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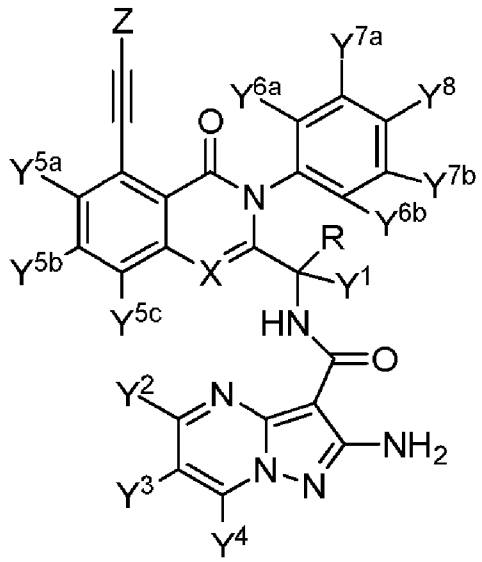

(AB'),

(57) Abstract: Provided are isotopologues of isoquinolinone and quinazolinone compounds of formula (AB') that modulate PI3 kinase activity, processes for the preparation of the compounds, pharmaceutical compositions comprising the compounds, and methods of treatment of diseases and disorders using the compounds or pharmaceutical compositions.

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ISOTOPOLOGUES OF ISOQUINOLINONE AND QUINAZOLINONE COMPOUNDS AND USES THEREOF AS PI3K KINASE INHIBITORS

[0001] This application claims priority to U.S. Provisional Application No. 62/309,769, filed March 17, 2016, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel *et al. Current Medicinal Chemistry* (2007) 14:2214–2234).

[0003] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (*i.e.,* autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (*e.g.,* erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (*e.g.,* mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0004] Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (*e.g.,* PI3-kinases, PI4-kinases), diacylglycerol kinases, and sphingosine kinases.

[0005] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K

signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0006] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PI3Ks are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K-δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K-δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, and auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K-γ, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus. For example, PI3K-γ and PI3K-δ are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3K isoforms can be important mediators in inflammatory disorders and hematologic malignancies.

[0008] The gamma (γ) isoform of class I PI3K consists of a catalytic subunit p110γ, which is associated with a p101 regulatory subunit. PI3K-γ is regulated by G protein-coupled receptors (GPCRs) via association with the β/γ subunits of heterotrimeric G proteins. PI3K-γ is expressed primarily in hematopoietic cells and cardiomyocytes and is involved in inflammation and mast cell function. Inhibitors of PI3K-γ are useful for treating a variety of inflammatory diseases, allergies, and cardiovascular diseases, among others.

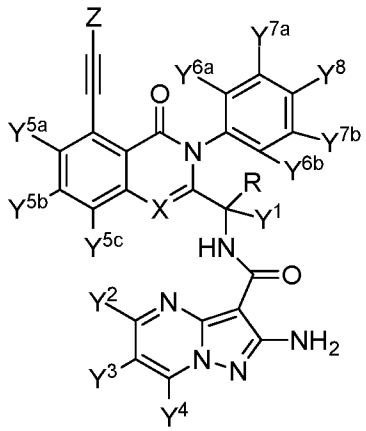
[0009] Unlike PI3K-δ, the beta (β) isoform of class I PI3K appears to be ubiquitously expressed. PI3K-β has been implicated primarily in various types of cancer including PTEN-negative cancer (Edgar et al. *Cancer Research* (2010) 70(3):1164-1172), and HER2-overexpressing cancer such as breast cancer and ovarian cancer.

[0010] Certain isoquinolinone or quinazolinone compounds that are capable of selectively inhibiting one or more isoform(s) of class I PI3K have been described in International Application Publication Nos. WO 2015/051244 and WO 2015/143012, the entireties of which are incorporated herein by reference. A need still exists for developing isotopologues of the isoquinolinone or quinazolinone compounds that are more metabolically stable, more therapeutically effective, or can be prepared by more efficient and scalable processes.

SUMMARY

[0011] Provided herein are isotopologues of certain isoquinolinone or quinazolinone compounds that are capable of selectively inhibiting one or more isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. For example, in some embodiments, non-limiting examples of inhibitors capable of selectively inhibiting PI3K-δ and/or PI3K-γ, but without substantially affecting the activity of PI3K-α and/or PI3K-β are provided. In one embodiment, the inhibitors provided herein can be effective in ameliorating disease conditions associated with PI3K-δ and/or PI3K-γ activity. In one embodiment, the compounds are capable of selectively inhibiting PI3K-γ over PI3K-δ.

[0012] In one embodiment, provided herein is a compound of Formula (AB'):



(AB'),

or a pharmaceutically acceptable form thereof, wherein R, X, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^8, and Z are defined herein.

INCORPORATION BY REFERENCE

[0013] 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. In case of conflict, the present application, including any definitions herein, will control.

DETAILED DESCRIPTION

DEFINITIONS

[0014] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0015] The term "isotopic composition" refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural isotopic composition.

[0016] The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. As used herein, an "isotopologue" is an isotopically enriched compound.

[0017] The term "isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic composition. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%.

[0018] The term "isotopic enrichment factor" refers to the ratio between the isotopic composition and the natural isotopic composition of a specified isotope.

[0019] With regard to the compounds provided herein, when a particular atomic position is designated as deuterium or "D," it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.0156%. A position designated as deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least about 1000 (about 15% deuterium incorporation), at least about 2000 (about 30% deuterium incorporation), at least about 3000 (about 45% deuterium incorporation), at least about 3500 (about 52.5% deuterium incorporation), at least about 4000 (about 60% deuterium incorporation), at least about 4500 (about 67.5% deuterium incorporation), at least about 5000 (about 75% deuterium incorporation), at least about 5500 (about 82.5% deuterium incorporation), at least about 6000 (about 90% deuterium incorporation), at least about 6333.3 (about 95% deuterium incorporation), at least about 6466.7 (about 97% deuterium incorporation), at least about 6600 (about 99% deuterium incorporation), or at least about 6633.3 (about 99.5% deuterium incorporation) at each designated deuterium atom.

[0020] The isotopic enrichment and isotopic enrichment factor of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0021] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th ed., John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, Some *Modern Methods of Organic Synthesis*, 3rd ed., Cambridge University Press, Cambridge, 1987.

[0022] As used herein, and unless otherwise specified, the term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having, in some embodiments, from one to ten carbon atoms (*e.g.*, C_1–C_{10} alkyl). Linear or straight alkyl refers to an alkyl with no branching, *e.g.*, methyl, ethyl, n-propyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the

occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1–C_6 alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0023] As used herein, and unless otherwise specified, the term "alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and in some embodiments, having from two to ten carbon atoms (*i.e.,* C_2–C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; *e.g.,* "2 to 10 carbon atoms" means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (*e.g.,* C_2-C_5 alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (*i.e., v*inyl), prop-1-enyl (*i.e.,* allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless stated otherwise in the specification, an alkenyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl,

cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0024] As used herein, and unless otherwise specified, the term "alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having, in some embodiments, from two to ten carbon atoms (*i.e.*, C_2–C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (*e.g.*, C_2–C_5 alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise in the specification, an alkynyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0025] As used herein, and unless otherwise specified, the term "cycloalkyl," or alternatively, "carbocyclyl," refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle

contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 10 ring atoms (*e.g.*, C_3–C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. In some embodiments, it is a C_3–C_8 cycloalkyl radical. In some embodiments, it is a C_3–C_5 cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro–1*H*–indenyl, decahydronaphthalenyl, spiro[4.5]decanyl, and the like. Unless stated otherwise in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "cycloalkyl" or "carbocyclyl" also includes ring systems wherein the cycloalkyl or carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment to the parent molecular structure is on the cycloalkyl or carbocyclyl ring.

[0026] As used herein, and unless otherwise specified, the term "heterocyclyl", "heterocycloalkyl" or 'heterocarbocyclyl" each refer to any 3- to 18-membered non-aromatic radical monocyclic or polycyclic moiety comprising at least one ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or more rings. A heterocyclyl group can be

saturated or partially unsaturated. Partially unsaturated heterocycloalkyl groups can be termed "heterocycloalkenyl" if the heterocyclyl contains at least one double bond, or "heterocycloalkynyl" if the heterocyclyl contains at least one triple bond. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; *e.g.,* "5 to 18 ring atoms" means that the heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, bivalent radicals derived from univalent heterocyclyl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.,* a piperidyl group with two points of attachment is a piperidylidene.

[0027] An N-containing heterocyclyl moiety refers to an non-aromatic group in which at least one of the ring atoms is a nitrogen atom. The heteroatom(s) in the heterocyclyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can be optionally quaternized. Heterocyclyl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as piperidinyl N-oxides. The heterocyclyl is attached to the parent molecular structure through any atom of any of the ring(s).

[0028] "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. In some embodiments, a heterocyclyl group is a 3- to 10-membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("3- to 10-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 8-membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 6-membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heterocyclyl"). In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[0029] Exemplary 3–membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro–1,8–naphthyridinyl, octahydropyrrolo[3,2–b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepinyl, 1,4,5,7–tetrahydro-pyrano[3,4–b]pyrrolyl, 5,6–dihydro–4H–furo[3,2–b]pyrrolyl, 6,7–dihydro–5H–furo[3,2–b]pyranyl, 5,7–dihydro–4H–thieno[2,3–c]pyranyl, 2,3–dihydro–1H–pyrrolo[2,3–b]pyridinyl, 2,3–dihydrofuro[2,3–b]pyridinyl, 4,5,6,7–tetrahydro–1H–pyrrolo[2,3–b]pyridinyl, 4,5,6,7–tetrahydrofuro[3,2–c]pyridinyl, 4,5,6,7–tetrahydrothieno[3,2–b]pyridinyl, 1,2,3,4–tetrahydro–1,6–naphthyridinyl, and the like.

[0030] Unless stated otherwise, heterocyclyl moieties are optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $–Si(R^a)_3$, $–OR^a$, $–SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $–N(R^a)C(O)N(R^a)_2$, $–N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $–O–P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0031] As used herein, and unless otherwise specified, the term "aryl" refers to a radical with six to fourteen ring atoms (*e.g.*, C_6–C_{14} or C_6–C_{10} aryl) which has at least one carbocyclic ring having a conjugated pi electron system which is aromatic (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) (*e.g.*, phenyl, fluorenyl, and naphthyl). In one embodiment, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals derived from univalent monocyclic or polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10 aryl" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise in the specification, an aryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the aryl ring.

[0032] As used herein, and unless otherwise specified, the term "heteroaryl", or alternatively, "heteroaromatic", refers to a radical of a 5- to 18-membered monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) aromatic ring system (*e.g.*, having 6, 10 or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1 to 6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 18-membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or more rings. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms,

7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.,* a pyridyl group with two points of attachment is a pyridylidene.

[0033] For example, an N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

[0034] "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl). In some embodiments, a heteroaryl group is a 5 to 10 membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 10-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heteroaryl"). In some embodiments, the 5- to 6-membered heteroaryl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 to 2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[0035] Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl,isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d] pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.,* thienyl).

[0036] Unless stated otherwise in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0037] As used herein, and unless otherwise specified, the term "halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo, or iodo.

[0038] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable form" of a compound provided herein includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of compounds provided herein.

[0039] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, naphthalene-*m,n*-bissulfonates, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, naphthalene-*m,n*-bissulfonic acids and the like.

[0040] Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide,

carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0041] As used herein, and unless otherwise specified, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a compound provided herein or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0042] As used herein, and unless otherwise specified, the term "prodrug" refers to compounds that are transformed *in vivo* to yield a compound provided herein or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.,* hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series,* Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it can enhance drug stability for long–term storage.

[0043] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to

the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York, 1985).

[0044] For example, if a compound provided herein or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise a pharmaceutically acceptable ester formed by the replacement of the hydrogen atom of the acid group with a group such as $(C_1$-$C_8)$alkyl, $(C_2$–$C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1$–$C_2)$alkylamino$(C_2$–$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$–$C_2)$alkyl, N,N-di$(C_1$–$C_2)$alkylcarbamoyl-$(C_1$–$C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$–$C_3)$alkyl.

[0045] Similarly, if a compound provided herein or a pharmaceutically acceptable form of the compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as $(C_1$–$C_6)$alkanoyloxymethyl, 1-$((C_1$–$C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1$-$C_6)$alkanoyloxy)ethyl $(C_1$–$C_6)$alkoxycarbonyloxymethyl, N-$(C_1$-$C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1$–$C_6)$alkanoyl, α-amino$(C_1$–$C_4)$alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)$alkyl$)_2$, and glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0046] If a compound provided herein or a pharmaceutically acceptable form of the compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR′-carbonyl where R and R′ are each independently $(C_1$-$C_{10})$alkyl, $(C_3$-$C_7)$cycloalkyl, benzyl, a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, $-C(OH)C(O)OY^1$ wherein Y^1 is H, $(C_1$-$C_6)$alkyl or benzyl, $-C(OY^2)Y^3$

wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N– or di-N,N–(C_1-C_6)alkylaminoalkyl, –C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N– or di-N,N–(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0047] As used herein, and unless otherwise specified, the term "isomers" refers to different compounds that have the same molecular formula. "Atropisomers" are stereoisomers from hindered rotation about single bonds and can be resolved or isolated by methods known to those skilled in the art.

[0048] As used herein, and unless otherwise specified, the term "stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond *cis*– and *trans*–isomers, also termed *E*– and *Z*– isomers; *R*– and *S*–enantiomers; diastereomers, (*d*)–isomers and (*l*)–isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

[0049] As used herein, and unless otherwise specified, the term "enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry can be specified according to the Cahn-Ingold-Prelog *R*-*S* system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (*R*)- or (*S*)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0050] The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, *e.g.,* an *S* enantiomer, and 10% of the other enantiomer, *e.g.,* an *R* enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

[0051] Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the *S* enantiomer. In other words, the compositions contain an enantiomeric excess of the *S* enantiomer over the *R* enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the *R* enantiomer. In other words, the compositions contain an enantiomeric excess of the *R* enantiomer over the *S* enantiomer.

[0052] For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as "optically enriched," "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein. These terms refer to compositions in which the amount of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (*e.g.*, greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the *S* enantiomer, means a preparation of the compound having greater than about 50% by weight of the *S* enantiomer relative to the total weight of the preparation (*e.g.*, total weight of *S* and *R* isomers). such as at least about 75% by weight, further such as at least about 80% by weight. In some embodiments, the enrichment can be much greater than about 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least about 85% by weight of one enantiomer relative to the total weight of the preparation, such as at least about 90% by weight, and further such as at least about 95% by weight. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments, the compound is made up of at least about 95%, about 98%, or about 99% by weight of one enantiomer.

[0053] In some embodiments, the compound is a racemic mixture of (*S*)- and (*R*)- isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (*S*)- or (*R*)- isomeric configuration. For example, in some embodiments, the compound mixture has an (*S*)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments,

the compound mixture has an (*S*)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (*S*)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0054] In other embodiments, the compound mixture has an (*R*)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments, the compound mixture has an (*R*)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (*R*)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0055] In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (*S*)- or (*R*)-isomers. For example, if a compound provided herein has –CH(R)– unit, and R is not hydrogen, then the –CH(R)– is in an (*S*)- or (*R*)- stereochemical orientation for each of the identical chemical entities (*i.e.*, (*S*)- or (*R*)-stereoisomers). In some embodiments, the mixture of identical chemical entities (*i.e.*, mixture of stereoisomers) is a racemic mixture of (*S*)- and (*R*)- isomers. In another embodiment, the mixture of the identical chemical entities (*i.e.*, mixture of stereoisomers) contains predominately (*S*)-isomer or predominately (*R*)-isomer. For example, in some embodiments, the (*S*)-isomer in the mixture of identical chemical entities (*i.e.*, mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (*S*)- and (*R*)-isomers. In some embodiments, the (*S*)-isomer in the mixture of identical chemical entities (*i.e.*, mixture of stereoisomers) is present at an (*S*)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about

30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0056] In other embodiments, the (*R*)-isomer in the mixture of identical chemical entities (*i.e.*, mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (*S*)- and (*R*)-isomers.. In some embodiments, the (*R*)-isomers in the mixture of identical chemical entities (*i.e.*, mixture of stereoisomers) is present at an (*R*)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about 30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0057] Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses. *See,* for example, *Enantiomers, Racemates and Resolutions* (Jacques, Ed., Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); *Stereochemistry of Carbon Compounds* (E.L. Eliel, Ed., McGraw–Hill, NY, 1962); and *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0058] As used herein, and unless otherwise specified, the term "tautomer" refers to a type of isomer that includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.,* a single bond to a double bond, a triple bond to a double bond, or a triple bond to a single bond, or *vice versa*). "Tautomerization" includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (*e.g.,* in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (*i.e.,* the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent.

Exemplary tautomerizations include, but are not limited to, keto-enol; amide-imide; lactam-lactim; enamine-imine; and enamine-(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0059] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as provided herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0060] As used herein, and unless otherwise specified, the term "subject" to which administration is contemplated includes, but is not limited to, humans (*e.g.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult or senior adult)) and/or other primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

[0061] As used herein, and unless otherwise specified, the term "treatment" or "treating" refers to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder.

[0062] As used herein, and unless otherwise specified, the term "prevention" or "preventing" refers to an approach for obtaining beneficial or desired results including, but not limited, to prophylactic benefit. For prophylactic benefit, the pharmaceutical compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0063] As used herein, and unless otherwise specified, the term "selective inhibition" or "selectively inhibit" as applied to a biologically active agent refers to the agent's ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with

the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least greater than about 1X against a first isoform relative to the compound's activity against the second isoform (*e.g.*, at least about 2X, 3X, 5X, 10X, 20X, 50X, 100X, 200X, 500X, or 1000X). In certain embodiments, these terms refer to (1) a compound of described herein that selectively inhibits the gamma isoform over the alpha, beta, or delta isoform; or (2) a compound described herein that selectively inhibits the delta isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 1, greater than a factor of about 2, greater than a factor of about 3, greater than a factor of about 5, greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, which in turn can be measured by, *e.g.*, *in vitro* or *in vivo* assays such as those described in Examples described herein. In one embodiment, the selectivity of a first PI3K isoform over a second PI3K isoform is measured by the ratio of the IC_{50} value against the second PI3K isoform to the IC_{50} value against the first PI3K gamma isoform. For example, a delta/gamma selectivity ratio of a compound can be measured by the ratio of the compound's inhibitory activity against the delta isoform in terms of IC_{50} or the like to the compound's inhibitory activity against the gamma isoform in terms of IC_{50} or the like. If the delta/gamma selectivity ratio is larger than 1, the compound selectively inhibits the gamma isoform over the delta isoform. In certain embodiments, the PI3K gamma isoform IC_{50} activity of a compound of provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM , less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In certain embodiments, the PI3K delta isoform IC_{50} activity of a compound provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM , less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM.

[0064] As used herein, and unless otherwise indicated, the term "about" or "approximately" refers to an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about"

or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

COMPOUNDS

[0065] Provided herein are isotopologues of certain isoquinolinone or quinazolinone compounds. In some embodiment, the compounds are capable of selectively inhibiting one or more isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. For example, in some embodiments, non-limiting examples of inhibitors capable of selectively inhibiting PI3K-δ and/or PI3K-γ, but without substantially affecting the activity of PI3K-α and/or PI3K-β are provided. In one embodiment, the inhibitors provided herein can be effective in ameliorating disease conditions associated with PI3K-δ and/or PI3K-γ activity. In one embodiment, the compounds are capable of selectively inhibiting PI3K-γ over PI3K-δ.

[0066] Isotopic enrichment (*e.g.*, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. (*See*, *e.g.*, Lijinsky *et. al.*, Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky *et. al.*, J. Nat. Cancer Inst., 69: 1127 (1982); Mangold *et. al.*, Mutation Res. 308: 33 (1994); Gordon *et. al.*, Drug Metab. Dispos., 15: 589 (1987); Zello *et. al.*, Metabolism, 43: 487 (1994); Gately *et. al.*, J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999)).

[0067] Without being limited by a particular theory, isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[0068] Replacement of an atom for one of its isotopes may often result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C–H bond is broken during a rate-determining step in a chemical reaction (*i.e.* the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (*See, e.g,* Foster *et al.*, Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.*, Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999)).

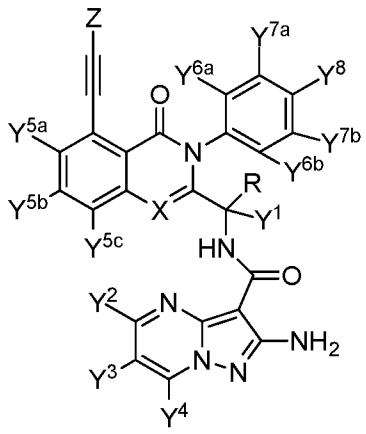
[0069] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C–H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. Without being limited by a particular theory, high DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

[0070] The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. Examples of such enzymes include the cytochrome P450 enzymes ("CYPs"), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

[0071] Therefore, isotopic enrichment at certain positions of a compound provided herein may produce a detectable KIE that affects the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition. In certain embodiments, the deuterium enrichment is performed on the site of C-H bond cleavage during metabolism.

[0072] Furthermore, racemization of many compounds involves the breaking of a C-H bond at the chiral center and may be retarded by selective incorporation of deuterium. Therefore, in certain embodiments, provided herein are compounds of Formula (AB') or (AB), in which racemization of the chiral center is retarded by selective incorporation of deuterium. In certain embodiments, provided herein is selective incorporation of deuterium at the Y^1 position of Formula (AB') or (AB).

[0073] In certain embodiments, provided herein is a compound of Formula (AB'):



(AB'),

or a pharmaceutically acceptable form thereof, wherein

R is C_1-C_3 alkyl optionally substituted with one or more deuterium or halogen;

X is CY^{5d} or N;

Y^1 is hydrogen or deuterium;

Y^2, Y^3, and Y^4 are each independently hydrogen or deuterium;

Y^{5a}, Y^{5b}, Y^{5c}, and Y^{5d} are each independently hydrogen or deuterium;

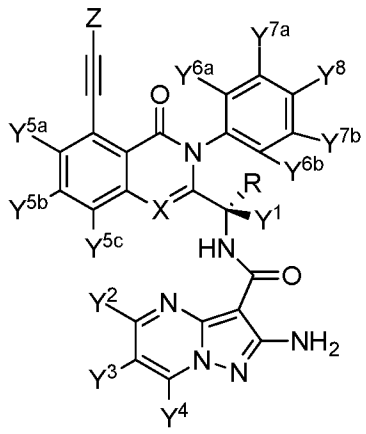
Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are each independently hydrogen, deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen;

Z is a 5- to 10-membered heteroaryl optionally substituted with one or more deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^8, and Z is or comprises a deuterium;

provided that, when Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all deuterium, at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, and Z is or comprises a deuterium.

[0074] In certain embodiments, provided herein is a compound of Formula (AB):



(AB),

or a pharmaceutically acceptable form thereof, wherein

R is C_1-C_3 alkyl optionally substituted with one or more deuterium or halogen;

X is CY^{5d} or N;

Y^1 is hydrogen or deuterium;

Y^2, Y^3, and Y^4 are each independently hydrogen or deuterium;

Y^{5a}, Y^{5b}, Y^{5c}, and Y^{5d} are each independently hydrogen or deuterium;

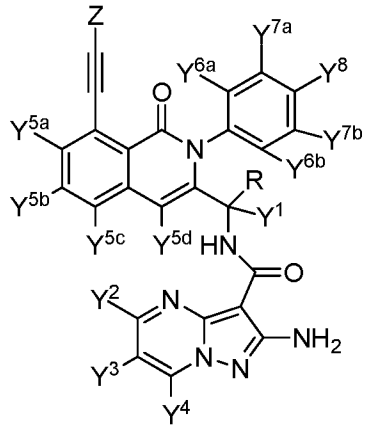
Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are each independently hydrogen, deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen;

Z is a 5- to 10-membered heteroaryl optionally substituted with one or more deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^8, and Z is or comprises a deuterium;

provided that, when Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all deuterium, at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, and Z is or comprises a deuterium.

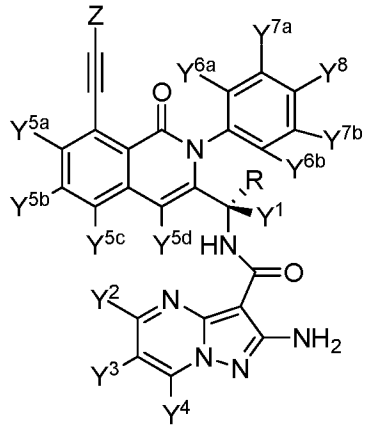
[0075] In one embodiment, the compound of Formula (AB') is a compound of Formula (A'):



(A'),

or a pharmaceutically acceptable form thereof.

[0076] In one embodiment, the compound of Formula (AB) is a compound of Formula (A):

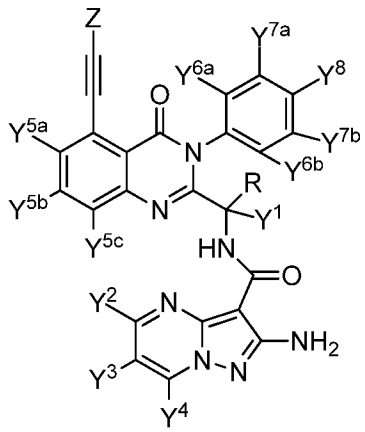


(A),

or a pharmaceutically acceptable form thereof.

[0077] In one embodiment, Y^{5d} is deuterium. In another embodiment, Y^{5d} is hydrogen.

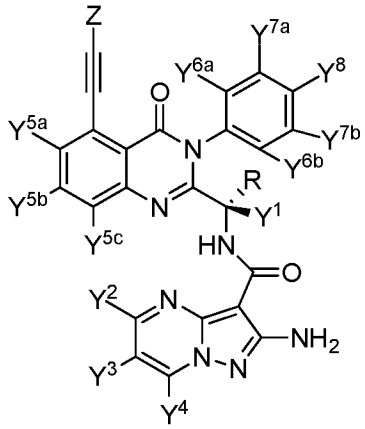
[0078] In one embodiment, the compound of Formula (AB') is a compound of Formula (B'):



(B'),

or a pharmaceutically acceptable form thereof.

[0079] In one embodiment, the compound of Formula (AB) is a compound of Formula (B):



(B),

or a pharmaceutically acceptable form thereof.

[0080] In one embodiment, Y^{5a} is deuterium. In another embodiment, Y^{5a} is hydrogen.

[0081] In one embodiment, Y^{5b} is deuterium. In another embodiment, Y^{5b} is hydrogen.

