (FG-4592) was 3-fold serial diluted from 400 μM for 10 doses in DMSO.
- The compounds were 3-fold serial diluted from 400 μM for 10 doses in DMSO.
- Prepared 200× positive control (400 μM, FG-4592) and 200× vehicle control (100% DMSO).
- Centrifuged compound plates at 1000rpm for 1min.

[00246] Compound screening:

- a) Transferred 40 nl compound dilutions into each well of assay plates using Echo 655;
- b) Sealed the assay plate and centrifuge compound plates at 1000rpm for 1min.
- c) Prepared and add 4 μL of the 2x PHD2 enzyme working solution to individual well of the assay plate.
- d) Sealed the assay plate and centrifuge compound plates at 1000rpm for 1min. Incubate plate at RT for 30min.
- e) Prepared and add 4 μl 2x PHD2 substrate working solution to each well of the assay plate.
- f) Prepared and added 4 μL 4x stop solution to the each well of the assay plate.
- g) Prepared 4x detection solution with AlphaScreen Streptavidin Donor beads, AlphaScreen Protein A Acceptor beads and Hydroxy-HIF-1α (Pro564) (D43B5) XP® Rabbit mAb.
- h) Added 4 μL 4x detection solution to the each well of the assay plate. repeat at step d.
- i) Read Alphascreen signal on Envision HTS plate reader.

[00247] Data analysis

ALPHASCREEN signal (ALPcmpd) is calculated for each well

2.2 %Inhibition is calculated as follow:

$$\%\text{Inhibition} = \left[1 - \frac{\overline{ALP}_{compound} - \overline{ALP}_{positive}}{\overline{ALP}_{vehicle} - \overline{ALP}_{positive}}\right] \times 100$$

$\overline{ALP}_{positive}$: The average ALP for the positive controls across the plate.

$\overline{ALP}_{vehicle}$: The average ALP for the negative controls across the plate.

2.3 Calculate IC_{50} and Plot effect-dose curve of compounds:

Calculated IC_{50} by fitting %inhibition values and log of compound concentrations to nonlinear regression (dose response – variable slope) with Graphpad 8.0.

Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope))

X: log of Inhibitor concentration; Y: % Inhibition.

Example B: EPO Elisa Assay

[00248] The compounds powder were dissolved in 100% DMSO. The compounds stock solution were kept in nitrogen cabinet.

Experimental Methods

[00249] Cell seeding: Added 100μl cell suspension contain 20k Hep3B cell per well.

[00250] Preparation of compound concentration gradient: Compounds at top dose of 100 μM, 3-fold dilution, 8 doses, singlet or duplicate. Prepare a solution of 200x the final concentration in a 96-well plate, dilute the compound by 200/3x with cell culture medium, and then pipette 50 μL to wells. Add 50 μL of culture medium containing DMSO to the minimum control well to make the final concentration contain 5‰ DMSO, and add 50 μL of the highest concentration of reference compound to the maximum control well, and incubate at 37°C for 24h.

- Washed the reaction plate twice with 400μL of 1x Wash Buffer per well.
- Added 100 μL of the diluted standard (including standard blank control) to the appropriate wells.
- Added 50 μL of sample and 50 μL of Sample Diluent to the sample well.
- Added 50 μL 1x Biotin Conjugated Antibody to all wells and incubate for 1 hour at room temperature.
- Washed the reaction plate 6 times with 400 μL 1x Wash Buffer per well.
- Added 100 μL 1x Streptavidin-HRP to each well. Incubate at room temperature for 15 minutes.
- Washed the reaction plate 6 times with 400 μL 1x Wash Buffer per well.
- Added 100 μL TMB Substrate Solution to each well. Incubate at room temperature for 10 minutes.
- Added 100 μL Stop Solution to each well.
- Read OD450 with EnSight.

Data Analysis

[00251] Using GraphPad Prism 5.

%Act. = (Compound signal - Min signal) / (Max signal - Min signal)*100.

[00252] Max signal was obtained from the maximum control wells.

[00253] Min signal was obtained from the minimum control wells.

[00254] Take the log value of the concentration as the X-axis, and the percentage inhibition rate on the Y-axis. Use the analysis software GraphPad Prism 5 log(inhibitor) vs. response -Variable slope to fit the dose-response curve to obtain the EC_{50} value of each compound.

Example C: Caco-2 HIF1α-HiBiT Assay

[00255] Cells: Caco2-HIF1α- HiBiT -clone-1 cells.