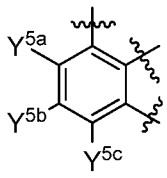
[0082] In one embodiment, Y^{5c} is deuterium. In another embodiment, Y^{5c} is hydrogen.

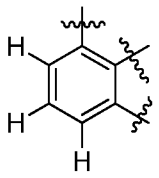
[0083] In one embodiment, Y^{5a}, Y^{5b}, and Y^{5c} are all hydrogen.

[0084] In one embodiment, one of Y^{5a}, Y^{5b}, and Y^{5c} is deuterium, and the other two of Y^{5a}, Y^{5b}, and Y^{5c} are hydrogen. In one embodiment, Y^{5a} is deuterium, and Y^{5b} and Y^{5c} are hydrogen. In one embodiment, Y^{5b} is deuterium, and Y^{5a} and Y^{5c} are hydrogen. In one embodiment, Y^{5c} is deuterium, and Y^{5a} and Y^{5b} are hydrogen.

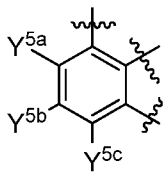
[0085] In one embodiment, two of Y^{5a}, Y^{5b}, and Y^{5c} are deuterium, and the other of Y^{5a}, Y^{5b}, and Y^{5c} is hydrogen. In one embodiment, Y^{5a} and Y^{5b} are deuterium, and Y^{5c} is hydrogen. In one embodiment, Y^{5a} and Y^{5c} are deuterium, and Y^{5b} is hydrogen. In one embodiment, Y^{5b} and Y^{5c} are deuterium, and Y^{5a} is hydrogen.

[0086] In one embodiment, Y^{5a}, Y^{5b}, and Y^{5c} are all deuterium.

[0087] In one embodiment, the 

moiety is 

.

[0088] In one embodiment, the 

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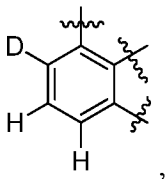
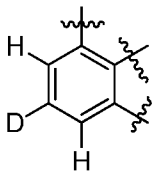
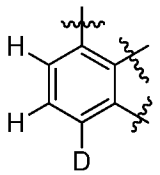
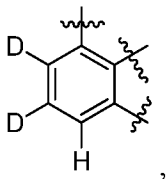
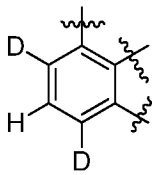
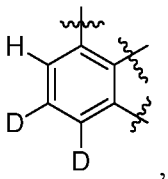


, 

, 

, 

, 

, 

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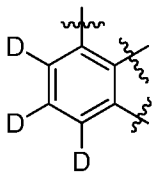


or .

[0089] In one embodiment, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are each independently hydrogen or deuterium.

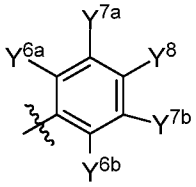
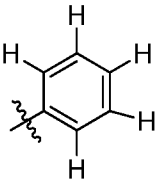
[0090] In one embodiment, Y^{6a} and Y^{6b} are both hydrogen. In one embodiment, at least one of Y^{6a} and Y^{6b} is deuterium. In one embodiment, one of Y^{6a} and Y^{6b} is deuterium, and the other is hydrogen. In one embodiment, Y^{6a} and Y^{6b} are both deuterium.

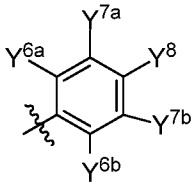
[0091] In one embodiment, Y^{7a} and Y^{7b} are both hydrogen. In one embodiment, at least one of Y^{7a} and Y^{7b} is deuterium. In one embodiment, one of Y^{7a} and Y^{7b} is deuterium, and the other is hydrogen. In one embodiment, Y^{7a} and Y^{7b} are both deuterium.

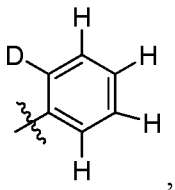
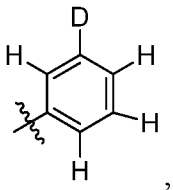
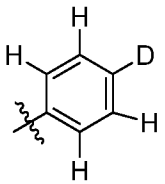
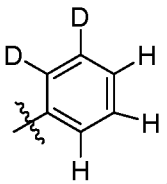
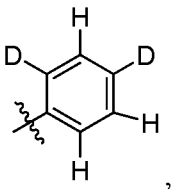
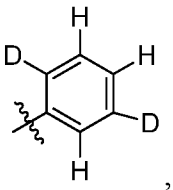
[0092] In one embodiment, Y^{8} is deuterium. In another embodiment, Y^{8} is hydrogen.

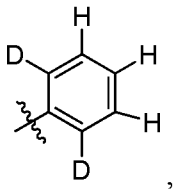
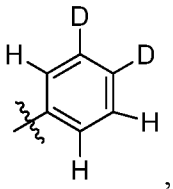
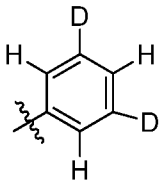
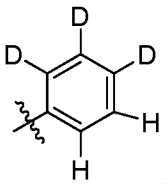
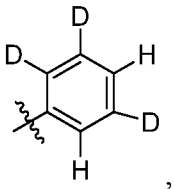
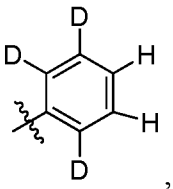
[0093] In one embodiment, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are all hydrogen. In one embodiment, one of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} is deuterium, and the other four of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are hydrogen. In one embodiment, two of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are deuterium, and the other three of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b},

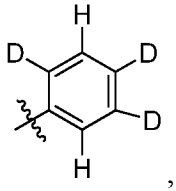
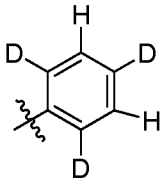
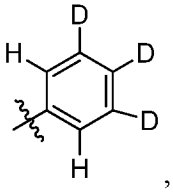
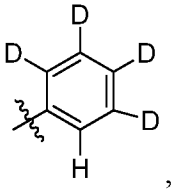
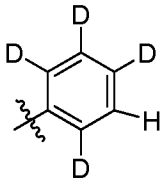
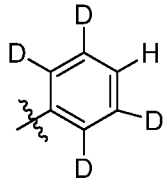
and Y^8 are hydrogen. In one embodiment, three of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are deuterium, and the other two of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are hydrogen. In one embodiment, four of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are deuterium, and the other one of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 is hydrogen. In one embodiment, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all deuterium.

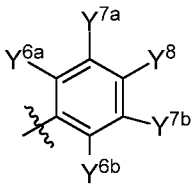
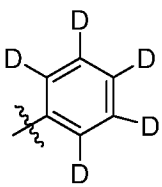
[0094] In one embodiment, the  moiety is  .

[0095] In one embodiment, the  moiety is

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  , or  .

[0096] In one embodiment, the  moiety is  , provided that at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, and Z is or comprises a deuterium.

[0097] In one embodiment, one or more of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are halogen. In one embodiment, one of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 is halogen. In one embodiment, two of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are halogen. In one embodiment, three of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are halogen. In one

embodiment, four of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are halogen. In one embodiment, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all halogen. Each instance of the halogen is independently F, Cl, Br, or I. In one embodiment, the halogen is F. In one embodiment, the halogen is Cl. In one embodiment, the halogen is Br. In one embodiment, the halogen is I.

[0098] In one embodiment, one or more of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more deuterium or halogen. In one embodiment, one of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl is optionally substituted with one or more deuterium or halogen. In one embodiment, two of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen. In one embodiment, three of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen. In one embodiment, four of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen. In one embodiment, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen. Each instance of the C_1-C_3 alkyl is independent of the other, and can be the same or different. In one embodiment, the C_1-C_3 alkyl is $-CH_3$. In one embodiment, the C_1-C_3 alkyl is $-CD_3$. In one embodiment, the C_1-C_3 alkyl is $-CF_3$.

[0099] In one embodiment, Z is a 6-membered heteroaryl. In one embodiment, Z is a pyridinyl or pyrimidinyl.

[00100] In one embodiment, Z is a 5-membered heteroaryl. In one embodiment, Z is a thiazolyl, pyrazolyl, or imidazolyl. In one embodiment, Z is a pyrazolyl. In one embodiment, Z is a 3-pyrazolyl. In one embodiment, Z is a 4-pyrazolyl. In one embodiment, Z is a 5-pyrazolyl.

[00101] In one embodiment, Z is substituted with one or more deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

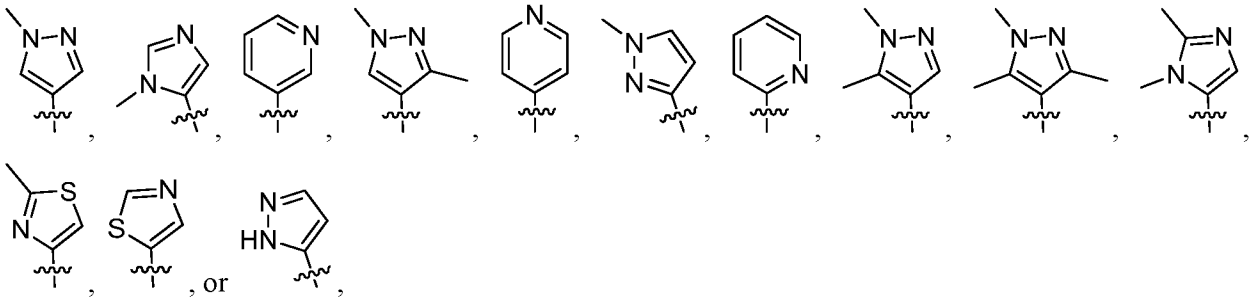
[00102] In one embodiment, Z is substituted with one or more C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

[00103] In one embodiment, Z is substituted with one or two C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

[00104] In one embodiment, Z is substituted with one or two methyl, wherein each instance of the methyl is independently optionally substituted with one or more deuterium or halogen. In one

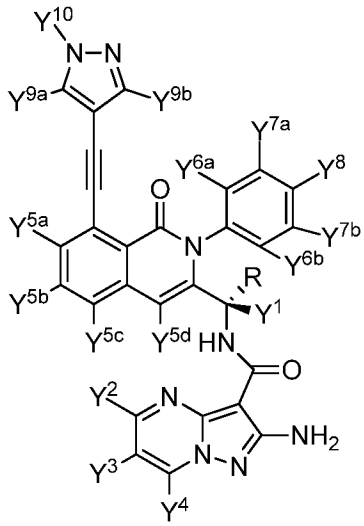
embodiment, Z is substituted with one or two $-CH_3$. In one embodiment, Z is substituted with one or two $-CD_3$. In one embodiment, Z is substituted with one or two $-CF_3$.

[00105] In one embodiment, Z is

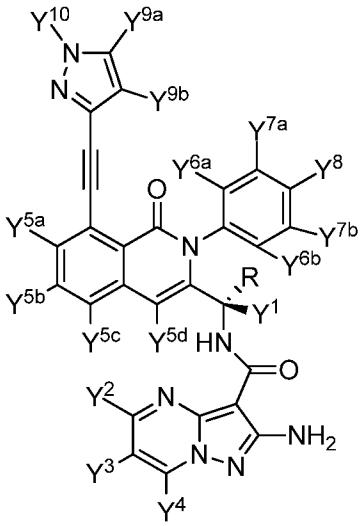


wherein each unspecified position is independently hydrogen or deuterium.

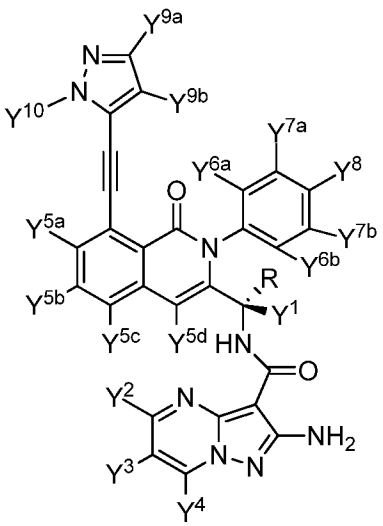
[00106] In one embodiment, the compound is a compound of Formula (A-I), (A-II), or (A-III):



(A-I),



(A-II), or



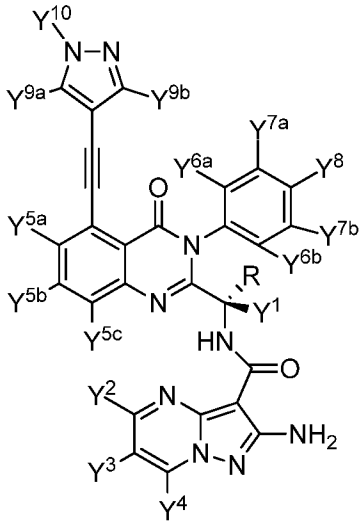
(A-III),

or a pharmaceutically acceptable form thereof, wherein

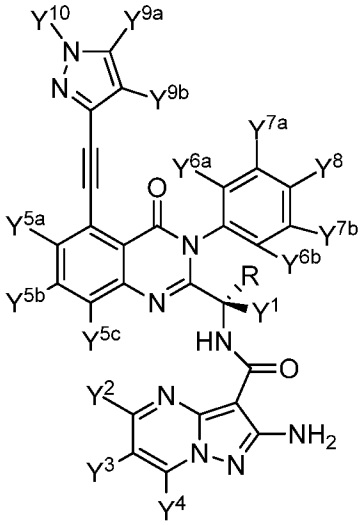
Y^{9a} and Y^{9b} are each independently hydrogen, deuterium, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

Y^{10} is hydrogen or C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

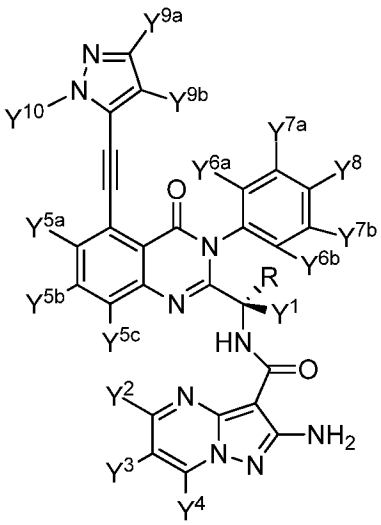
[00107] In one embodiment, the compound is a compound of Formula (B-I), (B-II), or (B-III):



(B-I),



(B-II), or



(B-III),

or a pharmaceutically acceptable form thereof, wherein

Y^{9a} and Y^{9b} are each independently hydrogen, deuterium, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

Y^{10} is hydrogen or C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

[00108] In one embodiment, Y^{9a} and Y^{9b} are each independently hydrogen or deuterium. In one embodiment, Y^{9a} and Y^{9b} are both hydrogen. In one embodiment, Y^{9a} is deuterium, and Y^{9b} is hydrogen. In one embodiment, Y^{9a} is hydrogen, and Y^{9b} is deuterium. In one embodiment, Y^{9a} and Y^{9b} are both deuterium.

[00109] In one embodiment, one of Y^{9a} and Y^{9b} is hydrogen or deuterium, and the other is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen. In one embodiment, Y^{9a} and Y^{9b} are both C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen. In one embodiment, the C_1-C_3 alkyl is $-CH_3$. In one embodiment, the C_1-C_3 alkyl is $-CD_3$. In one embodiment, the C_1-C_3 alkyl is $-CF_3$.

[00110] In one embodiment, Y^{10} is hydrogen.

[00111] In one embodiment, Y^{10} is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen. In one embodiment, the C_1-C_3 alkyl is $-CH_3$. In one embodiment, the C_1-C_3 alkyl is $-CD_3$. In one embodiment, the C_1-C_3 alkyl is $-CF_3$.

[00112] In one embodiment, R is C_1-C_3 alkyl optionally substituted with one or more deuterium. In one embodiment, R is methyl or ethyl optionally substituted with one or more deuterium.

[00113] In one embodiment, R is methyl optionally substituted with one or more deuterium. In one embodiment, R is $-CH_3$. In one embodiment, R is $-CH_2D$. In one embodiment, R is $-CHD_2$. In one embodiment, R is $-CD_3$.

[00114] In one embodiment, R is ethyl optionally substituted with one or more deuterium. In one embodiment, R is $-CH_2-CH_3$. In one embodiment, R is $-CH_2-CH_2D$. In one embodiment, R is $-CH_2-CHD_2$. In one embodiment, R is $-CH_2-CD_3$. In one embodiment, R is $-CHD-CH_3$. In one embodiment, R is $-CHD-CH_2D$. In one embodiment, R is $-CHD-CHD_2$. In one embodiment, R is $-CHD-CD_3$. In one embodiment, R is $-CD_2-CH_3$. In one embodiment, R is $-CD_2-CH_2D$. In one embodiment, R is $-CD_2-CHD_2$. In one embodiment, R is $-CD_2-CD_3$.

[00115] In one embodiment, R is C_1-C_3 alkyl optionally substituted with one or more halogen. In one embodiment, R is methyl or ethyl optionally substituted with one or more halogen. In one embodiment, R is methyl optionally substituted with one or more halogen. In one embodiment, R is $-CF_3$.

[00116] In one embodiment, Y^1 is deuterium. In one embodiment, Y^1 is hydrogen.

[00117] In one embodiment, Y^2 is deuterium. In one embodiment, Y^2 is hydrogen.

[00118] In one embodiment, Y^3 is deuterium. In one embodiment, Y^3 is hydrogen.

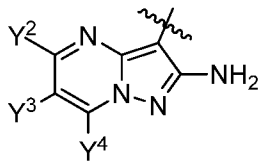
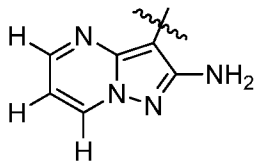
[00119] In one embodiment, Y^4 is deuterium. In one embodiment, Y^4 is hydrogen.

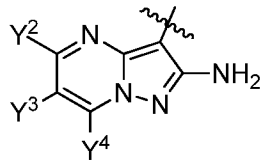
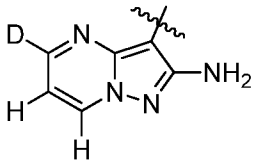
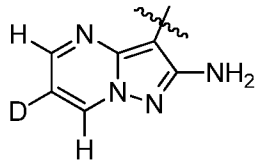
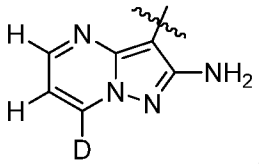
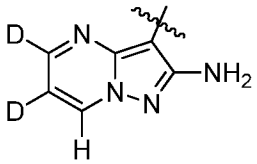
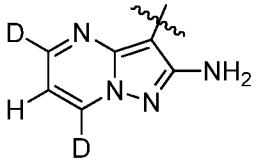
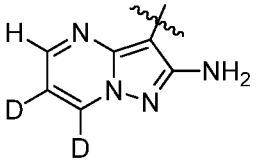
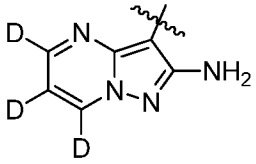
[00120] In one embodiment, Y^2, Y^3, and Y^4 are all hydrogen.

[00121] In one embodiment, one of Y^2, Y^3, and Y^4 is deuterium, and the other two of Y^2, Y^3, and Y^4 are hydrogen. In one embodiment, Y^2 is deuterium, and Y^3 and Y^4 are hydrogen. In one embodiment, Y^3 is deuterium, and Y^2 and Y^4 are hydrogen. In one embodiment, Y^4 is deuterium, and Y^2 and Y^3 are hydrogen.

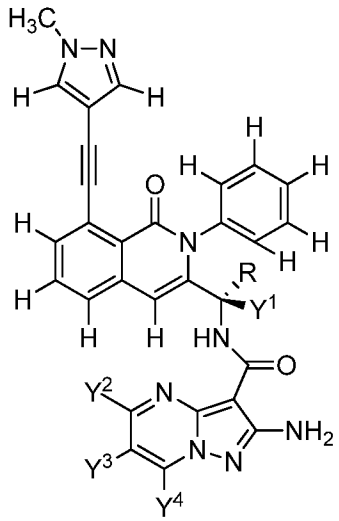
[00122] In one embodiment, two of Y^2, Y^3, and Y^4 are deuterium, and the other of Y^2, Y^3, and Y^4 is hydrogen. In one embodiment, Y^2 and Y^3 are deuterium, and Y^4 is hydrogen. In one embodiment, Y^2 and Y^4 are deuterium, and Y^3 is hydrogen. In one embodiment, Y^3 and Y^4 are deuterium, and Y^2 is hydrogen.

[00123] In one embodiment, Y^2, Y^3, and Y^4 are all deuterium.

[00124] In one embodiment, the  moiety is  .

[00125] In one embodiment, the  moiety is  ,  ,  ,  ,  ,  , or  .

[00126] In one embodiment, the compound is a compound of Formula (A-I-a):



(A-I-a),

or a pharmaceutically acceptable form thereof.

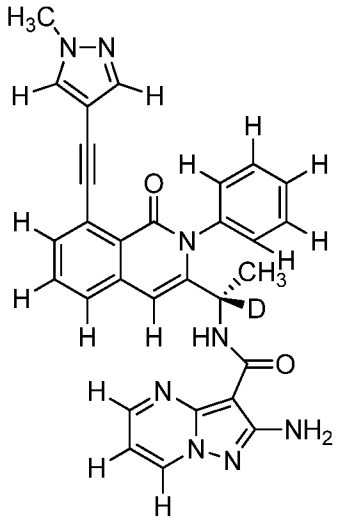
[00127] In one embodiment, the compound is a compound of Formula (A-I-a) selected from any one of the compounds in Table 1.

Table 1. Exemplary compounds of Formula (A-I-a)

Compound	Y^1	Y^2	Y^3	Y^4	R
101	D	H	H	H	$-CH_3$
102	H	D	H	H	$-CH_3$
103	H	H	D	H	$-CH_3$
104	H	H	H	D	$-CH_3$
105	D	D	H	H	$-CH_3$
106	D	H	D	H	$-CH_3$
107	D	H	H	D	$-CH_3$
108	H	D	D	H	$-CH_3$
109	H	D	H	D	$-CH_3$
110	H	H	D	D	$-CH_3$
111	D	D	D	H	$-CH_3$
112	D	D	H	D	$-CH_3$
113	D	H	D	D	$-CH_3$
114	H	D	D	D	$-CH_3$
115	D	D	D	D	$-CH_3$
116	H	H	H	H	$-CD_3$
117	D	H	H	H	$-CD_3$
118	H	D	H	H	$-CD_3$
119	H	H	D	H	$-CD_3$
120	H	H	H	D	$-CD_3$
121	D	D	H	H	$-CD_3$
122	D	H	D	H	$-CD_3$
123	D	H	H	D	$-CD_3$
124	H	D	D	H	$-CD_3$
125	H	D	H	D	$-CD_3$
126	H	H	D	D	$-CD_3$
127	D	D	D	H	$-CD_3$
128	D	D	H	D	$-CD_3$
129	D	H	D	D	$-CD_3$
130	H	D	D	D	$-CD_3$
131	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

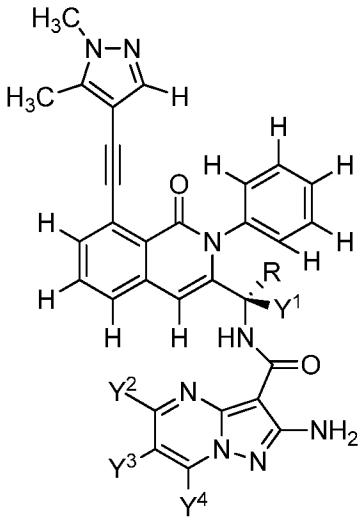
[00128] In one embodiment, the compound is a compound of the following Formula:



101,

or a pharmaceutically acceptable form thereof.

[00129] In one embodiment, the compound is a compound of Formula (A-I-b):



(A-I-b)

or a pharmaceutically acceptable form thereof.

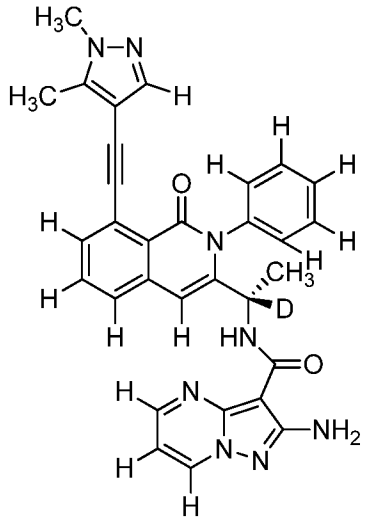
[00130] In one embodiment, the compound is a compound of Formula (A-I-b) selected from any one of the compounds in Table 2.

Table 2. Exemplary compounds of Formula (A-I-b)

Compound	Y^1	Y^2	Y^3	Y^4	R
201	D	H	H	H	$-CH_3$
202	H	D	H	H	$-CH_3$
203	H	H	D	H	$-CH_3$
204	H	H	H	D	$-CH_3$
205	D	D	H	H	$-CH_3$
206	D	H	D	H	$-CH_3$
207	D	H	H	D	$-CH_3$
208	H	D	D	H	$-CH_3$
209	H	D	H	D	$-CH_3$
210	H	H	D	D	$-CH_3$
211	D	D	D	H	$-CH_3$
212	D	D	H	D	$-CH_3$
213	D	H	D	D	$-CH_3$
214	H	D	D	D	$-CH_3$
215	D	D	D	D	$-CH_3$
216	H	H	H	H	$-CD_3$
217	D	H	H	H	$-CD_3$
218	H	D	H	H	$-CD_3$
219	H	H	D	H	$-CD_3$
220	H	H	H	D	$-CD_3$
221	D	D	H	H	$-CD_3$
222	D	H	D	H	$-CD_3$
223	D	H	H	D	$-CD_3$
224	H	D	D	H	$-CD_3$
225	H	D	H	D	$-CD_3$
226	H	H	D	D	$-CD_3$
227	D	D	D	H	$-CD_3$
228	D	D	H	D	$-CD_3$
229	D	H	D	D	$-CD_3$
230	H	D	D	D	$-CD_3$
231	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

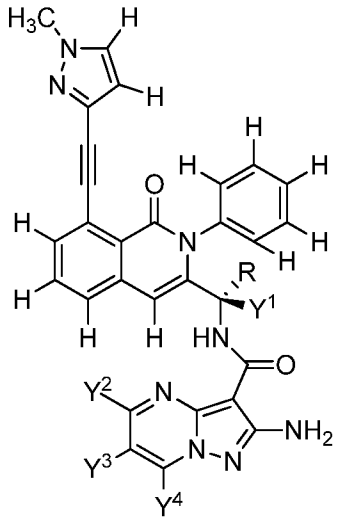
[00131] In one embodiment, the compound is a compound of the following Formula:



201,

or a pharmaceutically acceptable form thereof.

[00132] In one embodiment, the compound is a compound of Formula (A-II-a):



(A-II-a),

or a pharmaceutically acceptable form thereof.

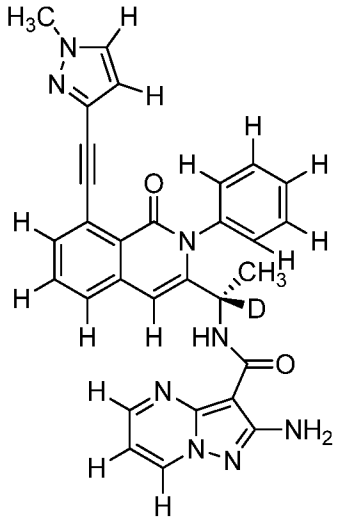
[00133] In one embodiment, the compound is a compound of Formula (A-II-a) selected from any one of the compounds in Table 3.

Table 3. Exemplary compounds of Formula (A-II-a)

Compound	Y^1	Y^2	Y^3	Y^4	R
301	D	H	H	H	$-CH_3$
302	H	D	H	H	$-CH_3$
303	H	H	D	H	$-CH_3$
304	H	H	H	D	$-CH_3$
305	D	D	H	H	$-CH_3$
306	D	H	D	H	$-CH_3$
307	D	H	H	D	$-CH_3$
308	H	D	D	H	$-CH_3$
309	H	D	H	D	$-CH_3$
310	H	H	D	D	$-CH_3$
311	D	D	D	H	$-CH_3$
312	D	D	H	D	$-CH_3$
313	D	H	D	D	$-CH_3$
314	H	D	D	D	$-CH_3$
315	D	D	D	D	$-CH_3$
316	H	H	H	H	$-CD_3$
317	D	H	H	H	$-CD_3$
318	H	D	H	H	$-CD_3$
319	H	H	D	H	$-CD_3$
320	H	H	H	D	$-CD_3$
321	D	D	H	H	$-CD_3$
322	D	H	D	H	$-CD_3$
323	D	H	H	D	$-CD_3$
324	H	D	D	H	$-CD_3$
325	H	D	H	D	$-CD_3$
326	H	H	D	D	$-CD_3$
327	D	D	D	H	$-CD_3$
328	D	D	H	D	$-CD_3$
329	D	H	D	D	$-CD_3$
330	H	D	D	D	$-CD_3$
331	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

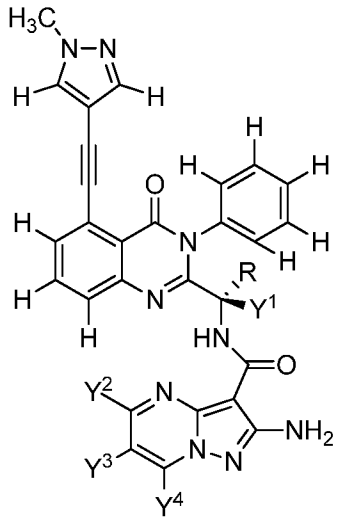
[00134] In one embodiment, the compound is a compound of the following Formula:



301,

or a pharmaceutically acceptable form thereof.

[00135] In one embodiment, the compound is a compound of Formula (B-I-a):



(B-I-a),

or a pharmaceutically acceptable form thereof.

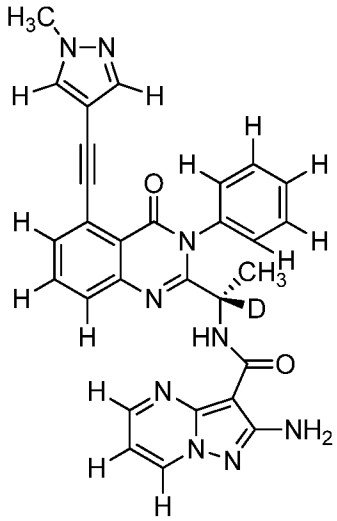
[00136] In one embodiment, the compound is a compound of Formula (B-I-a) selected from any one of the compounds in Table 4.

Table 4. Exemplary compounds of Formula (B-I-a)

Compound	Y^1	Y^2	Y^3	Y^4	R
401	D	H	H	H	$-CH_3$
402	H	D	H	H	$-CH_3$
403	H	H	D	H	$-CH_3$
404	H	H	H	D	$-CH_3$
405	D	D	H	H	$-CH_3$
406	D	H	D	H	$-CH_3$
407	D	H	H	D	$-CH_3$
408	H	D	D	H	$-CH_3$
409	H	D	H	D	$-CH_3$
410	H	H	D	D	$-CH_3$
411	D	D	D	H	$-CH_3$
412	D	D	H	D	$-CH_3$
413	D	H	D	D	$-CH_3$
414	H	D	D	D	$-CH_3$
415	D	D	D	D	$-CH_3$
416	H	H	H	H	$-CD_3$
417	D	H	H	H	$-CD_3$
418	H	D	H	H	$-CD_3$
419	H	H	D	H	$-CD_3$
420	H	H	H	D	$-CD_3$
421	D	D	H	H	$-CD_3$
422	D	H	D	H	$-CD_3$
423	D	H	H	D	$-CD_3$
424	H	D	D	H	$-CD_3$
425	H	D	H	D	$-CD_3$
426	H	H	D	D	$-CD_3$
427	D	D	D	H	$-CD_3$
428	D	D	H	D	$-CD_3$
429	D	H	D	D	$-CD_3$
430	H	D	D	D	$-CD_3$
431	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

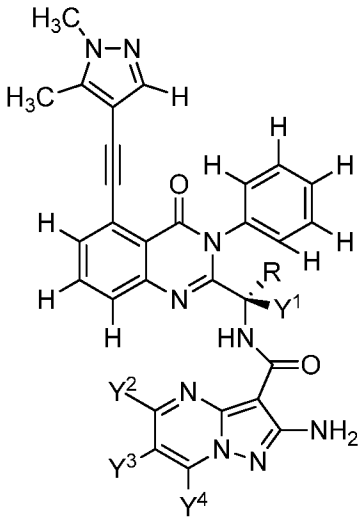
[00137] In one embodiment, the compound is a compound of the following Formula:



401,

or a pharmaceutically acceptable form thereof.

[00138] In one embodiment, the compound is a compound of Formula (B-I-b):



(B-I-b),

or a pharmaceutically acceptable form thereof.

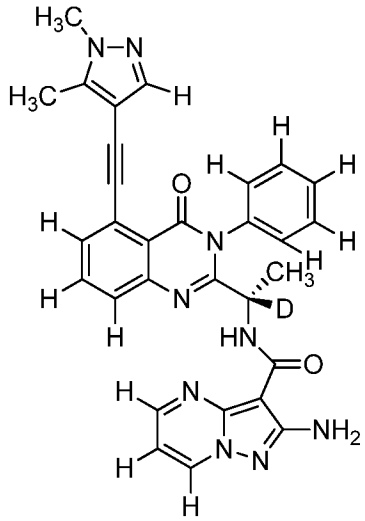
[00139] In one embodiment, the compound is a compound of Formula (B-I-b) selected from any one of the compounds in Table 5.

Table 5. Exemplary compounds of Formula (B-I-b)

Compound	Y^1	Y^2	Y^3	Y^4	R
501	D	H	H	H	$-CH_3$
502	H	D	H	H	$-CH_3$
503	H	H	D	H	$-CH_3$
504	H	H	H	D	$-CH_3$
505	D	D	H	H	$-CH_3$
506	D	H	D	H	$-CH_3$
507	D	H	H	D	$-CH_3$
508	H	D	D	H	$-CH_3$
509	H	D	H	D	$-CH_3$
510	H	H	D	D	$-CH_3$
511	D	D	D	H	$-CH_3$
512	D	D	H	D	$-CH_3$
513	D	H	D	D	$-CH_3$
514	H	D	D	D	$-CH_3$
515	D	D	D	D	$-CH_3$
516	H	H	H	H	$-CD_3$
517	D	H	H	H	$-CD_3$
518	H	D	H	H	$-CD_3$
519	H	H	D	H	$-CD_3$
520	H	H	H	D	$-CD_3$
521	D	D	H	H	$-CD_3$
522	D	H	D	H	$-CD_3$
523	D	H	H	D	$-CD_3$
524	H	D	D	H	$-CD_3$
525	H	D	H	D	$-CD_3$
526	H	H	D	D	$-CD_3$
527	D	D	D	H	$-CD_3$
528	D	D	H	D	$-CD_3$
529	D	H	D	D	$-CD_3$
530	H	D	D	D	$-CD_3$
531	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

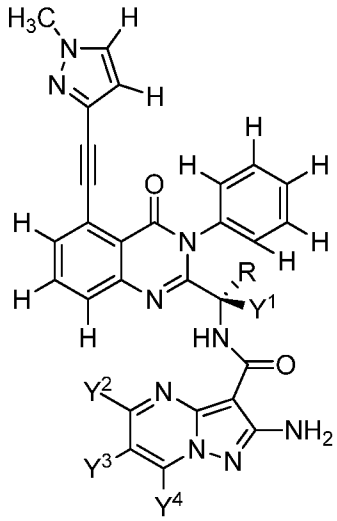
[00140] In one embodiment, the compound is a compound of the following Formula:



501,

or a pharmaceutically acceptable form thereof.

[00141] In one embodiment, the compound is a compound of Formula (B-II-a):



(B-II-a),

or a pharmaceutically acceptable form thereof.

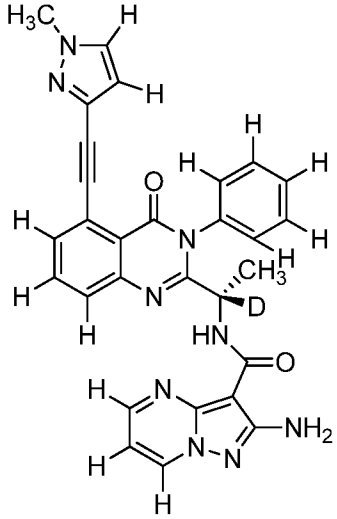
[00142] In one embodiment, the compound is a compound of Formula (B-II-a) selected from any one of the compounds in Table 6.

Table 6. Exemplary compounds of Formula (B-II-a)

Compound	Y^1	Y^2	Y^3	Y^4	R
601	D	H	H	H	$-CH_3$
602	H	D	H	H	$-CH_3$
603	H	H	D	H	$-CH_3$
604	H	H	H	D	$-CH_3$
605	D	D	H	H	$-CH_3$
606	D	H	D	H	$-CH_3$
607	D	H	H	D	$-CH_3$
608	H	D	D	H	$-CH_3$
609	H	D	H	D	$-CH_3$
610	H	H	D	D	$-CH_3$
611	D	D	D	H	$-CH_3$
612	D	D	H	D	$-CH_3$
613	D	H	D	D	$-CH_3$
614	H	D	D	D	$-CH_3$
615	D	D	D	D	$-CH_3$
616	H	H	H	H	$-CD_3$
617	D	H	H	H	$-CD_3$
618	H	D	H	H	$-CD_3$
619	H	H	D	H	$-CD_3$
620	H	H	H	D	$-CD_3$
621	D	D	H	H	$-CD_3$
622	D	H	D	H	$-CD_3$
623	D	H	H	D	$-CD_3$
624	H	D	D	H	$-CD_3$
625	H	D	H	D	$-CD_3$
626	H	H	D	D	$-CD_3$
627	D	D	D	H	$-CD_3$
628	D	D	H	D	$-CD_3$
629	D	H	D	D	$-CD_3$
630	H	D	D	D	$-CD_3$
631	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

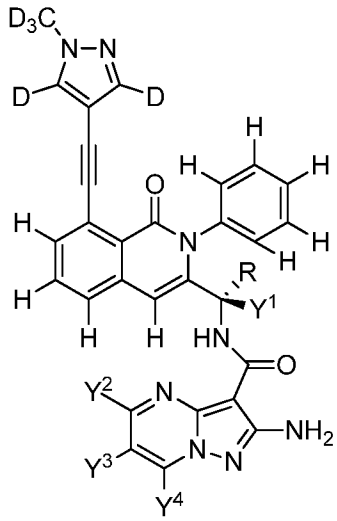
[00143] In one embodiment, the compound is a compound of the following Formula:



601,

or a pharmaceutically acceptable form thereof.

[00144] In one embodiment, the compound is a compound of Formula (A-I-c):



(A-I-c),

or a pharmaceutically acceptable form thereof.

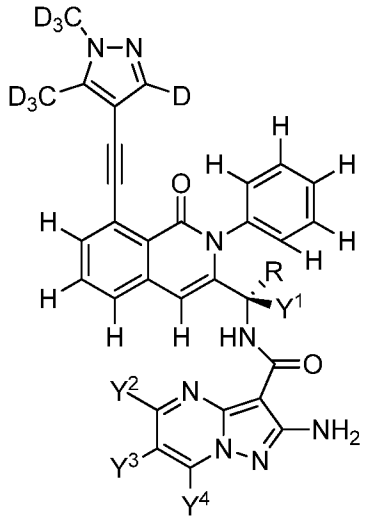
[00145] In one embodiment, the compound is a compound of Formula (A-I-c) selected from any one of the compounds in Table 7.

Table 7. Exemplary compounds of Formula (A-I-c)

Compound	Y^1	Y^2	Y^3	Y^4	R
701	H	H	H	H	$-CH_3$
702	D	H	H	H	$-CH_3$
703	H	D	H	H	$-CH_3$
704	H	H	D	H	$-CH_3$
705	H	H	H	D	$-CH_3$
706	D	D	H	H	$-CH_3$
707	D	H	D	H	$-CH_3$
708	D	H	H	D	$-CH_3$
709	H	D	D	H	$-CH_3$
710	H	D	H	D	$-CH_3$
711	H	H	D	D	$-CH_3$
712	D	D	D	H	$-CH_3$
713	D	D	H	D	$-CH_3$
714	D	H	D	D	$-CH_3$
715	H	D	D	D	$-CH_3$
716	D	D	D	D	$-CH_3$
717	H	H	H	H	$-CD_3$
718	D	H	H	H	$-CD_3$
719	H	D	H	H	$-CD_3$
720	H	H	D	H	$-CD_3$
721	H	H	H	D	$-CD_3$
722	D	D	H	H	$-CD_3$
723	D	H	D	H	$-CD_3$
724	D	H	H	D	$-CD_3$
725	H	D	D	H	$-CD_3$
726	H	D	H	D	$-CD_3$
727	H	H	D	D	$-CD_3$
728	D	D	D	H	$-CD_3$
729	D	D	H	D	$-CD_3$
730	D	H	D	D	$-CD_3$
731	H	D	D	D	$-CD_3$
732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00146] In one embodiment, the compound is a compound of Formula (A-I-d):



(A-I-d)

or a pharmaceutically acceptable form thereof.

[00147] In one embodiment, the compound is a compound of Formula (A-I-d) selected from any one of the compounds in Table 8.

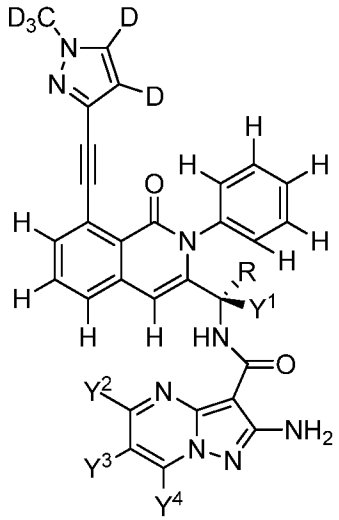
Table 8. Exemplary compounds of Formula (A-I-d)

Compound	Y^1	Y^2	Y^3	Y^4	R
801	H	H	H	H	$-CH_3$
802	D	H	H	H	$-CH_3$
803	H	D	H	H	$-CH_3$
804	H	H	D	H	$-CH_3$
805	H	H	H	D	$-CH_3$
806	D	D	H	H	$-CH_3$
807	D	H	D	H	$-CH_3$
808	D	H	H	D	$-CH_3$
809	H	D	D	H	$-CH_3$
810	H	D	H	D	$-CH_3$
811	H	H	D	D	$-CH_3$
812	D	D	D	H	$-CH_3$
813	D	D	H	D	$-CH_3$
814	D	H	D	D	$-CH_3$
815	H	D	D	D	$-CH_3$
816	D	D	D	D	$-CH_3$

817	H	H	H	H	$-CD_3$
818	D	H	H	H	$-CD_3$
819	H	D	H	H	$-CD_3$
820	H	H	D	H	$-CD_3$
821	H	H	H	D	$-CD_3$
822	D	D	H	H	$-CD_3$
823	D	H	D	H	$-CD_3$
824	D	H	H	D	$-CD_3$
825	H	D	D	H	$-CD_3$
826	H	D	H	D	$-CD_3$
827	H	H	D	D	$-CD_3$
828	D	D	D	H	$-CD_3$
829	D	D	H	D	$-CD_3$
830	D	H	D	D	$-CD_3$
831	H	D	D	D	$-CD_3$
832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00148] In one embodiment, the compound is a compound of Formula (A-II-b):



(A-II-b),

or a pharmaceutically acceptable form thereof.

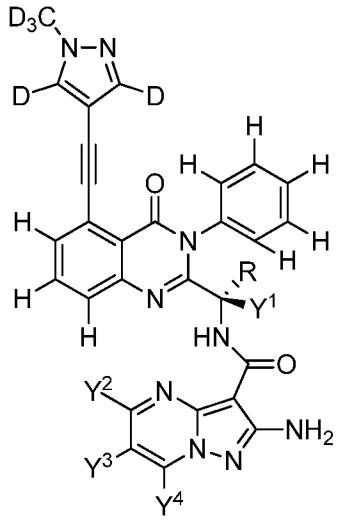
[00149] In one embodiment, the compound is a compound of Formula (A-II-b) selected from any one of the compounds in Table 9.

Table 9. Exemplary compounds of Formula (A-II-b)

Compound	Y^1	Y^2	Y^3	Y^4	R
901	H	H	H	H	$-CH_3$
902	D	H	H	H	$-CH_3$
903	H	D	H	H	$-CH_3$
904	H	H	D	H	$-CH_3$
905	H	H	H	D	$-CH_3$
906	D	D	H	H	$-CH_3$
907	D	H	D	H	$-CH_3$
908	D	H	H	D	$-CH_3$
909	H	D	D	H	$-CH_3$
910	H	D	H	D	$-CH_3$
911	H	H	D	D	$-CH_3$
912	D	D	D	H	$-CH_3$
913	D	D	H	D	$-CH_3$
914	D	H	D	D	$-CH_3$
915	H	D	D	D	$-CH_3$
916	D	D	D	D	$-CH_3$
917	H	H	H	H	$-CD_3$
918	D	H	H	H	$-CD_3$
919	H	D	H	H	$-CD_3$
920	H	H	D	H	$-CD_3$
921	H	H	H	D	$-CD_3$
922	D	D	H	H	$-CD_3$
923	D	H	D	H	$-CD_3$
924	D	H	H	D	$-CD_3$
925	H	D	D	H	$-CD_3$
926	H	D	H	D	$-CD_3$
927	H	H	D	D	$-CD_3$
928	D	D	D	H	$-CD_3$
929	D	D	H	D	$-CD_3$
930	D	H	D	D	$-CD_3$
931	H	D	D	D	$-CD_3$
932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00150] In one embodiment, the compound is a compound of Formula (B-I-c):



(B-I-c),

or a pharmaceutically acceptable form thereof.

[00151] In one embodiment, the compound is a compound of Formula (B-I-c) selected from any one of the compounds in Table 10.

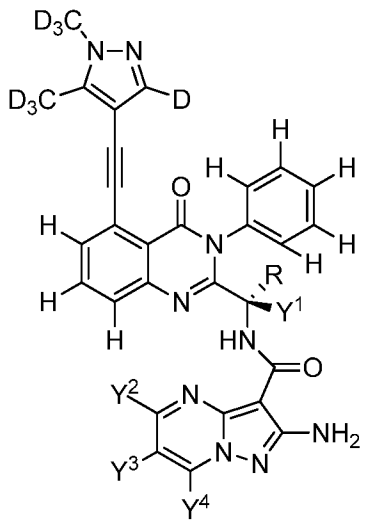
Table 10. Exemplary compounds of Formula (B-I-c)

Compound	Y^1	Y^2	Y^3	Y^4	R
1001	H	H	H	H	$-CH_3$
1002	D	H	H	H	$-CH_3$
1003	H	D	H	H	$-CH_3$
1004	H	H	D	H	$-CH_3$
1005	H	H	H	D	$-CH_3$
1006	D	D	H	H	$-CH_3$
1007	D	H	D	H	$-CH_3$
1008	D	H	H	D	$-CH_3$
1009	H	D	D	H	$-CH_3$
1010	H	D	H	D	$-CH_3$
1011	H	H	D	D	$-CH_3$
1012	D	D	D	H	$-CH_3$
1013	D	D	H	D	$-CH_3$
1014	D	H	D	D	$-CH_3$
1015	H	D	D	D	$-CH_3$
1016	D	D	D	D	$-CH_3$

1017	H	H	H	H	$-CD_3$
1018	D	H	H	H	$-CD_3$
1019	H	D	H	H	$-CD_3$
1020	H	H	D	H	$-CD_3$
1021	H	H	H	D	$-CD_3$
1022	D	D	H	H	$-CD_3$
1023	D	H	D	H	$-CD_3$
1024	D	H	H	D	$-CD_3$
1025	H	D	D	H	$-CD_3$
1026	H	D	H	D	$-CD_3$
1027	H	H	D	D	$-CD_3$
1028	D	D	D	H	$-CD_3$
1029	D	D	H	D	$-CD_3$
1030	D	H	D	D	$-CD_3$
1031	H	D	D	D	$-CD_3$
1032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00152] In one embodiment, the compound is a compound of Formula (B-I-d):



(B-I-d),

or a pharmaceutically acceptable form thereof.

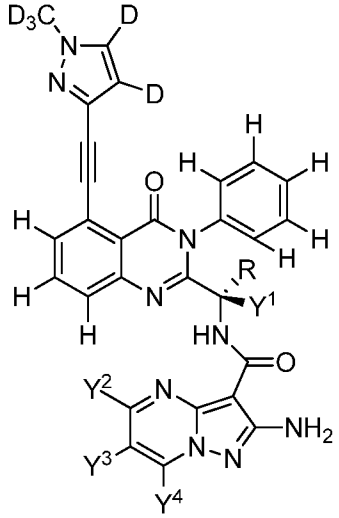
[00153] In one embodiment, the compound is a compound of Formula (B-I-d) selected from any one of the compounds in Table 11.

Table 11. Exemplary compounds of Formula (B-I-d)

Compound	Y^1	Y^2	Y^3	Y^4	R
1101	H	H	H	H	$-CH_3$
1102	D	H	H	H	$-CH_3$
1103	H	D	H	H	$-CH_3$
1104	H	H	D	H	$-CH_3$
1105	H	H	H	D	$-CH_3$
1106	D	D	H	H	$-CH_3$
1107	D	H	D	H	$-CH_3$
1108	D	H	H	D	$-CH_3$
1109	H	D	D	H	$-CH_3$
1110	H	D	H	D	$-CH_3$
1111	H	H	D	D	$-CH_3$
1112	D	D	D	H	$-CH_3$
1113	D	D	H	D	$-CH_3$
1114	D	H	D	D	$-CH_3$
1115	H	D	D	D	$-CH_3$
1116	D	D	D	D	$-CH_3$
1117	H	H	H	H	$-CD_3$
1118	D	H	H	H	$-CD_3$
1119	H	D	H	H	$-CD_3$
1120	H	H	D	H	$-CD_3$
1121	H	H	H	D	$-CD_3$
1122	D	D	H	H	$-CD_3$
1123	D	H	D	H	$-CD_3$
1124	D	H	H	D	$-CD_3$
1125	H	D	D	H	$-CD_3$
1126	H	D	H	D	$-CD_3$
1127	H	H	D	D	$-CD_3$
1128	D	D	D	H	$-CD_3$
1129	D	D	H	D	$-CD_3$
1130	D	H	D	D	$-CD_3$
1131	H	D	D	D	$-CD_3$
1132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00154] In one embodiment, the compound is a compound of Formula (B-II-b):



(B-II-b),

or a pharmaceutically acceptable form thereof.

[00155] In one embodiment, the compound is a compound of Formula (B-II-b) selected from any one of the compounds in Table 12.

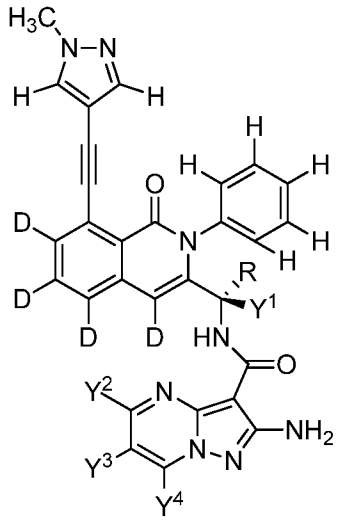
Table 12. Exemplary compounds of Formula (B-II-b)

Compound	Y^1	Y^2	Y^3	Y^4	R
1201	H	H	H	H	$-CH_3$
1202	D	H	H	H	$-CH_3$
1203	H	D	H	H	$-CH_3$
1204	H	H	D	H	$-CH_3$
1205	H	H	H	D	$-CH_3$
1206	D	D	H	H	$-CH_3$
1207	D	H	D	H	$-CH_3$
1208	D	H	H	D	$-CH_3$
1209	H	D	D	H	$-CH_3$
1210	H	D	H	D	$-CH_3$
1211	H	H	D	D	$-CH_3$
1212	D	D	D	H	$-CH_3$
1213	D	D	H	D	$-CH_3$
1214	D	H	D	D	$-CH_3$
1215	H	D	D	D	$-CH_3$
1216	D	D	D	D	$-CH_3$

1217	H	H	H	H	$-CD_3$
1218	D	H	H	H	$-CD_3$
1219	H	D	H	H	$-CD_3$
1220	H	H	D	H	$-CD_3$
1221	H	H	H	D	$-CD_3$
1222	D	D	H	H	$-CD_3$
1223	D	H	D	H	$-CD_3$
1224	D	H	H	D	$-CD_3$
1225	H	D	D	H	$-CD_3$
1226	H	D	H	D	$-CD_3$
1227	H	H	D	D	$-CD_3$
1228	D	D	D	H	$-CD_3$
1229	D	D	H	D	$-CD_3$
1230	D	H	D	D	$-CD_3$
1231	H	D	D	D	$-CD_3$
1232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00156] In one embodiment, the compound is a compound of Formula (A-I-e):



(A-I-e),

or a pharmaceutically acceptable form thereof.