[00256] Culture medium: EMEM contain 20% FBS, 1% Penicillin-Streptomycin for Caco-2

[00257] Cell passage procedure

- Cleaned working surface of bio-safety cabinet with 75% ethanol, allow approximately 5 minutes to elapse before using cabinet.
- Aspirated cell culture medium and rinse the cell layer gently with 5 ml DPBS for twice. Then remove DPBS.
- Added 2 ml 0.25% trypsin to the flask and place it at a 37 °C, 5% CO_2 incubator for 2 minutes.
- After 2 minutes tripsinization, quenched trypsin with 10 ml cell culture medium.

- Gently pipetted the cells up and down to dissociate cell clumps, transferred cell suspension into the 15 ml tube.
- Verified cell density using the cell counter.
- Diluted cell suspension with culture medium and transfer 2.0*106 cells to a T75 flask.
- Maintained cells at the 37 ℃, 5% CO_2 incubator under certain humidity for 3 days.

[00258] Plating cells (Day 1)

- Prepared plating medium.
- Aspirated cell culture medium. Wash cells gently with 10 ml PBS and remove PBS. Dissociated cells with 3 ml 0.25% trypsin and terminate digestion with 10 ml cell culture medium.
- Determined cell density with the cell counter.
- Plated Caco-2-HIF1α- HiBiT -clone-1 cells in a 384-well plate (Corning-3765) at the density of 5.5k cells per well within 20 μl medium. Maintain cells in the incubator overnight.

[00259] Compound Treatment (Day 3)

- Dissolved the compound stock solution in DMSO and conduct serial dilution with cell culture medium to achieve the working concentration.
- Added 20 μL of media containing desired concentration of distinct compound into per well to achieve the final compound concentration.
- Incubated cells at the 37 ℃， 5% CO_2 incubator for 6 h.

[00260] ***Detection (Day 3)***

- Prepared 2x detect solution: Dilute LgBiT Protein and Nano-Glo® HiBiT Lytic Substrate 1:2:100 into an appropriate volume of room temperature Nano-Glo® HiBiT Lytic Buffer in a new tube.
- Prepared 1x detect solution: Add equal volume PBS into 2x detect solution to prepare 1x detect solution.
- Washed cells with PBS and add 30ul 1x solution into well and mix.
- Waited at least 10 minutes for equilibration of LgBiT and HiBiT in the lysate. Measured luminescence using Envision.

[00261] The data from examples A, B, and C are shown in Table 3.

TABLE 3

Ex.	PHD2	Caco2-HIF1α-HiBit assay - EC50	HEP3B EPO assay EC50
1	C	C	E
2	B	E	E
3	B	A	E
4	B	E	D
5	B	D	E
6	B	B	
7	B	B	D
8	B	A	B
9	A	B	E
10	A	A	D

Ex.	PHD2	Caco2-HIF1α-HiBit assay - EC50	HEP3B EPO assay EC50
12	B	C	A
13	A	B	B
15	E	E	E
16	A	E	B
17	E	E	E
18	B	C	E
19	B	E	E
20	A	B	B
21	C	E	E
22	E	E	E
23	A	C	C
24	E	E	E
25	A	A	A
26	A	B	C
27	A	A	A
28	A	E	E
29	A	A	A
30		B	B
31		E	E
32	A	E	E
33		C	E
34	C	D	E
35	C	E	E
36	D	E	E
37	A	D	D
38	A	B	D
39	A	E	E
40	D	E	E
41	A	E	D
42	A	B	A
43	A	B	B
44	A	A	B
45	A	E	E
46	A	E	C
47	A	A	B
48	E	E	E
49	A	A	C
50	A	E	D
51	A	E	E
52	C	D	D
53	A	A	B
55	A	E	E
56	B	A	A
57	A	D	D
58	A	D	E
59	A	B	C
60	B	E	D
61	B	C	C
62	C	E	B
63	B	D	B
64	D	E	E
66	A	E	B
67	A	B	C
68	B	B	A

Ex.	PHD2	Caco2-HIF1α-HiBit assay - EC50	HEP3B EPO assay EC50
69	B	B	B
70	B	B	B
71	B	B	C
72	A	C	B
73	A	C	B
74	A	B	A
75	A	C	A
76	B	E	E
77	A	B	B
78	A	E	E
79	A	B	C
80	A	A	A
81	A	C	B
83	A	B	A
84	A	C	D
85	A	E	F
86	A	E	B
88	A	B	C
89	A	B	B
90	B	C	E
91	A	A	A
92	A	C	D
93	C	E	E
94	A	D	C
95	A	E	B
96	A	E	C
97	C	E	E
98	D	E	E
99	B	E	E
100	B	D	E
101	A	B	A
102	D		
103	A	B	B
104		D	C
106	A	A	A
107	A	C	C
108	A	B	B
110	A	C	B
115	A	E	E
116	A	E	E
117	A	A	B
118	A	A	B
119	A	E	C
120	A	E	E
121	A	D	E
122	B	C	E
123	A	B	E
124	A	E	C
125	A	A	A
126	A	E	E
127	A	A	A
128	C	C	E
129	A	C	B
130	A	B	B