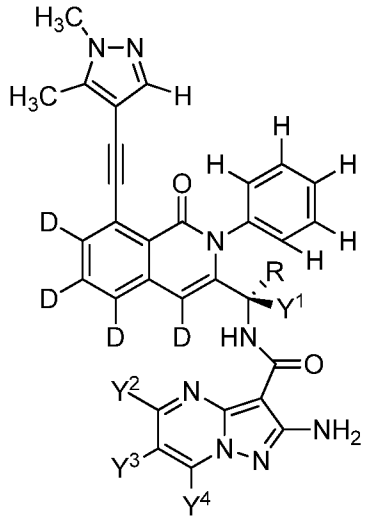
[00157] In one embodiment, the compound is a compound of Formula (A-I-e) selected from any one of the compounds in Table 13.

Table 13. Exemplary compounds of Formula (A-I-e)

Compound	Y^1	Y^2	Y^3	Y^4	R
1301	H	H	H	H	$-CH_3$
1302	D	H	H	H	$-CH_3$
1303	H	D	H	H	$-CH_3$
1304	H	H	D	H	$-CH_3$
1305	H	H	H	D	$-CH_3$
1306	D	D	H	H	$-CH_3$
1307	D	H	D	H	$-CH_3$
1308	D	H	H	D	$-CH_3$
1309	H	D	D	H	$-CH_3$
1310	H	D	H	D	$-CH_3$
1311	H	H	D	D	$-CH_3$
1312	D	D	D	H	$-CH_3$
1313	D	D	H	D	$-CH_3$
1314	D	H	D	D	$-CH_3$
1315	H	D	D	D	$-CH_3$
1316	D	D	D	D	$-CH_3$
1317	H	H	H	H	$-CD_3$
1318	D	H	H	H	$-CD_3$
1319	H	D	H	H	$-CD_3$
1320	H	H	D	H	$-CD_3$
1321	H	H	H	D	$-CD_3$
1322	D	D	H	H	$-CD_3$
1323	D	H	D	H	$-CD_3$
1324	D	H	H	D	$-CD_3$
1325	H	D	D	H	$-CD_3$
1326	H	D	H	D	$-CD_3$
1327	H	H	D	D	$-CD_3$
1328	D	D	D	H	$-CD_3$
1329	D	D	H	D	$-CD_3$
1330	D	H	D	D	$-CD_3$
1331	H	D	D	D	$-CD_3$
1332	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00158] In one embodiment, the compound is a compound of Formula (A-I-f):



(A-I-f)

or a pharmaceutically acceptable form thereof.

[00159] In one embodiment, the compound is a compound of Formula (A-I-f) selected from any one of the compounds in Table 14.

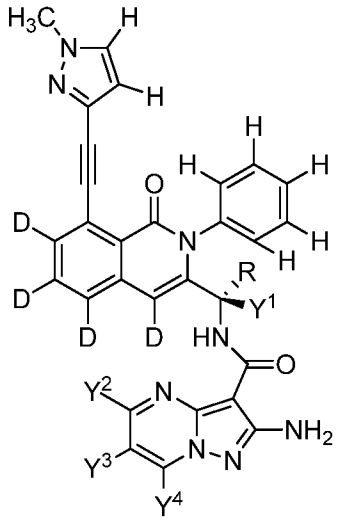
Table 14. Exemplary compounds of Formula (A-I-f)

Compound	Y^1	Y^2	Y^3	Y^4	R
1401	H	H	H	H	$-CH_3$
1402	D	H	H	H	$-CH_3$
1403	H	D	H	H	$-CH_3$
1404	H	H	D	H	$-CH_3$
1405	H	H	H	D	$-CH_3$
1406	D	D	H	H	$-CH_3$
1407	D	H	D	H	$-CH_3$
1408	D	H	H	D	$-CH_3$
1409	H	D	D	H	$-CH_3$
1410	H	D	H	D	$-CH_3$
1411	H	H	D	D	$-CH_3$
1412	D	D	D	H	$-CH_3$
1413	D	D	H	D	$-CH_3$
1414	D	H	D	D	$-CH_3$
1415	H	D	D	D	$-CH_3$
1416	D	D	D	D	$-CH_3$

1417	H	H	H	H	$-CD_3$
1418	D	H	H	H	$-CD_3$
1419	H	D	H	H	$-CD_3$
1420	H	H	D	H	$-CD_3$
1421	H	H	H	D	$-CD_3$
1422	D	D	H	H	$-CD_3$
1423	D	H	D	H	$-CD_3$
1424	D	H	H	D	$-CD_3$
1425	H	D	D	H	$-CD_3$
1426	H	D	H	D	$-CD_3$
1427	H	H	D	D	$-CD_3$
1428	D	D	D	H	$-CD_3$
1429	D	D	H	D	$-CD_3$
1430	D	H	D	D	$-CD_3$
1431	H	D	D	D	$-CD_3$
1432	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00160] In one embodiment, the compound is a compound of Formula (A-II-c):



(A-II-c),

or a pharmaceutically acceptable form thereof.

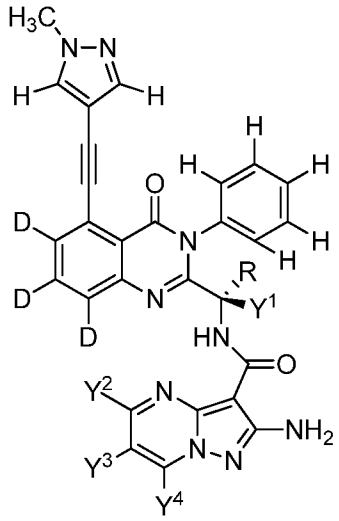
[00161] In one embodiment, the compound is a compound of Formula (A-II-c) selected from any one of the compounds in Table 15.

Table 15. Exemplary compounds of Formula (A-II-c)

Compound	Y^1	Y^2	Y^3	Y^4	R
1501	H	H	H	H	$-CH_3$
1502	D	H	H	H	$-CH_3$
1503	H	D	H	H	$-CH_3$
1504	H	H	D	H	$-CH_3$
1505	H	H	H	D	$-CH_3$
1506	D	D	H	H	$-CH_3$
1507	D	H	D	H	$-CH_3$
1508	D	H	H	D	$-CH_3$
1509	H	D	D	H	$-CH_3$
1510	H	D	H	D	$-CH_3$
1511	H	H	D	D	$-CH_3$
1512	D	D	D	H	$-CH_3$
1513	D	D	H	D	$-CH_3$
1514	D	H	D	D	$-CH_3$
1515	H	D	D	D	$-CH_3$
1516	D	D	D	D	$-CH_3$
1517	H	H	H	H	$-CD_3$
1518	D	H	H	H	$-CD_3$
1519	H	D	H	H	$-CD_3$
1520	H	H	D	H	$-CD_3$
1521	H	H	H	D	$-CD_3$
1522	D	D	H	H	$-CD_3$
1523	D	H	D	H	$-CD_3$
1524	D	H	H	D	$-CD_3$
1525	H	D	D	H	$-CD_3$
1526	H	D	H	D	$-CD_3$
1527	H	H	D	D	$-CD_3$
1528	D	D	D	H	$-CD_3$
1529	D	D	H	D	$-CD_3$
1530	D	H	D	D	$-CD_3$
1531	H	D	D	D	$-CD_3$
1532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00162] In one embodiment, the compound is a compound of Formula (B-I-e):



(B-I-e),

or a pharmaceutically acceptable form thereof.

[00163] In one embodiment, the compound is a compound of Formula (B-I-e) selected from any one of the compounds in Table 16.

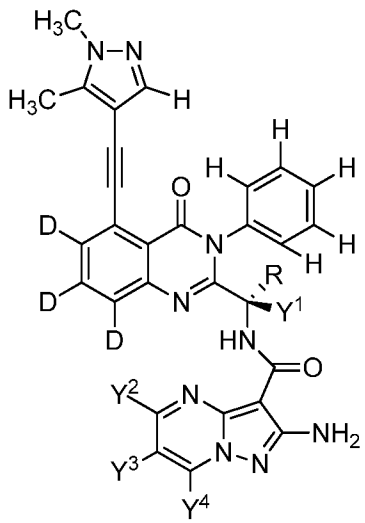
Table 16. Exemplary compounds of Formula (B-I-e)

Compound	Y^1	Y^2	Y^3	Y^4	R
1601	H	H	H	H	$-CH_3$
1602	D	H	H	H	$-CH_3$
1603	H	D	H	H	$-CH_3$
1604	H	H	D	H	$-CH_3$
1605	H	H	H	D	$-CH_3$
1606	D	D	H	H	$-CH_3$
1607	D	H	D	H	$-CH_3$
1608	D	H	H	D	$-CH_3$
1609	H	D	D	H	$-CH_3$
1610	H	D	H	D	$-CH_3$
1611	H	H	D	D	$-CH_3$
1612	D	D	D	H	$-CH_3$
1613	D	D	H	D	$-CH_3$
1614	D	H	D	D	$-CH_3$
1615	H	D	D	D	$-CH_3$
1616	D	D	D	D	$-CH_3$

1617	H	H	H	H	$-CD_3$
1618	D	H	H	H	$-CD_3$
1619	H	D	H	H	$-CD_3$
1620	H	H	D	H	$-CD_3$
1621	H	H	H	D	$-CD_3$
1622	D	D	H	H	$-CD_3$
1623	D	H	D	H	$-CD_3$
1624	D	H	H	D	$-CD_3$
1625	H	D	D	H	$-CD_3$
1626	H	D	H	D	$-CD_3$
1627	H	H	D	D	$-CD_3$
1628	D	D	D	H	$-CD_3$
1629	D	D	H	D	$-CD_3$
1630	D	H	D	D	$-CD_3$
1631	H	D	D	D	$-CD_3$
1632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00164] In one embodiment, the compound is a compound of Formula (B-I-f):



(B-I-f),

or a pharmaceutically acceptable form thereof.

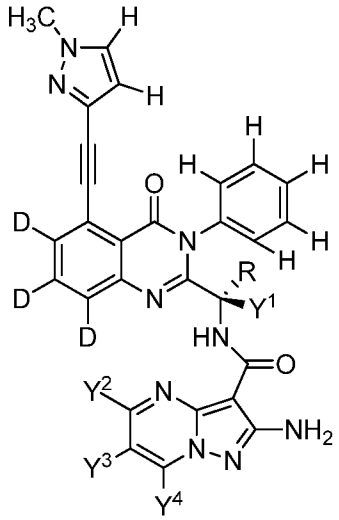
[00165] In one embodiment, the compound is a compound of Formula (B-I-f) selected from any one of the compounds in Table 17.

Table 17. Exemplary compounds of Formula (B-I-f)

Compound	Y^1	Y^2	Y^3	Y^4	R
1701	H	H	H	H	$-CH_3$
1702	D	H	H	H	$-CH_3$
1703	H	D	H	H	$-CH_3$
1704	H	H	D	H	$-CH_3$
1705	H	H	H	D	$-CH_3$
1706	D	D	H	H	$-CH_3$
1707	D	H	D	H	$-CH_3$
1708	D	H	H	D	$-CH_3$
1709	H	D	D	H	$-CH_3$
1710	H	D	H	D	$-CH_3$
1711	H	H	D	D	$-CH_3$
1712	D	D	D	H	$-CH_3$
1713	D	D	H	D	$-CH_3$
1714	D	H	D	D	$-CH_3$
1715	H	D	D	D	$-CH_3$
1716	D	D	D	D	$-CH_3$
1717	H	H	H	H	$-CD_3$
1718	D	H	H	H	$-CD_3$
1719	H	D	H	H	$-CD_3$
1720	H	H	D	H	$-CD_3$
1721	H	H	H	D	$-CD_3$
1722	D	D	H	H	$-CD_3$
1723	D	H	D	H	$-CD_3$
1724	D	H	H	D	$-CD_3$
1725	H	D	D	H	$-CD_3$
1726	H	D	H	D	$-CD_3$
1727	H	H	D	D	$-CD_3$
1728	D	D	D	H	$-CD_3$
1729	D	D	H	D	$-CD_3$
1730	D	H	D	D	$-CD_3$
1731	H	D	D	D	$-CD_3$
1732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00166] In one embodiment, the compound is a compound of Formula (B-II-c):



(B-II-c),

or a pharmaceutically acceptable form thereof.

[00167] In one embodiment, the compound is a compound of Formula (B-II-c) selected from any one of the compounds in Table 18.

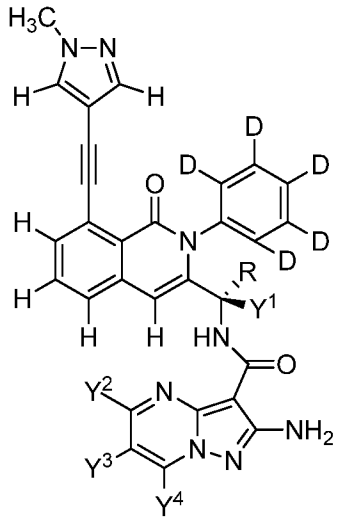
Table 18. Exemplary compounds of Formula (B-II-c)

Compound	Y^1	Y^2	Y^3	Y^4	R
1801	H	H	H	H	$-CH_3$
1802	D	H	H	H	$-CH_3$
1803	H	D	H	H	$-CH_3$
1804	H	H	D	H	$-CH_3$
1805	H	H	H	D	$-CH_3$
1806	D	D	H	H	$-CH_3$
1807	D	H	D	H	$-CH_3$
1808	D	H	H	D	$-CH_3$
1809	H	D	D	H	$-CH_3$
1810	H	D	H	D	$-CH_3$
1811	H	H	D	D	$-CH_3$
1812	D	D	D	H	$-CH_3$
1813	D	D	H	D	$-CH_3$
1814	D	H	D	D	$-CH_3$
1815	H	D	D	D	$-CH_3$
1816	D	D	D	D	$-CH_3$

1817	H	H	H	H	$-CD_3$
1818	D	H	H	H	$-CD_3$
1819	H	D	H	H	$-CD_3$
1820	H	H	D	H	$-CD_3$
1821	H	H	H	D	$-CD_3$
1822	D	D	H	H	$-CD_3$
1823	D	H	D	H	$-CD_3$
1824	D	H	H	D	$-CD_3$
1825	H	D	D	H	$-CD_3$
1826	H	D	H	D	$-CD_3$
1827	H	H	D	D	$-CD_3$
1828	D	D	D	H	$-CD_3$
1829	D	D	H	D	$-CD_3$
1830	D	H	D	D	$-CD_3$
1831	H	D	D	D	$-CD_3$
1832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00168] In one embodiment, the compound is a compound of Formula (A-I-g):



(A-I-g),

or a pharmaceutically acceptable form thereof.

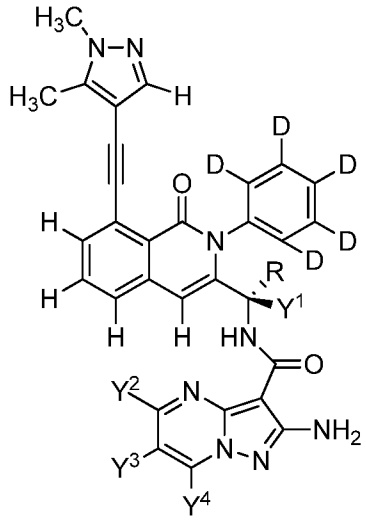
[00169] In one embodiment, the compound is a compound of Formula (A-I-g) selected from any one of the compounds in Table 19.

Table 19. Exemplary compounds of Formula (A-I-g)

Compound	Y^1	Y^2	Y^3	Y^4	R
1901	D	H	H	H	$-CH_3$
1902	H	D	H	H	$-CH_3$
1903	H	H	D	H	$-CH_3$
1904	H	H	H	D	$-CH_3$
1905	D	D	H	H	$-CH_3$
1906	D	H	D	H	$-CH_3$
1907	D	H	H	D	$-CH_3$
1908	H	D	D	H	$-CH_3$
1909	H	D	H	D	$-CH_3$
1910	H	H	D	D	$-CH_3$
1911	D	D	D	H	$-CH_3$
1912	D	D	H	D	$-CH_3$
1913	D	H	D	D	$-CH_3$
1914	H	D	D	D	$-CH_3$
1915	D	D	D	D	$-CH_3$
1916	H	H	H	H	$-CD_3$
1917	D	H	H	H	$-CD_3$
1918	H	D	H	H	$-CD_3$
1919	H	H	D	H	$-CD_3$
1920	H	H	H	D	$-CD_3$
1921	D	D	H	H	$-CD_3$
1922	D	H	D	H	$-CD_3$
1923	D	H	H	D	$-CD_3$
1924	H	D	D	H	$-CD_3$
1925	H	D	H	D	$-CD_3$
1926	H	H	D	D	$-CD_3$
1927	D	D	D	H	$-CD_3$
1928	D	D	H	D	$-CD_3$
1929	D	H	D	D	$-CD_3$
1930	H	D	D	D	$-CD_3$
1931	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00170] In one embodiment, the compound is a compound of Formula (A-I-h):



(A-I-h)

or a pharmaceutically acceptable form thereof.

[00171] In one embodiment, the compound is a compound of Formula (A-I-h) selected from any one of the compounds in Table 20.

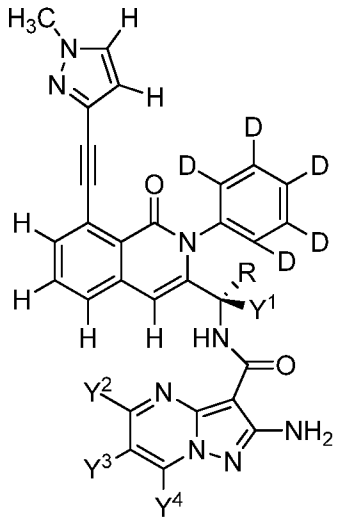
Table 20. Exemplary compounds of Formula (A-I-h)

Compound	Y^1	Y^2	Y^3	Y^4	R
2001	D	H	H	H	$-CH_3$
2002	H	D	H	H	$-CH_3$
2003	H	H	D	H	$-CH_3$
2004	H	H	H	D	$-CH_3$
2005	D	D	H	H	$-CH_3$
2006	D	H	D	H	$-CH_3$
2007	D	H	H	D	$-CH_3$
2008	H	D	D	H	$-CH_3$
2009	H	D	H	D	$-CH_3$
2010	H	H	D	D	$-CH_3$
2011	D	D	D	H	$-CH_3$
2012	D	D	H	D	$-CH_3$
2013	D	H	D	D	$-CH_3$
2014	H	D	D	D	$-CH_3$
2015	D	D	D	D	$-CH_3$
2016	H	H	H	H	$-CD_3$

2017	D	H	H	H	$-CD_3$
2018	H	D	H	H	$-CD_3$
2019	H	H	D	H	$-CD_3$
2020	H	H	H	D	$-CD_3$
2021	D	D	H	H	$-CD_3$
2022	D	H	D	H	$-CD_3$
2023	D	H	H	D	$-CD_3$
2024	H	D	D	H	$-CD_3$
2025	H	D	H	D	$-CD_3$
2026	H	H	D	D	$-CD_3$
2027	D	D	D	H	$-CD_3$
2028	D	D	H	D	$-CD_3$
2029	D	H	D	D	$-CD_3$
2030	H	D	D	D	$-CD_3$
2031	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00172] In one embodiment, the compound is a compound of Formula (A-II-d):



(A-II-d),

or a pharmaceutically acceptable form thereof.

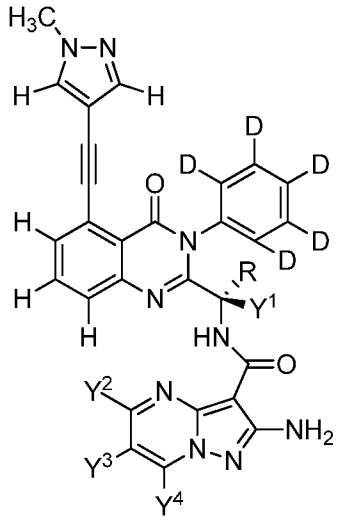
[00173] In one embodiment, the compound is a compound of Formula (A-II-d) selected from any one of the compounds in Table 21.

Table 21. Exemplary compounds of Formula (A-II-d)

Compound	Y^1	Y^2	Y^3	Y^4	R
2101	D	H	H	H	$-CH_3$
2102	H	D	H	H	$-CH_3$
2103	H	H	D	H	$-CH_3$
2104	H	H	H	D	$-CH_3$
2105	D	D	H	H	$-CH_3$
2106	D	H	D	H	$-CH_3$
2107	D	H	H	D	$-CH_3$
2108	H	D	D	H	$-CH_3$
2109	H	D	H	D	$-CH_3$
2110	H	H	D	D	$-CH_3$
2111	D	D	D	H	$-CH_3$
2112	D	D	H	D	$-CH_3$
2113	D	H	D	D	$-CH_3$
2114	H	D	D	D	$-CH_3$
2115	D	D	D	D	$-CH_3$
2116	H	H	H	H	$-CD_3$
2117	D	H	H	H	$-CD_3$
2118	H	D	H	H	$-CD_3$
2119	H	H	D	H	$-CD_3$
2120	H	H	H	D	$-CD_3$
2121	D	D	H	H	$-CD_3$
2122	D	H	D	H	$-CD_3$
2123	D	H	H	D	$-CD_3$
2124	H	D	D	H	$-CD_3$
2125	H	D	H	D	$-CD_3$
2126	H	H	D	D	$-CD_3$
2127	D	D	D	H	$-CD_3$
2128	D	D	H	D	$-CD_3$
2129	D	H	D	D	$-CD_3$
2130	H	D	D	D	$-CD_3$
2131	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00174] In one embodiment, the compound is a compound of Formula (B-I-g):



(B-I-g),

or a pharmaceutically acceptable form thereof.

[00175] In one embodiment, the compound is a compound of Formula (B-I-g) selected from any one of the compounds in Table 22.

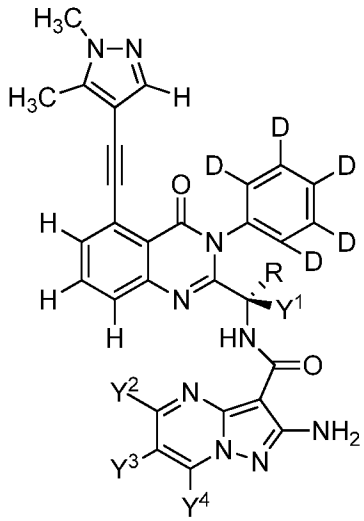
Table 22. Exemplary compounds of Formula (B-I-g)

Compound	Y^1	Y^2	Y^3	Y^4	R
2201	D	H	H	H	$-CH_3$
2202	H	D	H	H	$-CH_3$
2203	H	H	D	H	$-CH_3$
2204	H	H	H	D	$-CH_3$
2205	D	D	H	H	$-CH_3$
2206	D	H	D	H	$-CH_3$
2207	D	H	H	D	$-CH_3$
2208	H	D	D	H	$-CH_3$
2209	H	D	H	D	$-CH_3$
2210	H	H	D	D	$-CH_3$
2211	D	D	D	H	$-CH_3$
2212	D	D	H	D	$-CH_3$
2213	D	H	D	D	$-CH_3$
2214	H	D	D	D	$-CH_3$
2215	D	D	D	D	$-CH_3$
2216	H	H	H	H	$-CD_3$

2217	D	H	H	H	$-CD_3$
2218	H	D	H	H	$-CD_3$
2219	H	H	D	H	$-CD_3$
2220	H	H	H	D	$-CD_3$
2221	D	D	H	H	$-CD_3$
2222	D	H	D	H	$-CD_3$
2223	D	H	H	D	$-CD_3$
2224	H	D	D	H	$-CD_3$
2225	H	D	H	D	$-CD_3$
2226	H	H	D	D	$-CD_3$
2227	D	D	D	H	$-CD_3$
2228	D	D	H	D	$-CD_3$
2229	D	H	D	D	$-CD_3$
2230	H	D	D	D	$-CD_3$
2231	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00176] In one embodiment, the compound is a compound of Formula (B-I-h):



(B-I-h),

or a pharmaceutically acceptable form thereof.

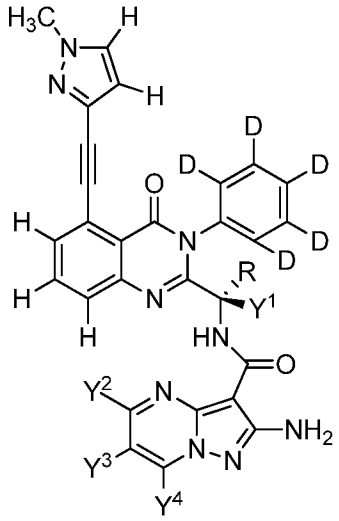
[00177] In one embodiment, the compound is a compound of Formula (B-I-h) selected from any one of the compounds in Table 23.

Table 23. Exemplary compounds of Formula (B-I-h)

Compound	Y^1	Y^2	Y^3	Y^4	R
2301	D	H	H	H	$-CH_3$
2302	H	D	H	H	$-CH_3$
2303	H	H	D	H	$-CH_3$
2304	H	H	H	D	$-CH_3$
2305	D	D	H	H	$-CH_3$
2306	D	H	D	H	$-CH_3$
2307	D	H	H	D	$-CH_3$
2308	H	D	D	H	$-CH_3$
2309	H	D	H	D	$-CH_3$
2310	H	H	D	D	$-CH_3$
2311	D	D	D	H	$-CH_3$
2312	D	D	H	D	$-CH_3$
2313	D	H	D	D	$-CH_3$
2314	H	D	D	D	$-CH_3$
2315	D	D	D	D	$-CH_3$
2316	H	H	H	H	$-CD_3$
2317	D	H	H	H	$-CD_3$
2318	H	D	H	H	$-CD_3$
2319	H	H	D	H	$-CD_3$
2320	H	H	H	D	$-CD_3$
2321	D	D	H	H	$-CD_3$
2322	D	H	D	H	$-CD_3$
2323	D	H	H	D	$-CD_3$
2324	H	D	D	H	$-CD_3$
2325	H	D	H	D	$-CD_3$
2326	H	H	D	D	$-CD_3$
2327	D	D	D	H	$-CD_3$
2328	D	D	H	D	$-CD_3$
2329	D	H	D	D	$-CD_3$
2330	H	D	D	D	$-CD_3$
2331	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00178] In one embodiment, the compound is a compound of Formula (B-II-d):



(B-II-d),

or a pharmaceutically acceptable form thereof.

[00179] In one embodiment, the compound is a compound of Formula (B-II-d) selected from any one of the compounds in Table 24.