Ex.	PHD2	Caco2-HIF1α-HiBit assay - EC50	HEP3B EPO assay EC50
131	C	E	E
132	A	C	E
133	B	B	B
134		E	
135		A	B
137	A	A	A
138	A	B	A
139	A	B	A
140	B	B	B
141	A	B	A
142	B	B	A
143	A	A	A
144	B	B	E
145	A	A	E
146	B	B	A
147	C	B	D
148	A	B	D
149	A	B	E
150	A	A	E
151		B	E
152	A	B	B
153		B	A
154		A	A
155		D	C
163	D		
167	A		

PHD2 (nM): 0<A≤5; 5<B≤20; 20<C≤100; 100<D≤1,000; 1,000<E<100,000

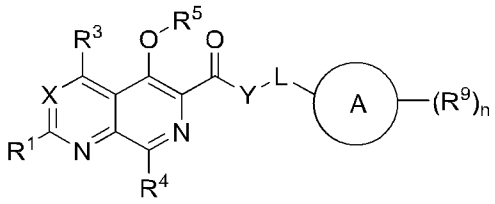
Caco2-HIF1α-HiBit assay (EC50, nM): 0<A≤2,500; 2,500<B≤5,000; 5,000<C≤7500; 7,500<D≤10,000; 10,000<E≤100,000

HEP3B EPO assay (EC50, nM): 0<A≤2,500; 2,500<B≤5,000; 5,000<C≤7500; 7,500<D≤10,000; 10,000<E≤100,000

CLAIMS

WHAT IS CLAIMED IS:

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



Formula (I),

wherein:

R^1 is hydrogen, halogen, -W-CN, -W-NO_2, -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-SH, -W-SR^a, -W-$S(=O)R^a$, -W-$S(=O)_2R^a$, -W-$S(=O)_2NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$NR^bS(=O)_2R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, 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_6alkylene(aryl), or C_1-C_6alkylene(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a};

each R^{1a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{1a} on the same atom are taken together to form an oxo;

W is absent or C_1-C_6alkylene;

X is N or CR^2;

R^2 is hydrogen, fluoro, chloro, bromo, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^4 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Y is -O-, -S-, or -NR^6-;

R^6 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

L is -$(CR^7R^8)_p$-;

each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl; each optionally substituted with one or more R^{7a};

each R^{7a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

p is 0-4;

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

each R^9 is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{9a};

or two R^9 on the same atom are taken together to form an oxo;

each R^{9a} is independently halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{9a} on the same atom are taken together to form an oxo;

n is 0-4;

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

each R^c and R^d are 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, 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, -OC$_1$-C$_6$alkyl, -S(=O)C$_1$-C$_6$alkyl, -S(=O)$_2$C$_1$-C$_6$alkyl, -S(=O)$_2$NH$_2$, -S(=O)$_2$NHC$_1$-C$_6$alkyl, -S(=O)$_2$N(C$_1$-C$_6$alkyl)$_2$, -NH$_2$, -NHC$_1$-C$_6$alkyl, -N(C$_1$-C$_6$alkyl)$_2$, -NHC(=O)OC$_1$-C$_6$alkyl, -C(=O)C$_1$-C$_6$alkyl, -C(=O)OH, -C(=O)OC$_1$-C$_6$alkyl, -C(=O)NH$_2$, -C(=O)N(C$_1$-C$_6$alkyl)$_2$, -C(=O)NHC$_1$-C$_6$alkyl, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, or C$_1$-C$_6$heteroalkyl; or

two R on the same atom are taken together to form an oxo.