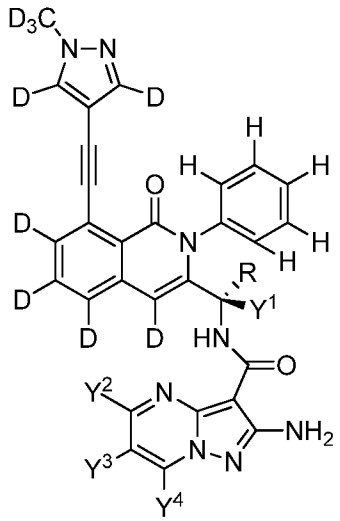
Table 24. Exemplary compounds of Formula (B-II-d)

Compound	Y^1	Y^2	Y^3	Y^4	R
2401	D	H	H	H	$-CH_3$
2402	H	D	H	H	$-CH_3$
2403	H	H	D	H	$-CH_3$
2404	H	H	H	D	$-CH_3$
2405	D	D	H	H	$-CH_3$
2406	D	H	D	H	$-CH_3$
2407	D	H	H	D	$-CH_3$
2408	H	D	D	H	$-CH_3$
2409	H	D	H	D	$-CH_3$
2410	H	H	D	D	$-CH_3$
2411	D	D	D	H	$-CH_3$
2412	D	D	H	D	$-CH_3$
2413	D	H	D	D	$-CH_3$
2414	H	D	D	D	$-CH_3$
2415	D	D	D	D	$-CH_3$
2416	H	H	H	H	$-CD_3$

2417	D	H	H	H	$-CD_3$
2418	H	D	H	H	$-CD_3$
2419	H	H	D	H	$-CD_3$
2420	H	H	H	D	$-CD_3$
2421	D	D	H	H	$-CD_3$
2422	D	H	D	H	$-CD_3$
2423	D	H	H	D	$-CD_3$
2424	H	D	D	H	$-CD_3$
2425	H	D	H	D	$-CD_3$
2426	H	H	D	D	$-CD_3$
2427	D	D	D	H	$-CD_3$
2428	D	D	H	D	$-CD_3$
2429	D	H	D	D	$-CD_3$
2430	H	D	D	D	$-CD_3$
2431	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00180] In one embodiment, the compound is a compound of Formula (A-I-i):



(A-I-i),

or a pharmaceutically acceptable form thereof.

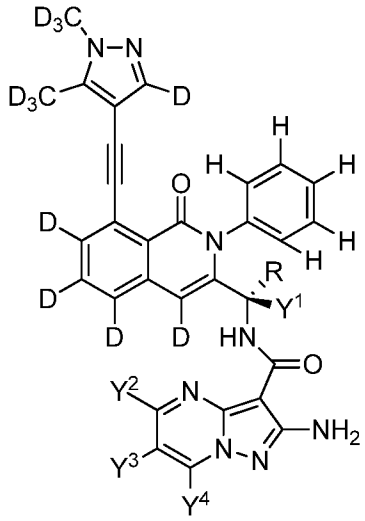
[00181] In one embodiment, the compound is a compound of Formula (A-I-i) selected from any one of the compounds in Table 25.

Table 25. Exemplary compounds of Formula (A-I-i)

Compound	Y^1	Y^2	Y^3	Y^4	R
2501	H	H	H	H	$-CH_3$
2502	D	H	H	H	$-CH_3$
2503	H	D	H	H	$-CH_3$
2504	H	H	D	H	$-CH_3$
2505	H	H	H	D	$-CH_3$
2506	D	D	H	H	$-CH_3$
2507	D	H	D	H	$-CH_3$
2508	D	H	H	D	$-CH_3$
2509	H	D	D	H	$-CH_3$
2510	H	D	H	D	$-CH_3$
2511	H	H	D	D	$-CH_3$
2512	D	D	D	H	$-CH_3$
2513	D	D	H	D	$-CH_3$
2514	D	H	D	D	$-CH_3$
2515	H	D	D	D	$-CH_3$
2516	D	D	D	D	$-CH_3$
2517	H	H	H	H	$-CD_3$
2518	D	H	H	H	$-CD_3$
2519	H	D	H	H	$-CD_3$
2520	H	H	D	H	$-CD_3$
2521	H	H	H	D	$-CD_3$
2522	D	D	H	H	$-CD_3$
2523	D	H	D	H	$-CD_3$
2524	D	H	H	D	$-CD_3$
2525	H	D	D	H	$-CD_3$
2526	H	D	H	D	$-CD_3$
2527	H	H	D	D	$-CD_3$
2528	D	D	D	H	$-CD_3$
2529	D	D	H	D	$-CD_3$
2530	D	H	D	D	$-CD_3$
2531	H	D	D	D	$-CD_3$
2532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00182] In one embodiment, the compound is a compound of Formula (A-I-j):



(A-I-j)

or a pharmaceutically acceptable form thereof.

[00183] In one embodiment, the compound is a compound of Formula (A-I-j) selected from any one of the compounds in Table 26.

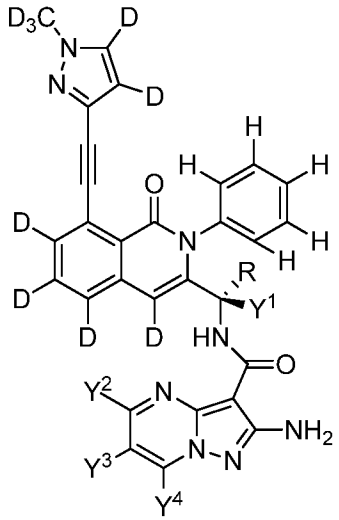
Table 26. Exemplary compounds of Formula (A-I-j)

Compound	Y^1	Y^2	Y^3	Y^4	R
2601	H	H	H	H	$-CH_3$
2602	D	H	H	H	$-CH_3$
2603	H	D	H	H	$-CH_3$
2604	H	H	D	H	$-CH_3$
2605	H	H	H	D	$-CH_3$
2606	D	D	H	H	$-CH_3$
2607	D	H	D	H	$-CH_3$
2608	D	H	H	D	$-CH_3$
2609	H	D	D	H	$-CH_3$
2610	H	D	H	D	$-CH_3$
2611	H	H	D	D	$-CH_3$
2612	D	D	D	H	$-CH_3$
2613	D	D	H	D	$-CH_3$
2614	D	H	D	D	$-CH_3$
2615	H	D	D	D	$-CH_3$
2616	D	D	D	D	$-CH_3$

2617	H	H	H	H	$-CD_3$
2618	D	H	H	H	$-CD_3$
2619	H	D	H	H	$-CD_3$
2620	H	H	D	H	$-CD_3$
2621	H	H	H	D	$-CD_3$
2622	D	D	H	H	$-CD_3$
2623	D	H	D	H	$-CD_3$
2624	D	H	H	D	$-CD_3$
2625	H	D	D	H	$-CD_3$
2626	H	D	H	D	$-CD_3$
2627	H	H	D	D	$-CD_3$
2628	D	D	D	H	$-CD_3$
2629	D	D	H	D	$-CD_3$
2630	D	H	D	D	$-CD_3$
2631	H	D	D	D	$-CD_3$
2632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00184] In one embodiment, the compound is a compound of Formula (A-II-e):



(A-II-e),

or a pharmaceutically acceptable form thereof.

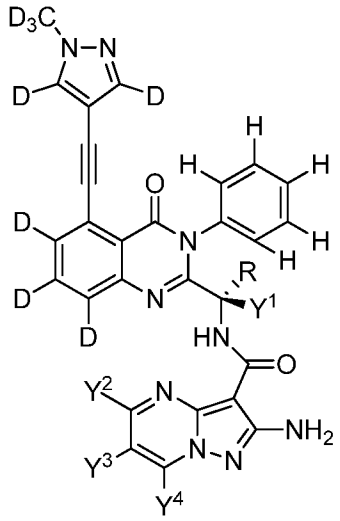
[00185] In one embodiment, the compound is a compound of Formula (A-II-e) selected from any one of the compounds in Table 27.

Table 27. Exemplary compounds of Formula (A-II-e)

Compound	Y^1	Y^2	Y^3	Y^4	R
2701	H	H	H	H	$-CH_3$
2702	D	H	H	H	$-CH_3$
2703	H	D	H	H	$-CH_3$
2704	H	H	D	H	$-CH_3$
2705	H	H	H	D	$-CH_3$
2706	D	D	H	H	$-CH_3$
2707	D	H	D	H	$-CH_3$
2708	D	H	H	D	$-CH_3$
2709	H	D	D	H	$-CH_3$
2710	H	D	H	D	$-CH_3$
2711	H	H	D	D	$-CH_3$
2712	D	D	D	H	$-CH_3$
2713	D	D	H	D	$-CH_3$
2714	D	H	D	D	$-CH_3$
2715	H	D	D	D	$-CH_3$
2716	D	D	D	D	$-CH_3$
2717	H	H	H	H	$-CD_3$
2718	D	H	H	H	$-CD_3$
2719	H	D	H	H	$-CD_3$
2720	H	H	D	H	$-CD_3$
2721	H	H	H	D	$-CD_3$
2722	D	D	H	H	$-CD_3$
2723	D	H	D	H	$-CD_3$
2724	D	H	H	D	$-CD_3$
2725	H	D	D	H	$-CD_3$
2726	H	D	H	D	$-CD_3$
2727	H	H	D	D	$-CD_3$
2728	D	D	D	H	$-CD_3$
2729	D	D	H	D	$-CD_3$
2730	D	H	D	D	$-CD_3$
2731	H	D	D	D	$-CD_3$
2732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00186] In one embodiment, the compound is a compound of Formula (B-I-i):



(B-I-i),

or a pharmaceutically acceptable form thereof.

[00187] In one embodiment, the compound is a compound of Formula (B-I-i) selected from any one of the compounds in Table 28.

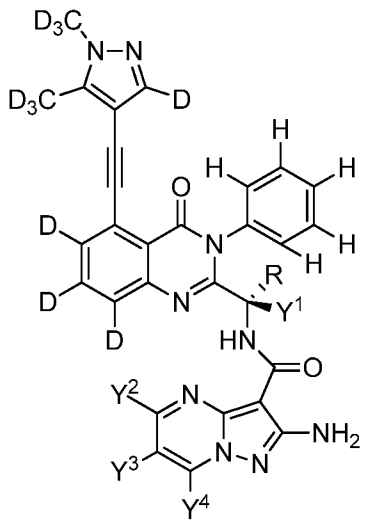
Table 28. Exemplary compounds of Formula (B-I-i)

Compound	Y^1	Y^2	Y^3	Y^4	R
2801	H	H	H	H	$-CH_3$
2802	D	H	H	H	$-CH_3$
2803	H	D	H	H	$-CH_3$
2804	H	H	D	H	$-CH_3$
2805	H	H	H	D	$-CH_3$
2806	D	D	H	H	$-CH_3$
2807	D	H	D	H	$-CH_3$
2808	D	H	H	D	$-CH_3$
2809	H	D	D	H	$-CH_3$
2810	H	D	H	D	$-CH_3$
2811	H	H	D	D	$-CH_3$
2812	D	D	D	H	$-CH_3$
2813	D	D	H	D	$-CH_3$
2814	D	H	D	D	$-CH_3$
2815	H	D	D	D	$-CH_3$
2816	D	D	D	D	$-CH_3$

2817	H	H	H	H	$-CD_3$
2818	D	H	H	H	$-CD_3$
2819	H	D	H	H	$-CD_3$
2820	H	H	D	H	$-CD_3$
2821	H	H	H	D	$-CD_3$
2822	D	D	H	H	$-CD_3$
2823	D	H	D	H	$-CD_3$
2824	D	H	H	D	$-CD_3$
2825	H	D	D	H	$-CD_3$
2826	H	D	H	D	$-CD_3$
2827	H	H	D	D	$-CD_3$
2828	D	D	D	H	$-CD_3$
2829	D	D	H	D	$-CD_3$
2830	D	H	D	D	$-CD_3$
2831	H	D	D	D	$-CD_3$
2832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00188] In one embodiment, the compound is a compound of Formula (B-I-j):



(B-I-j),

or a pharmaceutically acceptable form thereof.

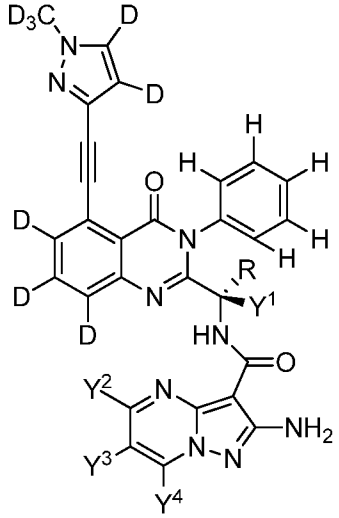
[00189] In one embodiment, the compound is a compound of Formula (B-I-j) selected from any one of the compounds in Table 29.

Table 29. Exemplary compounds of Formula (B-I-j)

Compound	Y^1	Y^2	Y^3	Y^4	R
2901	H	H	H	H	$-CH_3$
2902	D	H	H	H	$-CH_3$
2903	H	D	H	H	$-CH_3$
2904	H	H	D	H	$-CH_3$
2905	H	H	H	D	$-CH_3$
2906	D	D	H	H	$-CH_3$
2907	D	H	D	H	$-CH_3$
2908	D	H	H	D	$-CH_3$
2909	H	D	D	H	$-CH_3$
2910	H	D	H	D	$-CH_3$
2911	H	H	D	D	$-CH_3$
2912	D	D	D	H	$-CH_3$
2913	D	D	H	D	$-CH_3$
2914	D	H	D	D	$-CH_3$
2915	H	D	D	D	$-CH_3$
2916	D	D	D	D	$-CH_3$
2917	H	H	H	H	$-CD_3$
2918	D	H	H	H	$-CD_3$
2919	H	D	H	H	$-CD_3$
2920	H	H	D	H	$-CD_3$
2921	H	H	H	D	$-CD_3$
2922	D	D	H	H	$-CD_3$
2923	D	H	D	H	$-CD_3$
2924	D	H	H	D	$-CD_3$
2925	H	D	D	H	$-CD_3$
2926	H	D	H	D	$-CD_3$
2927	H	H	D	D	$-CD_3$
2928	D	D	D	H	$-CD_3$
2929	D	D	H	D	$-CD_3$
2930	D	H	D	D	$-CD_3$
2931	H	D	D	D	$-CD_3$
2932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00190] In one embodiment, the compound is a compound of Formula (B-II-e):



(B-II-e),

or a pharmaceutically acceptable form thereof.

[00191] In one embodiment, the compound is a compound of Formula (B-II-e) selected from any one of the compounds in Table 30.

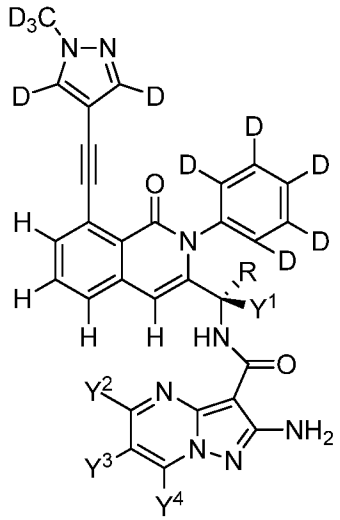
Table 30. Exemplary compounds of Formula (B-II-e)

Compound	Y^1	Y^2	Y^3	Y^4	R
3001	H	H	H	H	$-CH_3$
3002	D	H	H	H	$-CH_3$
3003	H	D	H	H	$-CH_3$
3004	H	H	D	H	$-CH_3$
3005	H	H	H	D	$-CH_3$
3006	D	D	H	H	$-CH_3$
3007	D	H	D	H	$-CH_3$
3008	D	H	H	D	$-CH_3$
3009	H	D	D	H	$-CH_3$
3010	H	D	H	D	$-CH_3$
3011	H	H	D	D	$-CH_3$
3012	D	D	D	H	$-CH_3$
3013	D	D	H	D	$-CH_3$
3014	D	H	D	D	$-CH_3$
3015	H	D	D	D	$-CH_3$
3016	D	D	D	D	$-CH_3$

3017	H	H	H	H	$-CD_3$
3018	D	H	H	H	$-CD_3$
3019	H	D	H	H	$-CD_3$
3020	H	H	D	H	$-CD_3$
3021	H	H	H	D	$-CD_3$
3022	D	D	H	H	$-CD_3$
3023	D	H	D	H	$-CD_3$
3024	D	H	H	D	$-CD_3$
3025	H	D	D	H	$-CD_3$
3026	H	D	H	D	$-CD_3$
3027	H	H	D	D	$-CD_3$
3028	D	D	D	H	$-CD_3$
3029	D	D	H	D	$-CD_3$
3030	D	H	D	D	$-CD_3$
3031	H	D	D	D	$-CD_3$
3032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00192] In one embodiment, the compound is a compound of Formula (A-I-k):



(A-I-k),

or a pharmaceutically acceptable form thereof.

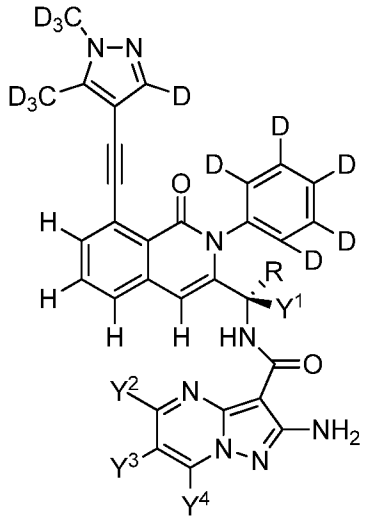
[00193] In one embodiment, the compound is a compound of Formula (A-I-k) selected from any one of the compounds in Table 31.

Table 31. Exemplary compounds of Formula (A-I-k)

Compound	Y^1	Y^2	Y^3	Y^4	R
3101	H	H	H	H	$-CH_3$
3102	D	H	H	H	$-CH_3$
3103	H	D	H	H	$-CH_3$
3104	H	H	D	H	$-CH_3$
3105	H	H	H	D	$-CH_3$
3106	D	D	H	H	$-CH_3$
3107	D	H	D	H	$-CH_3$
3108	D	H	H	D	$-CH_3$
3109	H	D	D	H	$-CH_3$
3110	H	D	H	D	$-CH_3$
3111	H	H	D	D	$-CH_3$
3112	D	D	D	H	$-CH_3$
3113	D	D	H	D	$-CH_3$
3114	D	H	D	D	$-CH_3$
3115	H	D	D	D	$-CH_3$
3116	D	D	D	D	$-CH_3$
3117	H	H	H	H	$-CD_3$
3118	D	H	H	H	$-CD_3$
3119	H	D	H	H	$-CD_3$
3120	H	H	D	H	$-CD_3$
3121	H	H	H	D	$-CD_3$
3122	D	D	H	H	$-CD_3$
3123	D	H	D	H	$-CD_3$
3124	D	H	H	D	$-CD_3$
3125	H	D	D	H	$-CD_3$
3126	H	D	H	D	$-CD_3$
3127	H	H	D	D	$-CD_3$
3128	D	D	D	H	$-CD_3$
3129	D	D	H	D	$-CD_3$
3130	D	H	D	D	$-CD_3$
3131	H	D	D	D	$-CD_3$
3132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00194] In one embodiment, the compound is a compound of Formula (A-I-l):



(A-I-l)

or a pharmaceutically acceptable form thereof.

[00195] In one embodiment, the compound is a compound of Formula (A-I-l) selected from any one of the compounds in Table 32.

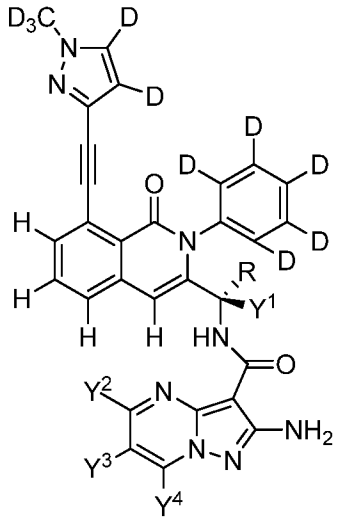
Table 32. Exemplary compounds of Formula (A-I-l)

Compound	Y^1	Y^2	Y^3	Y^4	R
3201	H	H	H	H	$-CH_3$
3202	D	H	H	H	$-CH_3$
3203	H	D	H	H	$-CH_3$
3204	H	H	D	H	$-CH_3$
3205	H	H	H	D	$-CH_3$
3206	D	D	H	H	$-CH_3$
3207	D	H	D	H	$-CH_3$
3208	D	H	H	D	$-CH_3$
3209	H	D	D	H	$-CH_3$
3210	H	D	H	D	$-CH_3$
3211	H	H	D	D	$-CH_3$
3212	D	D	D	H	$-CH_3$
3213	D	D	H	D	$-CH_3$
3214	D	H	D	D	$-CH_3$
3215	H	D	D	D	$-CH_3$
3216	D	D	D	D	$-CH_3$

3217	H	H	H	H	$-CD_3$
3218	D	H	H	H	$-CD_3$
3219	H	D	H	H	$-CD_3$
3220	H	H	D	H	$-CD_3$
3221	H	H	H	D	$-CD_3$
3222	D	D	H	H	$-CD_3$
3223	D	H	D	H	$-CD_3$
3224	D	H	H	D	$-CD_3$
3225	H	D	D	H	$-CD_3$
3226	H	D	H	D	$-CD_3$
3227	H	H	D	D	$-CD_3$
3228	D	D	D	H	$-CD_3$
3229	D	D	H	D	$-CD_3$
3230	D	H	D	D	$-CD_3$
3231	H	D	D	D	$-CD_3$
3232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00196] In one embodiment, the compound is a compound of Formula (A-II-f):



(A-II-f),

or a pharmaceutically acceptable form thereof.

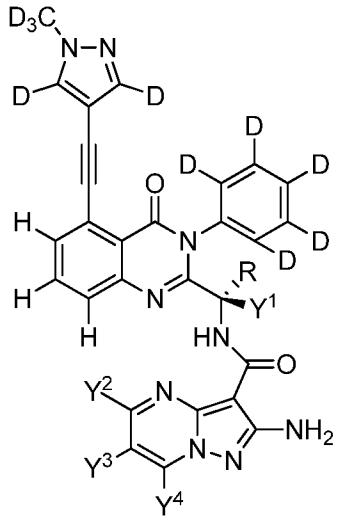
[00197] In one embodiment, the compound is a compound of Formula (A-II-f) selected from any one of the compounds in Table 33.

Table 33. Exemplary compounds of Formula (A-II-f)

Compound	Y^1	Y^2	Y^3	Y^4	R
3301	H	H	H	H	$-CH_3$
3302	D	H	H	H	$-CH_3$
3303	H	D	H	H	$-CH_3$
3304	H	H	D	H	$-CH_3$
3305	H	H	H	D	$-CH_3$
3306	D	D	H	H	$-CH_3$
3307	D	H	D	H	$-CH_3$
3308	D	H	H	D	$-CH_3$
3309	H	D	D	H	$-CH_3$
3310	H	D	H	D	$-CH_3$
3311	H	H	D	D	$-CH_3$
3312	D	D	D	H	$-CH_3$
3313	D	D	H	D	$-CH_3$
3314	D	H	D	D	$-CH_3$
3315	H	D	D	D	$-CH_3$
3316	D	D	D	D	$-CH_3$
3317	H	H	H	H	$-CD_3$
3318	D	H	H	H	$-CD_3$
3319	H	D	H	H	$-CD_3$
3320	H	H	D	H	$-CD_3$
3321	H	H	H	D	$-CD_3$
3322	D	D	H	H	$-CD_3$
3323	D	H	D	H	$-CD_3$
3324	D	H	H	D	$-CD_3$
3325	H	D	D	H	$-CD_3$
3326	H	D	H	D	$-CD_3$
3327	H	H	D	D	$-CD_3$
3328	D	D	D	H	$-CD_3$
3329	D	D	H	D	$-CD_3$
3330	D	H	D	D	$-CD_3$
3331	H	D	D	D	$-CD_3$
3332	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00198] In one embodiment, the compound is a compound of Formula (B-I-k):



(B-I-k),

or a pharmaceutically acceptable form thereof.

[00199] In one embodiment, the compound is a compound of Formula (B-I-k) selected from any one of the compounds in Table 34.

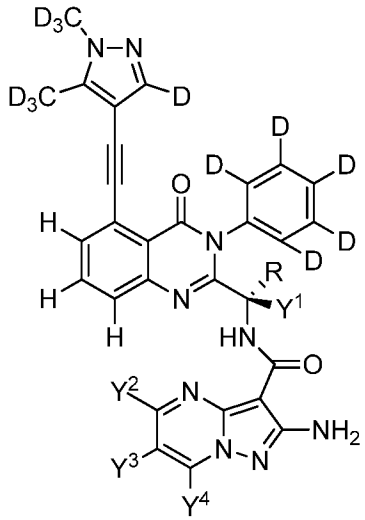
Table 34. Exemplary compounds of Formula (B-I-k)

Compound	Y^1	Y^2	Y^3	Y^4	R
3401	H	H	H	H	$-CH_3$
3402	D	H	H	H	$-CH_3$
3403	H	D	H	H	$-CH_3$
3404	H	H	D	H	$-CH_3$
3405	H	H	H	D	$-CH_3$
3406	D	D	H	H	$-CH_3$
3407	D	H	D	H	$-CH_3$
3408	D	H	H	D	$-CH_3$
3409	H	D	D	H	$-CH_3$
3410	H	D	H	D	$-CH_3$
3411	H	H	D	D	$-CH_3$
3412	D	D	D	H	$-CH_3$
3413	D	D	H	D	$-CH_3$
3414	D	H	D	D	$-CH_3$
3415	H	D	D	D	$-CH_3$
3416	D	D	D	D	$-CH_3$

3417	H	H	H	H	$-CD_3$
3418	D	H	H	H	$-CD_3$
3419	H	D	H	H	$-CD_3$
3420	H	H	D	H	$-CD_3$
3421	H	H	H	D	$-CD_3$
3422	D	D	H	H	$-CD_3$
3423	D	H	D	H	$-CD_3$
3424	D	H	H	D	$-CD_3$
3425	H	D	D	H	$-CD_3$
3426	H	D	H	D	$-CD_3$
3427	H	H	D	D	$-CD_3$
3428	D	D	D	H	$-CD_3$
3429	D	D	H	D	$-CD_3$
3430	D	H	D	D	$-CD_3$
3431	H	D	D	D	$-CD_3$
3432	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00200] In one embodiment, the compound is a compound of Formula (B-I-l):



(B-I-l),

or a pharmaceutically acceptable form thereof.

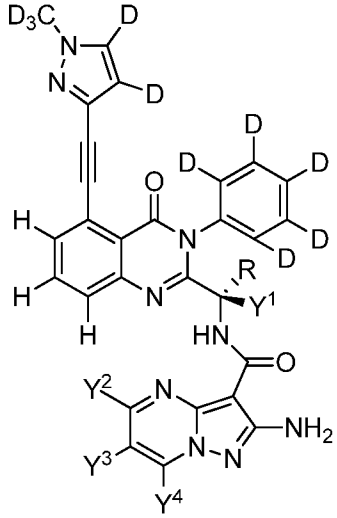
[00201] In one embodiment, the compound is a compound of Formula (B-I-l) selected from any one of the compounds in Table 35.

Table 35. Exemplary compounds of Formula (B-I-l)

Compound	Y^1	Y^2	Y^3	Y^4	R
3501	H	H	H	H	$-CH_3$
3502	D	H	H	H	$-CH_3$
3503	H	D	H	H	$-CH_3$
3504	H	H	D	H	$-CH_3$
3505	H	H	H	D	$-CH_3$
3506	D	D	H	H	$-CH_3$
3507	D	H	D	H	$-CH_3$
3508	D	H	H	D	$-CH_3$
3509	H	D	D	H	$-CH_3$
3510	H	D	H	D	$-CH_3$
3511	H	H	D	D	$-CH_3$
3512	D	D	D	H	$-CH_3$
3513	D	D	H	D	$-CH_3$
3514	D	H	D	D	$-CH_3$
3515	H	D	D	D	$-CH_3$
3516	D	D	D	D	$-CH_3$
3517	H	H	H	H	$-CD_3$
3518	D	H	H	H	$-CD_3$
3519	H	D	H	H	$-CD_3$
3520	H	H	D	H	$-CD_3$
3521	H	H	H	D	$-CD_3$
3522	D	D	H	H	$-CD_3$
3523	D	H	D	H	$-CD_3$
3524	D	H	H	D	$-CD_3$
3525	H	D	D	H	$-CD_3$
3526	H	D	H	D	$-CD_3$
3527	H	H	D	D	$-CD_3$
3528	D	D	D	H	$-CD_3$
3529	D	D	H	D	$-CD_3$
3530	D	H	D	D	$-CD_3$
3531	H	D	D	D	$-CD_3$
3532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00202] In one embodiment, the compound is a compound of Formula (B-II-f):



(B-II-f),

or a pharmaceutically acceptable form thereof.

[00203] In one embodiment, the compound is a compound of Formula (B-II-f) selected from any one of the compounds in Table 36.

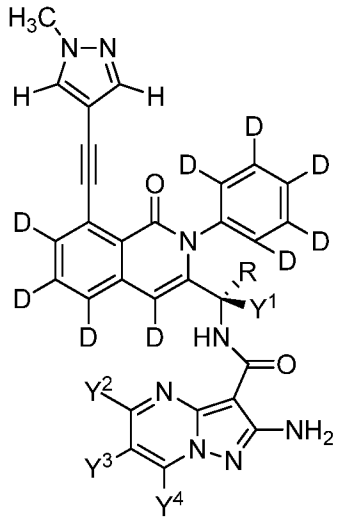
Table 36. Exemplary compounds of Formula (B-II-f)

Compound	Y^1	Y^2	Y^3	Y^4	R
3601	H	H	H	H	$-CH_3$
3602	D	H	H	H	$-CH_3$
3603	H	D	H	H	$-CH_3$
3604	H	H	D	H	$-CH_3$
3605	H	H	H	D	$-CH_3$
3606	D	D	H	H	$-CH_3$
3607	D	H	D	H	$-CH_3$
3608	D	H	H	D	$-CH_3$
3609	H	D	D	H	$-CH_3$
3610	H	D	H	D	$-CH_3$
3611	H	H	D	D	$-CH_3$
3612	D	D	D	H	$-CH_3$
3613	D	D	H	D	$-CH_3$
3614	D	H	D	D	$-CH_3$
3615	H	D	D	D	$-CH_3$
3616	D	D	D	D	$-CH_3$

3617	H	H	H	H	$-CD_3$
3618	D	H	H	H	$-CD_3$
3619	H	D	H	H	$-CD_3$
3620	H	H	D	H	$-CD_3$
3621	H	H	H	D	$-CD_3$
3622	D	D	H	H	$-CD_3$
3623	D	H	D	H	$-CD_3$
3624	D	H	H	D	$-CD_3$
3625	H	D	D	H	$-CD_3$
3626	H	D	H	D	$-CD_3$
3627	H	H	D	D	$-CD_3$
3628	D	D	D	H	$-CD_3$
3629	D	D	H	D	$-CD_3$
3630	D	H	D	D	$-CD_3$
3631	H	D	D	D	$-CD_3$
3632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00204] In one embodiment, the compound is a compound of Formula (A-I-m):



(A-I-m),

or a pharmaceutically acceptable form thereof.

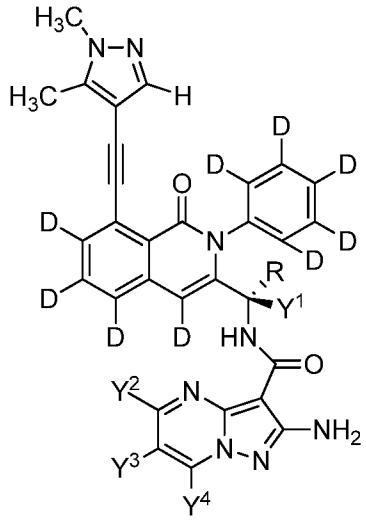
[00205] In one embodiment, the compound is a compound of Formula (A-I-m) selected from any one of the compounds in Table 37.

Table 37. Exemplary compounds of Formula (A-I-m)

Compound	Y^1	Y^2	Y^3	Y^4	R
3701	H	H	H	H	$-CH_3$
3702	D	H	H	H	$-CH_3$
3703	H	D	H	H	$-CH_3$
3704	H	H	D	H	$-CH_3$
3705	H	H	H	D	$-CH_3$
3706	D	D	H	H	$-CH_3$
3707	D	H	D	H	$-CH_3$
3708	D	H	H	D	$-CH_3$
3709	H	D	D	H	$-CH_3$
3710	H	D	H	D	$-CH_3$
3711	H	H	D	D	$-CH_3$
3712	D	D	D	H	$-CH_3$
3713	D	D	H	D	$-CH_3$
3714	D	H	D	D	$-CH_3$
3715	H	D	D	D	$-CH_3$
3716	D	D	D	D	$-CH_3$
3717	H	H	H	H	$-CD_3$
3718	D	H	H	H	$-CD_3$
3719	H	D	H	H	$-CD_3$
3720	H	H	D	H	$-CD_3$
3721	H	H	H	D	$-CD_3$
3722	D	D	H	H	$-CD_3$
3723	D	H	D	H	$-CD_3$
3724	D	H	H	D	$-CD_3$
3725	H	D	D	H	$-CD_3$
3726	H	D	H	D	$-CD_3$
3727	H	H	D	D	$-CD_3$
3728	D	D	D	H	$-CD_3$
3729	D	D	H	D	$-CD_3$
3730	D	H	D	D	$-CD_3$
3731	H	D	D	D	$-CD_3$
3732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00206] In one embodiment, the compound is a compound of Formula (A-I-n):



(A-I-n)

or a pharmaceutically acceptable form thereof.

[00207] In one embodiment, the compound is a compound of Formula (A-I-n) selected from any one of the compounds in Table 38.

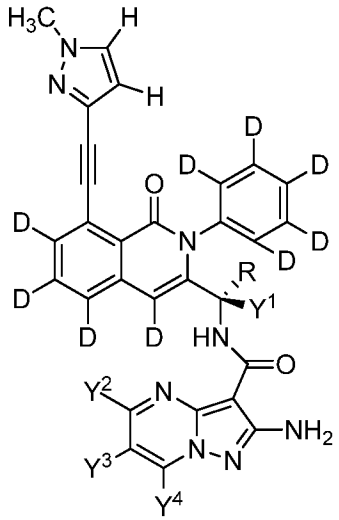
Table 38. Exemplary compounds of Formula (A-I-n)

Compound	Y^1	Y^2	Y^3	Y^4	R
3801	H	H	H	H	$-CH_3$
3802	D	H	H	H	$-CH_3$
3803	H	D	H	H	$-CH_3$
3804	H	H	D	H	$-CH_3$
3805	H	H	H	D	$-CH_3$
3806	D	D	H	H	$-CH_3$
3807	D	H	D	H	$-CH_3$
3808	D	H	H	D	$-CH_3$
3809	H	D	D	H	$-CH_3$
3810	H	D	H	D	$-CH_3$
3811	H	H	D	D	$-CH_3$
3812	D	D	D	H	$-CH_3$
3813	D	D	H	D	$-CH_3$
3814	D	H	D	D	$-CH_3$
3815	H	D	D	D	$-CH_3$
3816	D	D	D	D	$-CH_3$

3817	H	H	H	H	$-CD_3$
3818	D	H	H	H	$-CD_3$
3819	H	D	H	H	$-CD_3$
3820	H	H	D	H	$-CD_3$
3821	H	H	H	D	$-CD_3$
3822	D	D	H	H	$-CD_3$
3823	D	H	D	H	$-CD_3$
3824	D	H	H	D	$-CD_3$
3825	H	D	D	H	$-CD_3$
3826	H	D	H	D	$-CD_3$
3827	H	H	D	D	$-CD_3$
3828	D	D	D	H	$-CD_3$
3829	D	D	H	D	$-CD_3$
3830	D	H	D	D	$-CD_3$
3831	H	D	D	D	$-CD_3$
3832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00208] In one embodiment, the compound is a compound of Formula (A-II-g):



(A-II-g),

or a pharmaceutically acceptable form thereof.

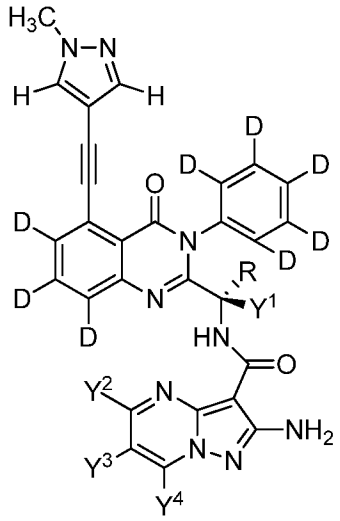
[00209] In one embodiment, the compound is a compound of Formula (A-II-g) selected from any one of the compounds in Table 39.

Table 39. Exemplary compounds of Formula (A-II-g)

Compound	Y^1	Y^2	Y^3	Y^4	R
3901	H	H	H	H	$-CH_3$
3902	D	H	H	H	$-CH_3$
3903	H	D	H	H	$-CH_3$
3904	H	H	D	H	$-CH_3$
3905	H	H	H	D	$-CH_3$
3906	D	D	H	H	$-CH_3$
3907	D	H	D	H	$-CH_3$
3908	D	H	H	D	$-CH_3$
3909	H	D	D	H	$-CH_3$
3910	H	D	H	D	$-CH_3$
3911	H	H	D	D	$-CH_3$
3912	D	D	D	H	$-CH_3$
3913	D	D	H	D	$-CH_3$
3914	D	H	D	D	$-CH_3$
3915	H	D	D	D	$-CH_3$
3916	D	D	D	D	$-CH_3$
3917	H	H	H	H	$-CD_3$
3918	D	H	H	H	$-CD_3$
3919	H	D	H	H	$-CD_3$
3920	H	H	D	H	$-CD_3$
3921	H	H	H	D	$-CD_3$
3922	D	D	H	H	$-CD_3$
3923	D	H	D	H	$-CD_3$
3924	D	H	H	D	$-CD_3$
3925	H	D	D	H	$-CD_3$
3926	H	D	H	D	$-CD_3$
3927	H	H	D	D	$-CD_3$
3928	D	D	D	H	$-CD_3$
3929	D	D	H	D	$-CD_3$
3930	D	H	D	D	$-CD_3$
3931	H	D	D	D	$-CD_3$
3932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00210] In one embodiment, the compound is a compound of Formula (B-I-m):



(B-I-m),

or a pharmaceutically acceptable form thereof.

[00211] In one embodiment, the compound is a compound of Formula (B-I-m) selected from any one of the compounds in Table 40.

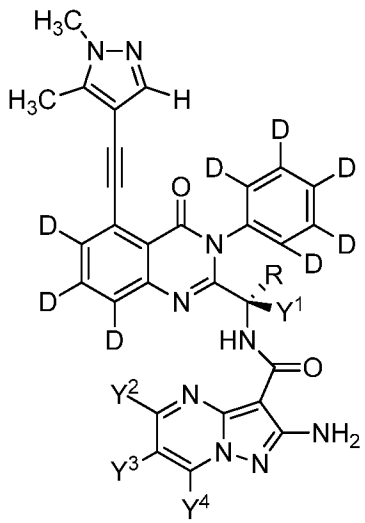
Table 40. Exemplary compounds of Formula (B-I-m)

Compound	Y^1	Y^2	Y^3	Y^4	R
4001	H	H	H	H	$-CH_3$
4002	D	H	H	H	$-CH_3$
4003	H	D	H	H	$-CH_3$
4004	H	H	D	H	$-CH_3$
4005	H	H	H	D	$-CH_3$
4006	D	D	H	H	$-CH_3$
4007	D	H	D	H	$-CH_3$
4008	D	H	H	D	$-CH_3$
4009	H	D	D	H	$-CH_3$
4010	H	D	H	D	$-CH_3$
4011	H	H	D	D	$-CH_3$
4012	D	D	D	H	$-CH_3$
4013	D	D	H	D	$-CH_3$
4014	D	H	D	D	$-CH_3$
4015	H	D	D	D	$-CH_3$
4016	D	D	D	D	$-CH_3$

4017	H	H	H	H	$-CD_3$
4018	D	H	H	H	$-CD_3$
4019	H	D	H	H	$-CD_3$
4020	H	H	D	H	$-CD_3$
4021	H	H	H	D	$-CD_3$
4022	D	D	H	H	$-CD_3$
4023	D	H	D	H	$-CD_3$
4024	D	H	H	D	$-CD_3$
4025	H	D	D	H	$-CD_3$
4026	H	D	H	D	$-CD_3$
4027	H	H	D	D	$-CD_3$
4028	D	D	D	H	$-CD_3$
4029	D	D	H	D	$-CD_3$
4030	D	H	D	D	$-CD_3$
4031	H	D	D	D	$-CD_3$
4032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00212] In one embodiment, the compound is a compound of Formula (B-I-n):



(B-I-n),

or a pharmaceutically acceptable form thereof.

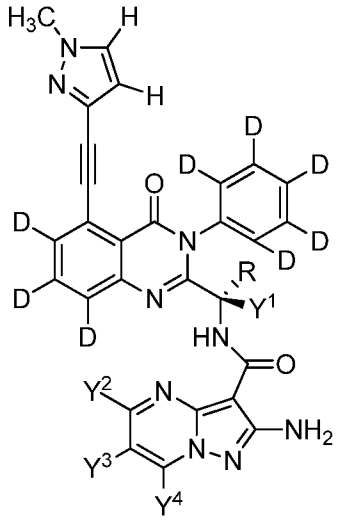
[00213] In one embodiment, the compound is a compound of Formula (B-I-n) selected from any one of the compounds in Table 41.

Table 41. Exemplary compounds of Formula (B-I-n)

Compound	Y^1	Y^2	Y^3	Y^4	R
4101	H	H	H	H	$-CH_3$
4102	D	H	H	H	$-CH_3$
4103	H	D	H	H	$-CH_3$
4104	H	H	D	H	$-CH_3$
4105	H	H	H	D	$-CH_3$
4106	D	D	H	H	$-CH_3$
4107	D	H	D	H	$-CH_3$
4108	D	H	H	D	$-CH_3$
4109	H	D	D	H	$-CH_3$
4110	H	D	H	D	$-CH_3$
4111	H	H	D	D	$-CH_3$
4112	D	D	D	H	$-CH_3$
4113	D	D	H	D	$-CH_3$
4114	D	H	D	D	$-CH_3$
4115	H	D	D	D	$-CH_3$
4116	D	D	D	D	$-CH_3$
4117	H	H	H	H	$-CD_3$
4118	D	H	H	H	$-CD_3$
4119	H	D	H	H	$-CD_3$
4120	H	H	D	H	$-CD_3$
4121	H	H	H	D	$-CD_3$
4122	D	D	H	H	$-CD_3$
4123	D	H	D	H	$-CD_3$
4124	D	H	H	D	$-CD_3$
4125	H	D	D	H	$-CD_3$
4126	H	D	H	D	$-CD_3$
4127	H	H	D	D	$-CD_3$
4128	D	D	D	H	$-CD_3$
4129	D	D	H	D	$-CD_3$
4130	D	H	D	D	$-CD_3$
4131	H	D	D	D	$-CD_3$
4132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00214] In one embodiment, the compound is a compound of Formula (B-II-g):



(B-II-g),

or a pharmaceutically acceptable form thereof.

[00215] In one embodiment, the compound is a compound of Formula (B-II-g) selected from any one of the compounds in Table 42.

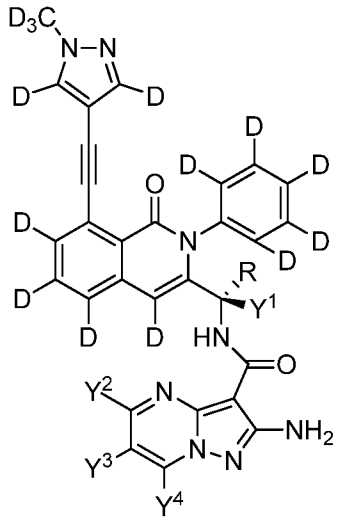
Table 42. Exemplary compounds of Formula (B-II-g)

Compound	Y^1	Y^2	Y^3	Y^4	R
4201	H	H	H	H	$-CH_3$
4202	D	H	H	H	$-CH_3$
4203	H	D	H	H	$-CH_3$
4204	H	H	D	H	$-CH_3$
4205	H	H	H	D	$-CH_3$
4206	D	D	H	H	$-CH_3$
4207	D	H	D	H	$-CH_3$
4208	D	H	H	D	$-CH_3$
4209	H	D	D	H	$-CH_3$
4210	H	D	H	D	$-CH_3$
4211	H	H	D	D	$-CH_3$
4212	D	D	D	H	$-CH_3$
4213	D	D	H	D	$-CH_3$
4214	D	H	D	D	$-CH_3$
4215	H	D	D	D	$-CH_3$
4216	D	D	D	D	$-CH_3$

4217	H	H	H	H	$-CD_3$
4218	D	H	H	H	$-CD_3$
4219	H	D	H	H	$-CD_3$
4220	H	H	D	H	$-CD_3$
4221	H	H	H	D	$-CD_3$
4222	D	D	H	H	$-CD_3$
4223	D	H	D	H	$-CD_3$
4224	D	H	H	D	$-CD_3$
4225	H	D	D	H	$-CD_3$
4226	H	D	H	D	$-CD_3$
4227	H	H	D	D	$-CD_3$
4228	D	D	D	H	$-CD_3$
4229	D	D	H	D	$-CD_3$
4230	D	H	D	D	$-CD_3$
4231	H	D	D	D	$-CD_3$
4232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00216] In one embodiment, the compound is a compound of Formula (A-I-o):



(A-I-o),

or a pharmaceutically acceptable form thereof.

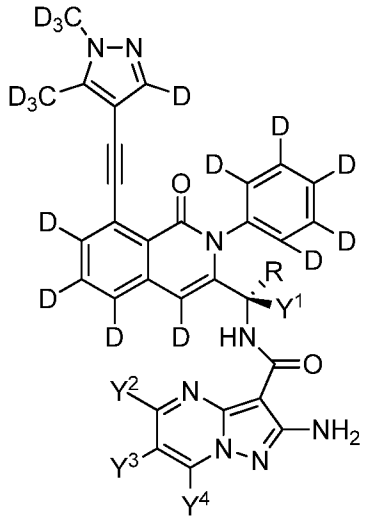
[00217] In one embodiment, the compound is a compound of Formula (A-I-o) selected from any one of the compounds in Table 43.

Table 43. Exemplary compounds of Formula (A-I-o)

Compound	Y^1	Y^2	Y^3	Y^4	R
4301	H	H	H	H	$-CH_3$
4302	D	H	H	H	$-CH_3$
4303	H	D	H	H	$-CH_3$
4304	H	H	D	H	$-CH_3$
4305	H	H	H	D	$-CH_3$
4306	D	D	H	H	$-CH_3$
4307	D	H	D	H	$-CH_3$
4308	D	H	H	D	$-CH_3$
4309	H	D	D	H	$-CH_3$
4310	H	D	H	D	$-CH_3$
4311	H	H	D	D	$-CH_3$
4312	D	D	D	H	$-CH_3$
4313	D	D	H	D	$-CH_3$
4314	D	H	D	D	$-CH_3$
4315	H	D	D	D	$-CH_3$
4316	D	D	D	D	$-CH_3$
4317	H	H	H	H	$-CD_3$
4318	D	H	H	H	$-CD_3$
4319	H	D	H	H	$-CD_3$
4320	H	H	D	H	$-CD_3$
4321	H	H	H	D	$-CD_3$
4322	D	D	H	H	$-CD_3$
4323	D	H	D	H	$-CD_3$
4324	D	H	H	D	$-CD_3$
4325	H	D	D	H	$-CD_3$
4326	H	D	H	D	$-CD_3$
4327	H	H	D	D	$-CD_3$
4328	D	D	D	H	$-CD_3$
4329	D	D	H	D	$-CD_3$
4330	D	H	D	D	$-CD_3$
4331	H	D	D	D	$-CD_3$
4332	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00218] In one embodiment, the compound is a compound of Formula (A-I-p):



(A-I-p)

or a pharmaceutically acceptable form thereof.

[00219] In one embodiment, the compound is a compound of Formula (A-I-p) selected from any one of the compounds in Table 44.

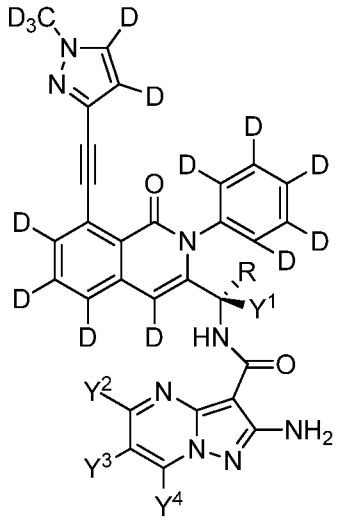
Table 44. Exemplary compounds of Formula (A-I-p)

Compound	Y^1	Y^2	Y^3	Y^4	R
4401	H	H	H	H	$-CH_3$
4402	D	H	H	H	$-CH_3$
4403	H	D	H	H	$-CH_3$
4404	H	H	D	H	$-CH_3$
4405	H	H	H	D	$-CH_3$
4406	D	D	H	H	$-CH_3$
4407	D	H	D	H	$-CH_3$
4408	D	H	H	D	$-CH_3$
4409	H	D	D	H	$-CH_3$
4410	H	D	H	D	$-CH_3$
4411	H	H	D	D	$-CH_3$
4412	D	D	D	H	$-CH_3$
4413	D	D	H	D	$-CH_3$
4414	D	H	D	D	$-CH_3$
4415	H	D	D	D	$-CH_3$
4416	D	D	D	D	$-CH_3$

4417	H	H	H	H	$-CD_3$
4418	D	H	H	H	$-CD_3$
4419	H	D	H	H	$-CD_3$
4420	H	H	D	H	$-CD_3$
4421	H	H	H	D	$-CD_3$
4422	D	D	H	H	$-CD_3$
4423	D	H	D	H	$-CD_3$
4424	D	H	H	D	$-CD_3$
4425	H	D	D	H	$-CD_3$
4426	H	D	H	D	$-CD_3$
4427	H	H	D	D	$-CD_3$
4428	D	D	D	H	$-CD_3$
4429	D	D	H	D	$-CD_3$
4430	D	H	D	D	$-CD_3$
4431	H	D	D	D	$-CD_3$
4432	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00220] In one embodiment, the compound is a compound of Formula (A-II-h):



(A-II-h),

or a pharmaceutically acceptable form thereof.

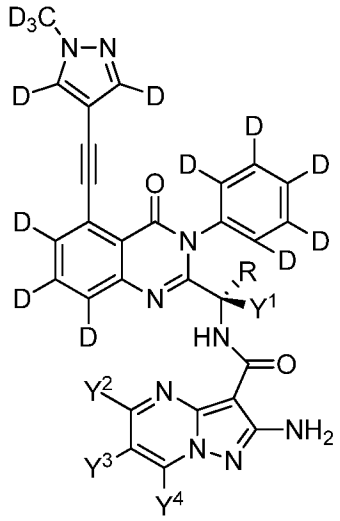
[00221] In one embodiment, the compound is a compound of Formula (A-II-h) selected from any one of the compounds in Table 45.

Table 45. Exemplary compounds of Formula (A-II-h)

Compound	Y^1	Y^2	Y^3	Y^4	R
4501	H	H	H	H	$-CH_3$
4502	D	H	H	H	$-CH_3$
4503	H	D	H	H	$-CH_3$
4504	H	H	D	H	$-CH_3$
4505	H	H	H	D	$-CH_3$
4506	D	D	H	H	$-CH_3$
4507	D	H	D	H	$-CH_3$
4508	D	H	H	D	$-CH_3$
4509	H	D	D	H	$-CH_3$
4510	H	D	H	D	$-CH_3$
4511	H	H	D	D	$-CH_3$
4512	D	D	D	H	$-CH_3$
4513	D	D	H	D	$-CH_3$
4514	D	H	D	D	$-CH_3$
4515	H	D	D	D	$-CH_3$
4516	D	D	D	D	$-CH_3$
4517	H	H	H	H	$-CD_3$
4518	D	H	H	H	$-CD_3$
4519	H	D	H	H	$-CD_3$
4520	H	H	D	H	$-CD_3$
4521	H	H	H	D	$-CD_3$
4522	D	D	H	H	$-CD_3$
4523	D	H	D	H	$-CD_3$
4524	D	H	H	D	$-CD_3$
4525	H	D	D	H	$-CD_3$
4526	H	D	H	D	$-CD_3$
4527	H	H	D	D	$-CD_3$
4528	D	D	D	H	$-CD_3$
4529	D	D	H	D	$-CD_3$
4530	D	H	D	D	$-CD_3$
4531	H	D	D	D	$-CD_3$
4532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00222] In one embodiment, the compound is a compound of Formula (B-I-o):



(B-I-o),

or a pharmaceutically acceptable form thereof.