2. The compound of claim 1, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein X is N.
3. The compound of claim 1, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein X is CR^2.
4. The compound of claim 1 or 3, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^2 is hydrogen, fluoro, or C$_1$-C$_6$alkyl.
5. The compound of claim 1 or 3 or 4, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^2 is hydrogen.
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^3 is hydrogen, halogen, C$_1$-C$_6$alkyl, or C$_1$-C$_6$haloalkyl.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^3 is hydrogen.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^4 is hydrogen, halogen, C$_1$-C$_6$alkyl, or C$_1$-C$_6$haloalkyl.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^4 is hydrogen.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^5 is hydrogen or C$_1$-C$_6$alkyl.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^5 is hydrogen.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Y is -O- or -NR^6-.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Y is -NR^6-.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^6 is hydrogen or C$_1$-C$_6$alkyl.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^6 is hydrogen.
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein p is 1 or 2.
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein p is 1.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^7 and R^8 are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6hydroxyalkyl; or R^7 and R^8 on the same carbon are taken together to form a cycloalkyl or heterocycloalkyl.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^7 and R^8 are independently hydrogen or C_1-C_6alkyl.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^7 and R^8 are hydrogen.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Ring A is aryl or heteroaryl.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Ring A is phenyl.

23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Ring A is 5- or 6-membered heteroaryl.

24. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein Ring A is 6-membered heteroaryl.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein n is 1 or 2.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein n is 1.

27. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein n is 2.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^9 is independently halogen, -CN, -OH, -OR^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, or C_1-C_6heteroalkyl.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^9 is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, C_1-C_6alkyl, or C_1-C_6haloalkyl.

30. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^9 is independently halogen or -CN.

31. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^9 is -CN.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is halogen, -W-CN, -OH, -W-OR^a, -W-OC(=O)R^a, -W-OC(=O)OR^b, -W-OC(=O)NR^cR^d, -W-NR^cR^d, -W-NR^bC(=O)NR^cR^d, -W-NR^bC(=O)R^a, -W-NR^bC(=O)OR^b, -W-C(=O)R^a, -W-C(=O)OR^b, -W-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, aryl, or heteroaryl; wherein the

alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{1a}.

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-$OC(=O)OR^b$, -W-$OC(=O)NR^cR^d$, -W-NR^cR^d, -W-$NR^bC(=O)NR^cR^d$, -W-$NR^bC(=O)R^a$, -W-$NR^bC(=O)OR^b$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, cycloalkyl, or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally and independently substituted with one or more R^{1a}.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-NR^cR^d, -W-$NR^bC(=O)R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, or heterocycloalkyl optionally and independently substituted with one or more R^{1a}.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is -OH, -W-OR^a, -W-$OC(=O)R^a$, -W-NR^cR^d, -W-$NR^bC(=O)R^a$, -W-$C(=O)R^a$, -W-$C(=O)OR^b$, -W-$C(=O)NR^cR^d$, or heterocycloalkyl.

36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is heterocycloalkyl optionally and independently substituted with one or more R^{1a} (e.g., 1 or 2 R^{1a}).

37. The compound of claim 36, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is monocyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}.

38. The compound of claim 37, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is 5-7 membered (e.g., 6 membered) monocyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}, and wherein the monocyclic heterocycloalkyl contains 1-3 ring nitrogen atoms.

39. The compound of claim 36, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is bicyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}.

40. The compound of claim 39, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is 7-9 membered bicyclic heterocycloalkyl optionally and independently substituted with 1 or 2 R^{1a}, and wherein the bicyclic heterocycloalkyl contains 0-1 ring oxygen and 1-2 ring nitrogen atoms.

41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein W is absent.

42. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein W is C_1-C_2alkylene.

43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^{1a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl,

heterocycloalkyl, aryl, or heteroaryl; or two R^{1a} on the same atom are taken together to form an oxo.

44. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^{1a} is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -$NR^bC(=O)R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, or heterocycloalkyl; or two R^{1a} on the same atom are taken together to form an oxo.

45. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^{1a} is independently halogen, -OH, -OR^a, -$NR^bC(=O)R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6heteroalkyl, or cycloalkyl; or two R^{1a} on the same atom are taken together to form an oxo.

46. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein each R^{1a} is independently C_1-C_6alkyl (e.g., methyl), C_1-C_6haloalkyl, or -$C(=O)OR^b$ (e.g., -$C(=O)O(C_1$-C_6alkyl)).

47. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein R^1 is unsubstituted.

48. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein the abundance of deuterium in each of R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or 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% of a total number of hydrogen and deuterium.

49. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein one or more of R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or R^d groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

50. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, or stereoisomer thereof, wherein one or more hydrogens are replaced with one or more deuteriums in one or more of the following groups R, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^8, R^9, R^{9a}, W, R^a, R^b, R^c, and/or R^d.

51. The compound of claim 1 selected from a compound of table 1, or a pharmaceutically acceptable salt, or stereoisomer thereof.

52. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-51, or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

53. A method of treating a disease or disorder associated with PHD, the method comprising administering to the subject a compound of any one of claims 1-51, or a pharmaceutically acceptable salt, or stereoisomer thereof, or a pharmaceutical composition of claim 52.

54. A method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound of any one of claims 1-51, or a pharmaceutically acceptable salt, or stereoisomer thereof, or a pharmaceutical composition of claim 52, wherein the disease or disorder is cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, or cancer.

55. A method of treating a disease or disorder in a subject, the method comprising administering to the subject a compound of any one of claims 1-51, or a pharmaceutically acceptable salt, or stereoisomer thereof, or a pharmaceutical composition of claim 52, wherein the disease or disorder is stroke, myocardial infarction, congestive heart failure, atherosclerosis, chronic venous insufficiency, cardiac cirrhosis, acute decompensated heart failure, heart failure following a heart attack, peripheral artery disease, occlusive artery disease, diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, impaired glucose tolerance, non-alcoholic liver steatosis, chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension, mountain sickness, acute respiratory failure, interstitial lung disease, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, acute kidney failure, acute kidney injury, renal ischemia reperfusion injury, hepatic ischemia reperfusion injury, diabetic foot ulcers, pressure ulcers, venous ulcers, arterial ulcers, epidermolysis bullosa, pemphigus, Sjogren's syndrome, anemia, inflammatory bowel disease (IBD), chronic kidney disease (CKD), Parkinson's disease (PD), or Alzheimer's disease (AD).

56. The method of claim 55, wherein the disease or disorder is Parkinson's disease (PD).

57. The method of claim 55, wherein the disease or disorder is Alzheimer's disease (AD).

58. The method of claim 55, wherein the disease or disorder is anemia, inflammatory bowel disease (IBD), or chronic kidney disease (CKD).

59. The method of claim 55, wherein the disease or disorder is anemia.

60. The method of claim 55, wherein the disease or disorder is inflammatory bowel disease (IBD).

61. The method of claim 60, wherein the disease or disorder is ulcerative colitis (“UC”) or Crohn’s disease (“CD”).

62. The method of claim 55, wherein the disease or disorder is chronic kidney disease (CKD).

63. A method of stabilizing hypoxia inducible factor (HIF) in a subject, the method comprising administering to the subject a compound of any one of claims 1-51, or a pharmaceutically acceptable salt, or stereoisomer thereof, or a pharmaceutical composition of claim 52.

64. The method of claim 63, wherein the HIF is HIF-1α.

65. The method of any one of claims 53-64, further comprising administration of an additional active agent.

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04(2006.01)i; C07D 401/14(2006.01)i; A61K 31/166(2006.01)i; A61P 9/10(2006.01)i; A61P 3/10(2006.01)i; A61P 25/28(2006.01)i; A61P 35/00(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)

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)

CNABS, CNTXT, SIPOABS, DWPI, WOTXT, EPTXT, USTXT, CNKI, PUBMED, ISI_Web of Science, Science Direct, STNext: INSILICO MEDICINE IP LIMITED, prolyl hydroxylase domain containing protein, PHD, PHD1, PHD2, PHD3, HIF, hypoxia inducible factor, 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 2013134660 A1 (FIBROGEN INC.) 12 September 2013 (2013-09-12) the abstract, claims 1-30, description paragraphs 3-4, Table 1, Examples 15, 16, 19, 29, 132, 137	1-65
A	WO 2019060850 A1 (TAKEDA PHARMACEUTICALS CO., LTD. et al.) 28 March 2019 (2019-03-28) the abstract, claims 1-41, description examples 3-8	1-65
A	WO 2004019933 A1 (PHARMACIA & UPJOHN CO. et al.) 11 March 2004 (2004-03-11) the abstract, claims 1-24	1-65
A	WO 0204443 A2 (PHARMACIA & UPJOHN CO. et al.) 17 January 2002 (2002-01-17) the abstract, preparation 13 and example 4	1-65
A	WO 2009037570 A2 (CRYSTALGENOMICS INC. et al.) 26 March 2009 (2009-03-26) the abstract, claims 1-51	1-65

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"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
13 January 2023	**28 January 2023**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **CUI,Chuanming** Telephone No. **(86-10)53961869**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/128237

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.: **53-65**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 53-65 relate to a method of treating a disease or disorder or a method of stabilizing hypoxia inducible factor (HIF), and thus do not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). The search has been made and based on the subject-matter of the manufacture of a medicament correspondingly.

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/CN2022/128237

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