[00223] In one embodiment, the compound is a compound of Formula (B-I-o) selected from any one of the compounds in Table 46.

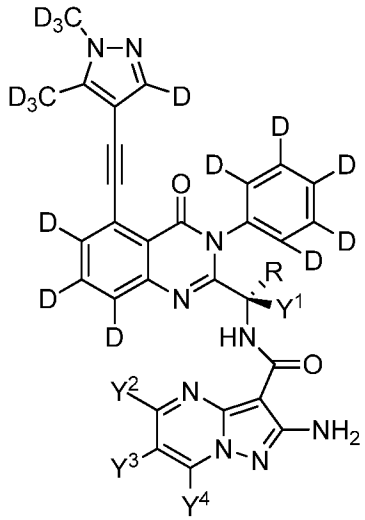
Table 46. Exemplary compounds of Formula (B-I-o)

Compound	Y^1	Y^2	Y^3	Y^4	R
4601	H	H	H	H	$-CH_3$
4602	D	H	H	H	$-CH_3$
4603	H	D	H	H	$-CH_3$
4604	H	H	D	H	$-CH_3$
4605	H	H	H	D	$-CH_3$
4606	D	D	H	H	$-CH_3$
4607	D	H	D	H	$-CH_3$
4608	D	H	H	D	$-CH_3$
4609	H	D	D	H	$-CH_3$
4610	H	D	H	D	$-CH_3$
4611	H	H	D	D	$-CH_3$
4612	D	D	D	H	$-CH_3$
4613	D	D	H	D	$-CH_3$
4614	D	H	D	D	$-CH_3$
4615	H	D	D	D	$-CH_3$
4616	D	D	D	D	$-CH_3$

4617	H	H	H	H	$-CD_3$
4618	D	H	H	H	$-CD_3$
4619	H	D	H	H	$-CD_3$
4620	H	H	D	H	$-CD_3$
4621	H	H	H	D	$-CD_3$
4622	D	D	H	H	$-CD_3$
4623	D	H	D	H	$-CD_3$
4624	D	H	H	D	$-CD_3$
4625	H	D	D	H	$-CD_3$
4626	H	D	H	D	$-CD_3$
4627	H	H	D	D	$-CD_3$
4628	D	D	D	H	$-CD_3$
4629	D	D	H	D	$-CD_3$
4630	D	H	D	D	$-CD_3$
4631	H	D	D	D	$-CD_3$
4632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00224] In one embodiment, the compound is a compound of Formula (B-I-p):



(B-I-p),

or a pharmaceutically acceptable form thereof.

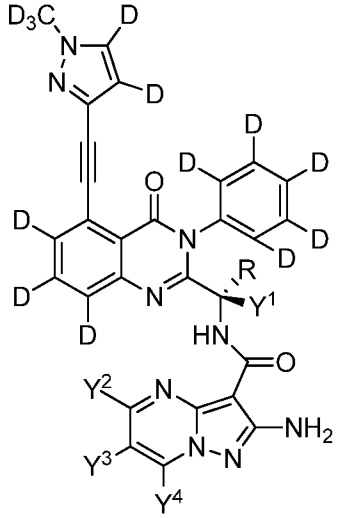
[00225] In one embodiment, the compound is a compound of Formula (B-I-p) selected from any one of the compounds in Table 47.

Table 47. Exemplary compounds of Formula (B-I-p)

Compound	Y^1	Y^2	Y^3	Y^4	R
4701	H	H	H	H	$-CH_3$
4702	D	H	H	H	$-CH_3$
4703	H	D	H	H	$-CH_3$
4704	H	H	D	H	$-CH_3$
4705	H	H	H	D	$-CH_3$
4706	D	D	H	H	$-CH_3$
4707	D	H	D	H	$-CH_3$
4708	D	H	H	D	$-CH_3$
4709	H	D	D	H	$-CH_3$
4710	H	D	H	D	$-CH_3$
4711	H	H	D	D	$-CH_3$
4712	D	D	D	H	$-CH_3$
4713	D	D	H	D	$-CH_3$
4714	D	H	D	D	$-CH_3$
4715	H	D	D	D	$-CH_3$
4716	D	D	D	D	$-CH_3$
4717	H	H	H	H	$-CD_3$
4718	D	H	H	H	$-CD_3$
4719	H	D	H	H	$-CD_3$
4720	H	H	D	H	$-CD_3$
4721	H	H	H	D	$-CD_3$
4722	D	D	H	H	$-CD_3$
4723	D	H	D	H	$-CD_3$
4724	D	H	H	D	$-CD_3$
4725	H	D	D	H	$-CD_3$
4726	H	D	H	D	$-CD_3$
4727	H	H	D	D	$-CD_3$
4728	D	D	D	H	$-CD_3$
4729	D	D	H	D	$-CD_3$
4730	D	H	D	D	$-CD_3$
4731	H	D	D	D	$-CD_3$
4732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00226] In one embodiment, the compound is a compound of Formula (B-II-h):



(B-II-h),

or a pharmaceutically acceptable form thereof.

[00227] In one embodiment, the compound is a compound of Formula (B-II-h) selected from any one of the compounds in Table 48.

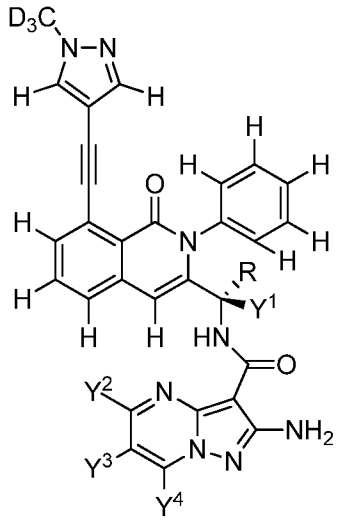
Table 48. Exemplary compounds of Formula (B-II-h)

Compound	Y^1	Y^2	Y^3	Y^4	R
4801	H	H	H	H	$-CH_3$
4802	D	H	H	H	$-CH_3$
4803	H	D	H	H	$-CH_3$
4804	H	H	D	H	$-CH_3$
4805	H	H	H	D	$-CH_3$
4806	D	D	H	H	$-CH_3$
4807	D	H	D	H	$-CH_3$
4808	D	H	H	D	$-CH_3$
4809	H	D	D	H	$-CH_3$
4810	H	D	H	D	$-CH_3$
4811	H	H	D	D	$-CH_3$
4812	D	D	D	H	$-CH_3$
4813	D	D	H	D	$-CH_3$
4814	D	H	D	D	$-CH_3$
4815	H	D	D	D	$-CH_3$
4816	D	D	D	D	$-CH_3$

4817	H	H	H	H	$-CD_3$
4818	D	H	H	H	$-CD_3$
4819	H	D	H	H	$-CD_3$
4820	H	H	D	H	$-CD_3$
4821	H	H	H	D	$-CD_3$
4822	D	D	H	H	$-CD_3$
4823	D	H	D	H	$-CD_3$
4824	D	H	H	D	$-CD_3$
4825	H	D	D	H	$-CD_3$
4826	H	D	H	D	$-CD_3$
4827	H	H	D	D	$-CD_3$
4828	D	D	D	H	$-CD_3$
4829	D	D	H	D	$-CD_3$
4830	D	H	D	D	$-CD_3$
4831	H	D	D	D	$-CD_3$
4832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00228] In one embodiment, the compound is a compound of Formula (A-I-q):



(A-I-q),

or a pharmaceutically acceptable form thereof.

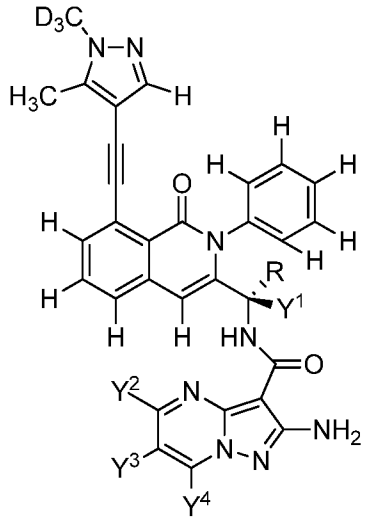
[00229] In one embodiment, the compound is a compound of Formula (A-I-q) selected from any one of the compounds in Table 49.

Table 49. Exemplary compounds of Formula (A-I-q)

Compound	Y^1	Y^2	Y^3	Y^4	R
4901	H	H	H	H	$-CH_3$
4902	D	H	H	H	$-CH_3$
4903	H	D	H	H	$-CH_3$
4904	H	H	D	H	$-CH_3$
4905	H	H	H	D	$-CH_3$
4906	D	D	H	H	$-CH_3$
4907	D	H	D	H	$-CH_3$
4908	D	H	H	D	$-CH_3$
4909	H	D	D	H	$-CH_3$
4910	H	D	H	D	$-CH_3$
4911	H	H	D	D	$-CH_3$
4912	D	D	D	H	$-CH_3$
4913	D	D	H	D	$-CH_3$
4914	D	H	D	D	$-CH_3$
4915	H	D	D	D	$-CH_3$
4916	D	D	D	D	$-CH_3$
4917	H	H	H	H	$-CD_3$
4918	D	H	H	H	$-CD_3$
4919	H	D	H	H	$-CD_3$
4920	H	H	D	H	$-CD_3$
4921	H	H	H	D	$-CD_3$
4922	D	D	H	H	$-CD_3$
4923	D	H	D	H	$-CD_3$
4924	D	H	H	D	$-CD_3$
4925	H	D	D	H	$-CD_3$
4926	H	D	H	D	$-CD_3$
4927	H	H	D	D	$-CD_3$
4928	D	D	D	H	$-CD_3$
4929	D	D	H	D	$-CD_3$
4930	D	H	D	D	$-CD_3$
4931	H	D	D	D	$-CD_3$
4932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00230] In one embodiment, the compound is a compound of Formula (A-I-r):



(A-I-r)

or a pharmaceutically acceptable form thereof.

[00231] In one embodiment, the compound is a compound of Formula (A-I-r) selected from any one of the compounds in Table 50.

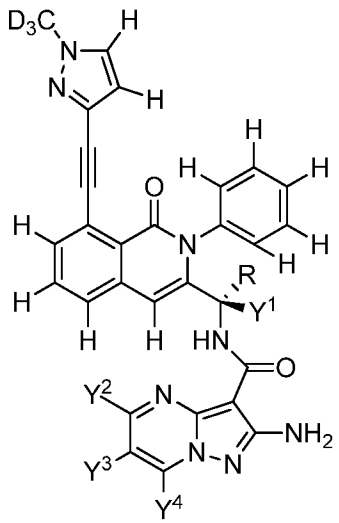
Table 50. Exemplary compounds of Formula (A-I-r)

Compound	Y^1	Y^2	Y^3	Y^4	R
5001	H	H	H	H	$-CH_3$
5002	D	H	H	H	$-CH_3$
5003	H	D	H	H	$-CH_3$
5004	H	H	D	H	$-CH_3$
5005	H	H	H	D	$-CH_3$
5006	D	D	H	H	$-CH_3$
5007	D	H	D	H	$-CH_3$
5008	D	H	H	D	$-CH_3$
5009	H	D	D	H	$-CH_3$
5010	H	D	H	D	$-CH_3$
5011	H	H	D	D	$-CH_3$
5012	D	D	D	H	$-CH_3$
5013	D	D	H	D	$-CH_3$
5014	D	H	D	D	$-CH_3$
5015	H	D	D	D	$-CH_3$
5016	D	D	D	D	$-CH_3$

5017	H	H	H	H	$-CD_3$
5018	D	H	H	H	$-CD_3$
5019	H	D	H	H	$-CD_3$
5020	H	H	D	H	$-CD_3$
5021	H	H	H	D	$-CD_3$
5022	D	D	H	H	$-CD_3$
5023	D	H	D	H	$-CD_3$
5024	D	H	H	D	$-CD_3$
5025	H	D	D	H	$-CD_3$
5026	H	D	H	D	$-CD_3$
5027	H	H	D	D	$-CD_3$
5028	D	D	D	H	$-CD_3$
5029	D	D	H	D	$-CD_3$
5030	D	H	D	D	$-CD_3$
5031	H	D	D	D	$-CD_3$
5032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00232] In one embodiment, the compound is a compound of Formula (A-II-i):



(A-II-i),

or a pharmaceutically acceptable form thereof.

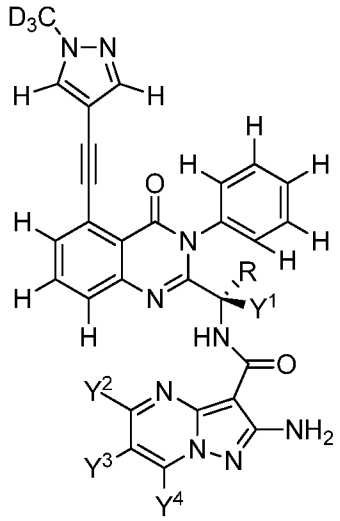
[00233] In one embodiment, the compound is a compound of Formula (A-II-i) selected from any one of the compounds in Table 51.

Table 51. Exemplary compounds of Formula (A-II-i)

Compound	Y^1	Y^2	Y^3	Y^4	R
5101	H	H	H	H	$-CH_3$
5102	D	H	H	H	$-CH_3$
5103	H	D	H	H	$-CH_3$
5104	H	H	D	H	$-CH_3$
5105	H	H	H	D	$-CH_3$
5106	D	D	H	H	$-CH_3$
5107	D	H	D	H	$-CH_3$
5108	D	H	H	D	$-CH_3$
5109	H	D	D	H	$-CH_3$
5110	H	D	H	D	$-CH_3$
5111	H	H	D	D	$-CH_3$
5112	D	D	D	H	$-CH_3$
5113	D	D	H	D	$-CH_3$
5114	D	H	D	D	$-CH_3$
5115	H	D	D	D	$-CH_3$
5116	D	D	D	D	$-CH_3$
5117	H	H	H	H	$-CD_3$
5118	D	H	H	H	$-CD_3$
5119	H	D	H	H	$-CD_3$
5120	H	H	D	H	$-CD_3$
5121	H	H	H	D	$-CD_3$
5122	D	D	H	H	$-CD_3$
5123	D	H	D	H	$-CD_3$
5124	D	H	H	D	$-CD_3$
5125	H	D	D	H	$-CD_3$
5126	H	D	H	D	$-CD_3$
5127	H	H	D	D	$-CD_3$
5128	D	D	D	H	$-CD_3$
5129	D	D	H	D	$-CD_3$
5130	D	H	D	D	$-CD_3$
5131	H	D	D	D	$-CD_3$
5132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00234] In one embodiment, the compound is a compound of Formula (B-I-q):



(B-I-q),

or a pharmaceutically acceptable form thereof.

[00235] In one embodiment, the compound is a compound of Formula (B-I-q) selected from any one of the compounds in Table 52.

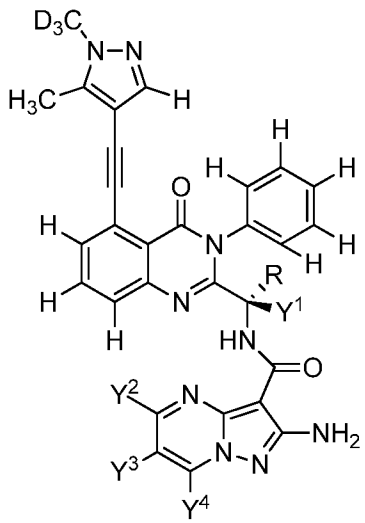
Table 52. Exemplary compounds of Formula (B-I-q)

Compound	Y^1	Y^2	Y^3	Y^4	R
5201	H	H	H	H	$-CH_3$
5202	D	H	H	H	$-CH_3$
5203	H	D	H	H	$-CH_3$
5204	H	H	D	H	$-CH_3$
5205	H	H	H	D	$-CH_3$
5206	D	D	H	H	$-CH_3$
5207	D	H	D	H	$-CH_3$
5208	D	H	H	D	$-CH_3$
5209	H	D	D	H	$-CH_3$
5210	H	D	H	D	$-CH_3$
5211	H	H	D	D	$-CH_3$
5212	D	D	D	H	$-CH_3$
5213	D	D	H	D	$-CH_3$
5214	D	H	D	D	$-CH_3$
5215	H	D	D	D	$-CH_3$
5216	D	D	D	D	$-CH_3$

5217	H	H	H	H	$-CD_3$
5218	D	H	H	H	$-CD_3$
5219	H	D	H	H	$-CD_3$
5220	H	H	D	H	$-CD_3$
5221	H	H	H	D	$-CD_3$
5222	D	D	H	H	$-CD_3$
5223	D	H	D	H	$-CD_3$
5224	D	H	H	D	$-CD_3$
5225	H	D	D	H	$-CD_3$
5226	H	D	H	D	$-CD_3$
5227	H	H	D	D	$-CD_3$
5228	D	D	D	H	$-CD_3$
5229	D	D	H	D	$-CD_3$
5230	D	H	D	D	$-CD_3$
5231	H	D	D	D	$-CD_3$
5232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00236] In one embodiment, the compound is a compound of Formula (B-I-r):



(B-I-r),

or a pharmaceutically acceptable form thereof.

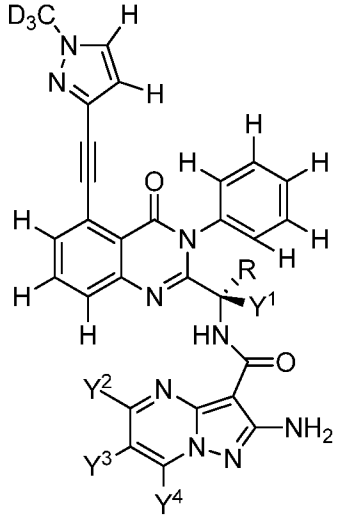
[00237] In one embodiment, the compound is a compound of Formula (B-I-r) selected from any one of the compounds in Table 53.

Table 53. Exemplary compounds of Formula (B-I-r)

Compound	Y^1	Y^2	Y^3	Y^4	R
5301	H	H	H	H	$-CH_3$
5302	D	H	H	H	$-CH_3$
5303	H	D	H	H	$-CH_3$
5304	H	H	D	H	$-CH_3$
5305	H	H	H	D	$-CH_3$
5306	D	D	H	H	$-CH_3$
5307	D	H	D	H	$-CH_3$
5308	D	H	H	D	$-CH_3$
5309	H	D	D	H	$-CH_3$
5310	H	D	H	D	$-CH_3$
5311	H	H	D	D	$-CH_3$
5312	D	D	D	H	$-CH_3$
5313	D	D	H	D	$-CH_3$
5314	D	H	D	D	$-CH_3$
5315	H	D	D	D	$-CH_3$
5316	D	D	D	D	$-CH_3$
5317	H	H	H	H	$-CD_3$
5318	D	H	H	H	$-CD_3$
5319	H	D	H	H	$-CD_3$
5320	H	H	D	H	$-CD_3$
5321	H	H	H	D	$-CD_3$
5322	D	D	H	H	$-CD_3$
5323	D	H	D	H	$-CD_3$
5324	D	H	H	D	$-CD_3$
5325	H	D	D	H	$-CD_3$
5326	H	D	H	D	$-CD_3$
5327	H	H	D	D	$-CD_3$
5328	D	D	D	H	$-CD_3$
5329	D	D	H	D	$-CD_3$
5330	D	H	D	D	$-CD_3$
5331	H	D	D	D	$-CD_3$
5332	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00238] In one embodiment, the compound is a compound of Formula (B-II-i):



(B-II-i),

or a pharmaceutically acceptable form thereof.

[00239] In one embodiment, the compound is a compound of Formula (B-II-i) selected from any one of the compounds in Table 54.

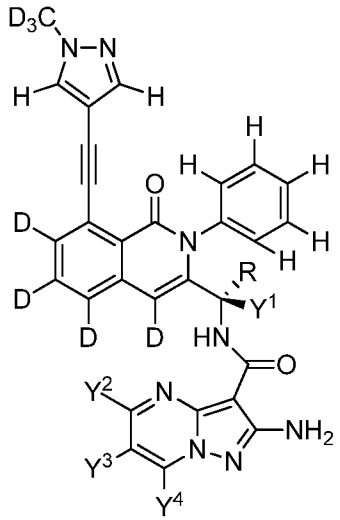
Table 54. Exemplary compounds of Formula (B-II-i)

Compound	Y^1	Y^2	Y^3	Y^4	R
5401	H	H	H	H	$-CH_3$
5402	D	H	H	H	$-CH_3$
5403	H	D	H	H	$-CH_3$
5404	H	H	D	H	$-CH_3$
5405	H	H	H	D	$-CH_3$
5406	D	D	H	H	$-CH_3$
5407	D	H	D	H	$-CH_3$
5408	D	H	H	D	$-CH_3$
5409	H	D	D	H	$-CH_3$
5410	H	D	H	D	$-CH_3$
5411	H	H	D	D	$-CH_3$
5412	D	D	D	H	$-CH_3$
5413	D	D	H	D	$-CH_3$
5414	D	H	D	D	$-CH_3$
5415	H	D	D	D	$-CH_3$
5416	D	D	D	D	$-CH_3$

5417	H	H	H	H	$-CD_3$
5418	D	H	H	H	$-CD_3$
5419	H	D	H	H	$-CD_3$
5420	H	H	D	H	$-CD_3$
5421	H	H	H	D	$-CD_3$
5422	D	D	H	H	$-CD_3$
5423	D	H	D	H	$-CD_3$
5424	D	H	H	D	$-CD_3$
5425	H	D	D	H	$-CD_3$
5426	H	D	H	D	$-CD_3$
5427	H	H	D	D	$-CD_3$
5428	D	D	D	H	$-CD_3$
5429	D	D	H	D	$-CD_3$
5430	D	H	D	D	$-CD_3$
5431	H	D	D	D	$-CD_3$
5432	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00240] In one embodiment, the compound is a compound of Formula (A-I-s):



(A-I-s),

or a pharmaceutically acceptable form thereof.

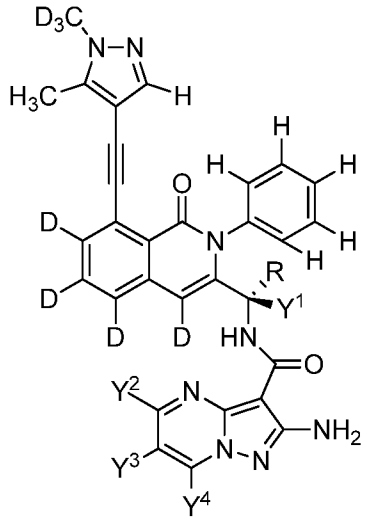
[00241] In one embodiment, the compound is a compound of Formula (A-I-s) selected from any one of the compounds in Table 55.

Table 55. Exemplary compounds of Formula (A-I-s)

Compound	Y^1	Y^2	Y^3	Y^4	R
5501	H	H	H	H	$-CH_3$
5502	D	H	H	H	$-CH_3$
5503	H	D	H	H	$-CH_3$
5504	H	H	D	H	$-CH_3$
5505	H	H	H	D	$-CH_3$
5506	D	D	H	H	$-CH_3$
5507	D	H	D	H	$-CH_3$
5508	D	H	H	D	$-CH_3$
5509	H	D	D	H	$-CH_3$
5510	H	D	H	D	$-CH_3$
5511	H	H	D	D	$-CH_3$
5512	D	D	D	H	$-CH_3$
5513	D	D	H	D	$-CH_3$
5514	D	H	D	D	$-CH_3$
5515	H	D	D	D	$-CH_3$
5516	D	D	D	D	$-CH_3$
5517	H	H	H	H	$-CD_3$
5518	D	H	H	H	$-CD_3$
5519	H	D	H	H	$-CD_3$
5520	H	H	D	H	$-CD_3$
5521	H	H	H	D	$-CD_3$
5522	D	D	H	H	$-CD_3$
5523	D	H	D	H	$-CD_3$
5524	D	H	H	D	$-CD_3$
5525	H	D	D	H	$-CD_3$
5526	H	D	H	D	$-CD_3$
5527	H	H	D	D	$-CD_3$
5528	D	D	D	H	$-CD_3$
5529	D	D	H	D	$-CD_3$
5530	D	H	D	D	$-CD_3$
5531	H	D	D	D	$-CD_3$
5532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00242] In one embodiment, the compound is a compound of Formula (A-I-t):



(A-I-t)

or a pharmaceutically acceptable form thereof.

[00243] In one embodiment, the compound is a compound of Formula (A-I-t) selected from any one of the compounds in Table 56.

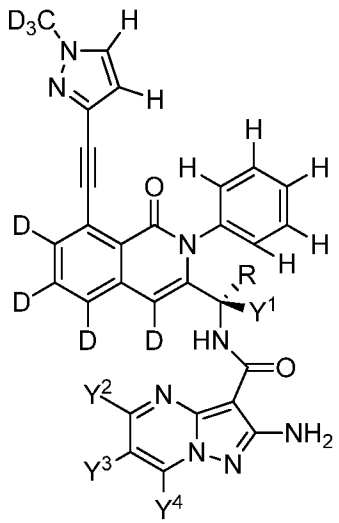
Table 56. Exemplary compounds of Formula (A-I-t)

Compound	Y^1	Y^2	Y^3	Y^4	R
5601	H	H	H	H	$-CH_3$
5602	D	H	H	H	$-CH_3$
5603	H	D	H	H	$-CH_3$
5604	H	H	D	H	$-CH_3$
5605	H	H	H	D	$-CH_3$
5606	D	D	H	H	$-CH_3$
5607	D	H	D	H	$-CH_3$
5608	D	H	H	D	$-CH_3$
5609	H	D	D	H	$-CH_3$
5610	H	D	H	D	$-CH_3$
5611	H	H	D	D	$-CH_3$
5612	D	D	D	H	$-CH_3$
5613	D	D	H	D	$-CH_3$
5614	D	H	D	D	$-CH_3$
5615	H	D	D	D	$-CH_3$
5616	D	D	D	D	$-CH_3$

5617	H	H	H	H	$-CD_3$
5618	D	H	H	H	$-CD_3$
5619	H	D	H	H	$-CD_3$
5620	H	H	D	H	$-CD_3$
5621	H	H	H	D	$-CD_3$
5622	D	D	H	H	$-CD_3$
5623	D	H	D	H	$-CD_3$
5624	D	H	H	D	$-CD_3$
5625	H	D	D	H	$-CD_3$
5626	H	D	H	D	$-CD_3$
5627	H	H	D	D	$-CD_3$
5628	D	D	D	H	$-CD_3$
5629	D	D	H	D	$-CD_3$
5630	D	H	D	D	$-CD_3$
5631	H	D	D	D	$-CD_3$
5632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00244] In one embodiment, the compound is a compound of Formula (A-II-j):



(A-II-j),

or a pharmaceutically acceptable form thereof.

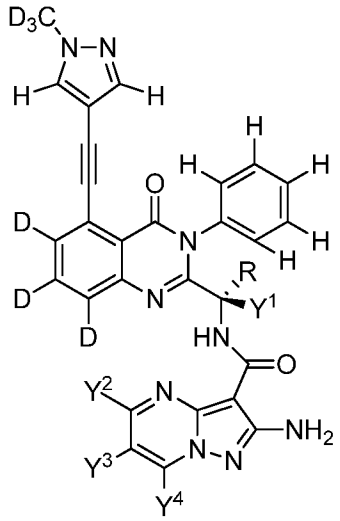
[00245] In one embodiment, the compound is a compound of Formula (A-II-j) selected from any one of the compounds in Table 57.

Table 57. Exemplary compounds of Formula (A-II-j)

Compound	Y^1	Y^2	Y^3	Y^4	R
5701	H	H	H	H	$-CH_3$
5702	D	H	H	H	$-CH_3$
5703	H	D	H	H	$-CH_3$
5704	H	H	D	H	$-CH_3$
5705	H	H	H	D	$-CH_3$
5706	D	D	H	H	$-CH_3$
5707	D	H	D	H	$-CH_3$
5708	D	H	H	D	$-CH_3$
5709	H	D	D	H	$-CH_3$
5710	H	D	H	D	$-CH_3$
5711	H	H	D	D	$-CH_3$
5712	D	D	D	H	$-CH_3$
5713	D	D	H	D	$-CH_3$
5714	D	H	D	D	$-CH_3$
5715	H	D	D	D	$-CH_3$
5716	D	D	D	D	$-CH_3$
5717	H	H	H	H	$-CD_3$
5718	D	H	H	H	$-CD_3$
5719	H	D	H	H	$-CD_3$
5720	H	H	D	H	$-CD_3$
5721	H	H	H	D	$-CD_3$
5722	D	D	H	H	$-CD_3$
5723	D	H	D	H	$-CD_3$
5724	D	H	H	D	$-CD_3$
5725	H	D	D	H	$-CD_3$
5726	H	D	H	D	$-CD_3$
5727	H	H	D	D	$-CD_3$
5728	D	D	D	H	$-CD_3$
5729	D	D	H	D	$-CD_3$
5730	D	H	D	D	$-CD_3$
5731	H	D	D	D	$-CD_3$
5732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00246] In one embodiment, the compound is a compound of Formula (B-I-s):



(B-I-s),

or a pharmaceutically acceptable form thereof.

[00247] In one embodiment, the compound is a compound of Formula (B-I-s) selected from any one of the compounds in Table 58.

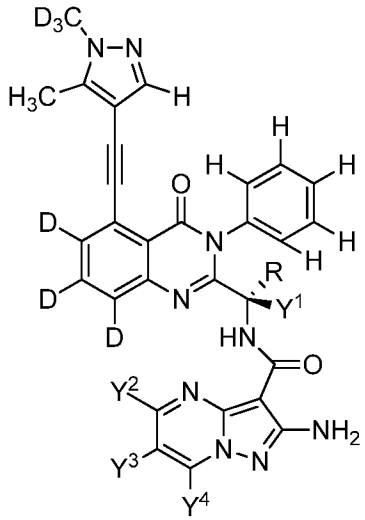
Table 58. Exemplary compounds of Formula (B-I-s)

Compound	Y^1	Y^2	Y^3	Y^4	R
5801	H	H	H	H	$-CH_3$
5802	D	H	H	H	$-CH_3$
5803	H	D	H	H	$-CH_3$
5804	H	H	D	H	$-CH_3$
5805	H	H	H	D	$-CH_3$
5806	D	D	H	H	$-CH_3$
5807	D	H	D	H	$-CH_3$
5808	D	H	H	D	$-CH_3$
5809	H	D	D	H	$-CH_3$
5810	H	D	H	D	$-CH_3$
5811	H	H	D	D	$-CH_3$
5812	D	D	D	H	$-CH_3$
5813	D	D	H	D	$-CH_3$
5814	D	H	D	D	$-CH_3$
5815	H	D	D	D	$-CH_3$
5816	D	D	D	D	$-CH_3$

5817	H	H	H	H	$-CD_3$
5818	D	H	H	H	$-CD_3$
5819	H	D	H	H	$-CD_3$
5820	H	H	D	H	$-CD_3$
5821	H	H	H	D	$-CD_3$
5822	D	D	H	H	$-CD_3$
5823	D	H	D	H	$-CD_3$
5824	D	H	H	D	$-CD_3$
5825	H	D	D	H	$-CD_3$
5826	H	D	H	D	$-CD_3$
5827	H	H	D	D	$-CD_3$
5828	D	D	D	H	$-CD_3$
5829	D	D	H	D	$-CD_3$
5830	D	H	D	D	$-CD_3$
5831	H	D	D	D	$-CD_3$
5832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00248] In one embodiment, the compound is a compound of Formula (B-I-t):



(B-I-t),

or a pharmaceutically acceptable form thereof.

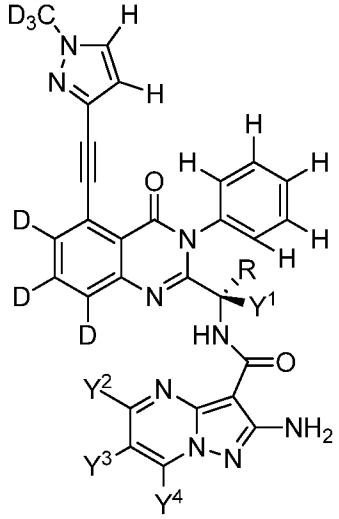
[00249] In one embodiment, the compound is a compound of Formula (B-I-t) selected from any one of the compounds in Table 59.

Table 59. Exemplary compounds of Formula (B-I-t)

Compound	Y^1	Y^2	Y^3	Y^4	R
5901	H	H	H	H	$-CH_3$
5902	D	H	H	H	$-CH_3$
5903	H	D	H	H	$-CH_3$
5904	H	H	D	H	$-CH_3$
5905	H	H	H	D	$-CH_3$
5906	D	D	H	H	$-CH_3$
5907	D	H	D	H	$-CH_3$
5908	D	H	H	D	$-CH_3$
5909	H	D	D	H	$-CH_3$
5910	H	D	H	D	$-CH_3$
5911	H	H	D	D	$-CH_3$
5912	D	D	D	H	$-CH_3$
5913	D	D	H	D	$-CH_3$
5914	D	H	D	D	$-CH_3$
5915	H	D	D	D	$-CH_3$
5916	D	D	D	D	$-CH_3$
5917	H	H	H	H	$-CD_3$
5918	D	H	H	H	$-CD_3$
5919	H	D	H	H	$-CD_3$
5920	H	H	D	H	$-CD_3$
5921	H	H	H	D	$-CD_3$
5922	D	D	H	H	$-CD_3$
5923	D	H	D	H	$-CD_3$
5924	D	H	H	D	$-CD_3$
5925	H	D	D	H	$-CD_3$
5926	H	D	H	D	$-CD_3$
5927	H	H	D	D	$-CD_3$
5928	D	D	D	H	$-CD_3$
5929	D	D	H	D	$-CD_3$
5930	D	H	D	D	$-CD_3$
5931	H	D	D	D	$-CD_3$
5932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00250] In one embodiment, the compound is a compound of Formula (B-II-j):



(B-II-j),

or a pharmaceutically acceptable form thereof.

[00251] In one embodiment, the compound is a compound of Formula (B-II-j) selected from any one of the compounds in Table 60.

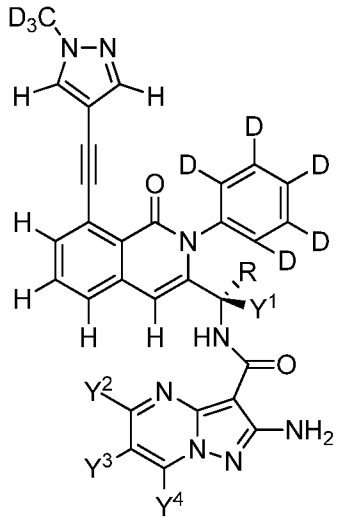
Table 60. Exemplary compounds of Formula (B-II-j)

Compound	Y^1	Y^2	Y^3	Y^4	R
6001	H	H	H	H	$-CH_3$
6002	D	H	H	H	$-CH_3$
6003	H	D	H	H	$-CH_3$
6004	H	H	D	H	$-CH_3$
6005	H	H	H	D	$-CH_3$
6006	D	D	H	H	$-CH_3$
6007	D	H	D	H	$-CH_3$
6008	D	H	H	D	$-CH_3$
6009	H	D	D	H	$-CH_3$
6010	H	D	H	D	$-CH_3$
6011	H	H	D	D	$-CH_3$
6012	D	D	D	H	$-CH_3$
6013	D	D	H	D	$-CH_3$
6014	D	H	D	D	$-CH_3$
6015	H	D	D	D	$-CH_3$
6016	D	D	D	D	$-CH_3$

6017	H	H	H	H	$-CD_3$
6018	D	H	H	H	$-CD_3$
6019	H	D	H	H	$-CD_3$
6020	H	H	D	H	$-CD_3$
6021	H	H	H	D	$-CD_3$
6022	D	D	H	H	$-CD_3$
6023	D	H	D	H	$-CD_3$
6024	D	H	H	D	$-CD_3$
6025	H	D	D	H	$-CD_3$
6026	H	D	H	D	$-CD_3$
6027	H	H	D	D	$-CD_3$
6028	D	D	D	H	$-CD_3$
6029	D	D	H	D	$-CD_3$
6030	D	H	D	D	$-CD_3$
6031	H	D	D	D	$-CD_3$
6032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00252] In one embodiment, the compound is a compound of Formula (A-I-u):



(A-I-u),

or a pharmaceutically acceptable form thereof.

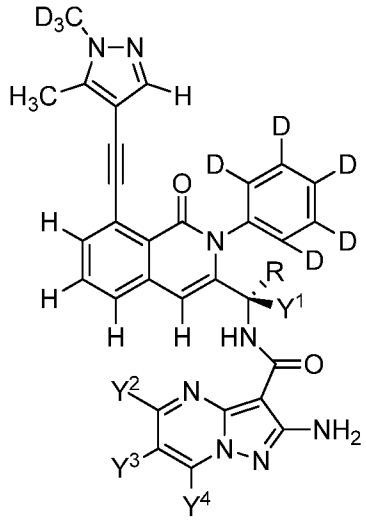
[00253] In one embodiment, the compound is a compound of Formula (A-I-u) selected from any one of the compounds in Table 61.

Table 61. Exemplary compounds of Formula (A-I-u)

Compound	Y^1	Y^2	Y^3	Y^4	R
6101	H	H	H	H	$-CH_3$
6102	D	H	H	H	$-CH_3$
6103	H	D	H	H	$-CH_3$
6104	H	H	D	H	$-CH_3$
6105	H	H	H	D	$-CH_3$
6106	D	D	H	H	$-CH_3$
6107	D	H	D	H	$-CH_3$
6108	D	H	H	D	$-CH_3$
6109	H	D	D	H	$-CH_3$
6110	H	D	H	D	$-CH_3$
6111	H	H	D	D	$-CH_3$
6112	D	D	D	H	$-CH_3$
6113	D	D	H	D	$-CH_3$
6114	D	H	D	D	$-CH_3$
6115	H	D	D	D	$-CH_3$
6116	D	D	D	D	$-CH_3$
6117	H	H	H	H	$-CD_3$
6118	D	H	H	H	$-CD_3$
6119	H	D	H	H	$-CD_3$
6120	H	H	D	H	$-CD_3$
6121	H	H	H	D	$-CD_3$
6122	D	D	H	H	$-CD_3$
6123	D	H	D	H	$-CD_3$
6124	D	H	H	D	$-CD_3$
6125	H	D	D	H	$-CD_3$
6126	H	D	H	D	$-CD_3$
6127	H	H	D	D	$-CD_3$
6128	D	D	D	H	$-CD_3$
6129	D	D	H	D	$-CD_3$
6130	D	H	D	D	$-CD_3$
6131	H	D	D	D	$-CD_3$
6132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00254] In one embodiment, the compound is a compound of Formula (A-I-v):



(A-I-v)

or a pharmaceutically acceptable form thereof.

[00255] In one embodiment, the compound is a compound of Formula (A-I-v) selected from any one of the compounds in Table 62.

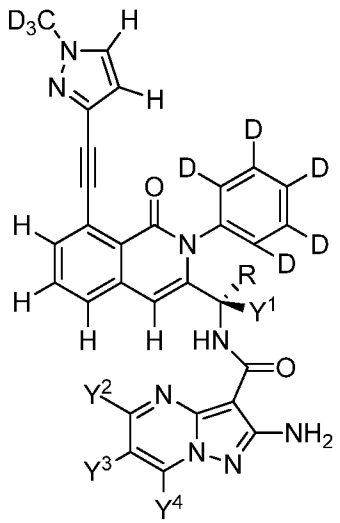
Table 62. Exemplary compounds of Formula (A-I-v)

Compound	Y^1	Y^2	Y^3	Y^4	R
6201	H	H	H	H	$-CH_3$
6202	D	H	H	H	$-CH_3$
6203	H	D	H	H	$-CH_3$
6204	H	H	D	H	$-CH_3$
6205	H	H	H	D	$-CH_3$
6206	D	D	H	H	$-CH_3$
6207	D	H	D	H	$-CH_3$
6208	D	H	H	D	$-CH_3$
6209	H	D	D	H	$-CH_3$
6210	H	D	H	D	$-CH_3$
6211	H	H	D	D	$-CH_3$
6212	D	D	D	H	$-CH_3$
6213	D	D	H	D	$-CH_3$
6214	D	H	D	D	$-CH_3$
6215	H	D	D	D	$-CH_3$
6216	D	D	D	D	$-CH_3$

6217	H	H	H	H	$-CD_3$
6218	D	H	H	H	$-CD_3$
6219	H	D	H	H	$-CD_3$
6220	H	H	D	H	$-CD_3$
6221	H	H	H	D	$-CD_3$
6222	D	D	H	H	$-CD_3$
6223	D	H	D	H	$-CD_3$
6224	D	H	H	D	$-CD_3$
6225	H	D	D	H	$-CD_3$
6226	H	D	H	D	$-CD_3$
6227	H	H	D	D	$-CD_3$
6228	D	D	D	H	$-CD_3$
6229	D	D	H	D	$-CD_3$
6230	D	H	D	D	$-CD_3$
6231	H	D	D	D	$-CD_3$
6232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00256] In one embodiment, the compound is a compound of Formula (A-II-l):



(A-II-l),

or a pharmaceutically acceptable form thereof.

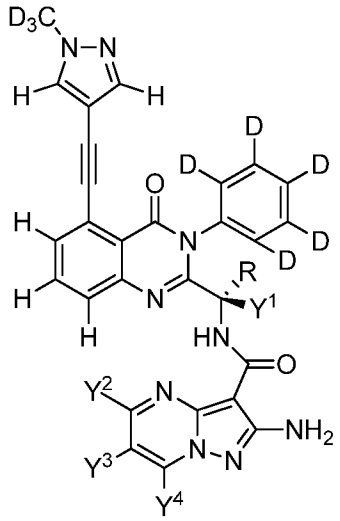
[00257] In one embodiment, the compound is a compound of Formula (A-II-l) selected from any one of the compounds in Table 63.

Table 63. Exemplary compounds of Formula (A-II-l)

Compound	Y^1	Y^2	Y^3	Y^4	R
6301	H	H	H	H	$-CH_3$
6302	D	H	H	H	$-CH_3$
6303	H	D	H	H	$-CH_3$
6304	H	H	D	H	$-CH_3$
6305	H	H	H	D	$-CH_3$
6306	D	D	H	H	$-CH_3$
6307	D	H	D	H	$-CH_3$
6308	D	H	H	D	$-CH_3$
6309	H	D	D	H	$-CH_3$
6310	H	D	H	D	$-CH_3$
6311	H	H	D	D	$-CH_3$
6312	D	D	D	H	$-CH_3$
6313	D	D	H	D	$-CH_3$
6314	D	H	D	D	$-CH_3$
6315	H	D	D	D	$-CH_3$
6316	D	D	D	D	$-CH_3$
6317	H	H	H	H	$-CD_3$
6318	D	H	H	H	$-CD_3$
6319	H	D	H	H	$-CD_3$
6320	H	H	D	H	$-CD_3$
6321	H	H	H	D	$-CD_3$
6322	D	D	H	H	$-CD_3$
6323	D	H	D	H	$-CD_3$
6324	D	H	H	D	$-CD_3$
6325	H	D	D	H	$-CD_3$
6326	H	D	H	D	$-CD_3$
6327	H	H	D	D	$-CD_3$
6328	D	D	D	H	$-CD_3$
6329	D	D	H	D	$-CD_3$
6330	D	H	D	D	$-CD_3$
6331	H	D	D	D	$-CD_3$
6332	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00258] In one embodiment, the compound is a compound of Formula (B-I-u):



(B-I-u),

or a pharmaceutically acceptable form thereof.

[00259] In one embodiment, the compound is a compound of Formula (B-I-u) selected from any one of the compounds in Table 64.

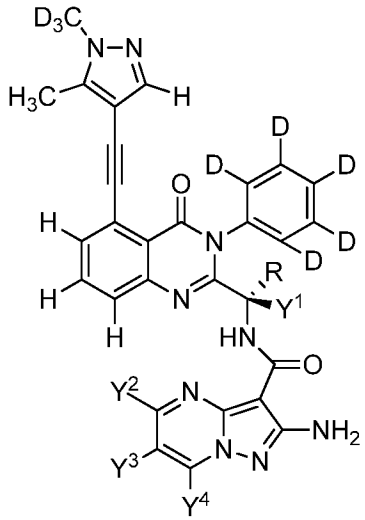
Table 64. Exemplary compounds of Formula (B-I-u)

Compound	Y^1	Y^2	Y^3	Y^4	R
6401	H	H	H	H	$-CH_3$
6402	D	H	H	H	$-CH_3$
6403	H	D	H	H	$-CH_3$
6404	H	H	D	H	$-CH_3$
6405	H	H	H	D	$-CH_3$
6406	D	D	H	H	$-CH_3$
6407	D	H	D	H	$-CH_3$
6408	D	H	H	D	$-CH_3$
6409	H	D	D	H	$-CH_3$
6410	H	D	H	D	$-CH_3$
6411	H	H	D	D	$-CH_3$
6412	D	D	D	H	$-CH_3$
6413	D	D	H	D	$-CH_3$
6414	D	H	D	D	$-CH_3$
6415	H	D	D	D	$-CH_3$
6416	D	D	D	D	$-CH_3$

6417	H	H	H	H	$-CD_3$
6418	D	H	H	H	$-CD_3$
6419	H	D	H	H	$-CD_3$
6420	H	H	D	H	$-CD_3$
6421	H	H	H	D	$-CD_3$
6422	D	D	H	H	$-CD_3$
6423	D	H	D	H	$-CD_3$
6424	D	H	H	D	$-CD_3$
6425	H	D	D	H	$-CD_3$
6426	H	D	H	D	$-CD_3$
6427	H	H	D	D	$-CD_3$
6428	D	D	D	H	$-CD_3$
6429	D	D	H	D	$-CD_3$
6430	D	H	D	D	$-CD_3$
6431	H	D	D	D	$-CD_3$
6432	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00260] In one embodiment, the compound is a compound of Formula (B-I-v):



(B-I-v),

or a pharmaceutically acceptable form thereof.

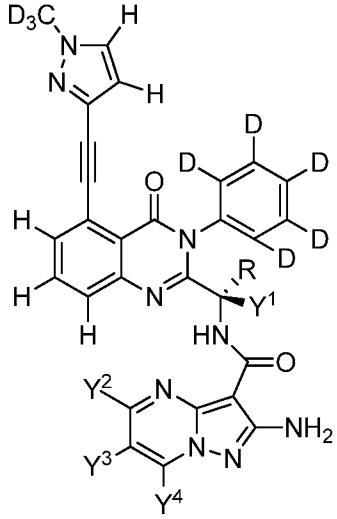
[00261] In one embodiment, the compound is a compound of Formula (B-I-v) selected from any one of the compounds in Table 65.

Table 65. Exemplary compounds of Formula (B-I-v)

Compound	Y^1	Y^2	Y^3	Y^4	R
6501	H	H	H	H	$-CH_3$
6502	D	H	H	H	$-CH_3$
6503	H	D	H	H	$-CH_3$
6504	H	H	D	H	$-CH_3$
6505	H	H	H	D	$-CH_3$
6506	D	D	H	H	$-CH_3$
6507	D	H	D	H	$-CH_3$
6508	D	H	H	D	$-CH_3$
6509	H	D	D	H	$-CH_3$
6510	H	D	H	D	$-CH_3$
6511	H	H	D	D	$-CH_3$
6512	D	D	D	H	$-CH_3$
6513	D	D	H	D	$-CH_3$
6514	D	H	D	D	$-CH_3$
6515	H	D	D	D	$-CH_3$
6516	D	D	D	D	$-CH_3$
6517	H	H	H	H	$-CD_3$
6518	D	H	H	H	$-CD_3$
6519	H	D	H	H	$-CD_3$
6520	H	H	D	H	$-CD_3$
6521	H	H	H	D	$-CD_3$
6522	D	D	H	H	$-CD_3$
6523	D	H	D	H	$-CD_3$
6524	D	H	H	D	$-CD_3$
6525	H	D	D	H	$-CD_3$
6526	H	D	H	D	$-CD_3$
6527	H	H	D	D	$-CD_3$
6528	D	D	D	H	$-CD_3$
6529	D	D	H	D	$-CD_3$
6530	D	H	D	D	$-CD_3$
6531	H	D	D	D	$-CD_3$
6532	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00262] In one embodiment, the compound is a compound of Formula (B-II-l):



(B-II-l),

or a pharmaceutically acceptable form thereof.

[00263] In one embodiment, the compound is a compound of Formula (B-II-l) selected from any one of the compounds in Table 66.

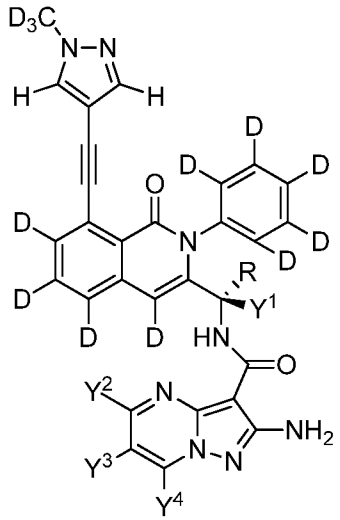
Table 66. Exemplary compounds of Formula (B-II-l)

Compound	Y^1	Y^2	Y^3	Y^4	R
6601	H	H	H	H	$-CH_3$
6602	D	H	H	H	$-CH_3$
6603	H	D	H	H	$-CH_3$
6604	H	H	D	H	$-CH_3$
6605	H	H	H	D	$-CH_3$
6606	D	D	H	H	$-CH_3$
6607	D	H	D	H	$-CH_3$
6608	D	H	H	D	$-CH_3$
6609	H	D	D	H	$-CH_3$
6610	H	D	H	D	$-CH_3$
6611	H	H	D	D	$-CH_3$
6612	D	D	D	H	$-CH_3$
6613	D	D	H	D	$-CH_3$
6614	D	H	D	D	$-CH_3$
6615	H	D	D	D	$-CH_3$
6616	D	D	D	D	$-CH_3$

6617	H	H	H	H	$-CD_3$
6618	D	H	H	H	$-CD_3$
6619	H	D	H	H	$-CD_3$
6620	H	H	D	H	$-CD_3$
6621	H	H	H	D	$-CD_3$
6622	D	D	H	H	$-CD_3$
6623	D	H	D	H	$-CD_3$
6624	D	H	H	D	$-CD_3$
6625	H	D	D	H	$-CD_3$
6626	H	D	H	D	$-CD_3$
6627	H	H	D	D	$-CD_3$
6628	D	D	D	H	$-CD_3$
6629	D	D	H	D	$-CD_3$
6630	D	H	D	D	$-CD_3$
6631	H	D	D	D	$-CD_3$
6632	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00264] In one embodiment, the compound is a compound of Formula (A-I-w):



(A-I-w),

or a pharmaceutically acceptable form thereof.

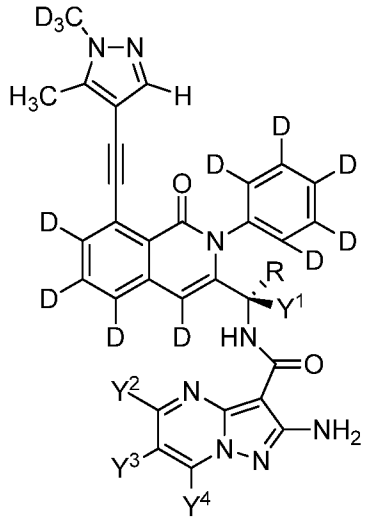
[00265] In one embodiment, the compound is a compound of Formula (A-I-w) selected from any one of the compounds in Table 67.

Table 67. Exemplary compounds of Formula (A-I-w)

Compound	Y^1	Y^2	Y^3	Y^4	R
6701	H	H	H	H	$-CH_3$
6702	D	H	H	H	$-CH_3$
6703	H	D	H	H	$-CH_3$
6704	H	H	D	H	$-CH_3$
6705	H	H	H	D	$-CH_3$
6706	D	D	H	H	$-CH_3$
6707	D	H	D	H	$-CH_3$
6708	D	H	H	D	$-CH_3$
6709	H	D	D	H	$-CH_3$
6710	H	D	H	D	$-CH_3$
6711	H	H	D	D	$-CH_3$
6712	D	D	D	H	$-CH_3$
6713	D	D	H	D	$-CH_3$
6714	D	H	D	D	$-CH_3$
6715	H	D	D	D	$-CH_3$
6716	D	D	D	D	$-CH_3$
6717	H	H	H	H	$-CD_3$
6718	D	H	H	H	$-CD_3$
6719	H	D	H	H	$-CD_3$
6720	H	H	D	H	$-CD_3$
6721	H	H	H	D	$-CD_3$
6722	D	D	H	H	$-CD_3$
6723	D	H	D	H	$-CD_3$
6724	D	H	H	D	$-CD_3$
6725	H	D	D	H	$-CD_3$
6726	H	D	H	D	$-CD_3$
6727	H	H	D	D	$-CD_3$
6728	D	D	D	H	$-CD_3$
6729	D	D	H	D	$-CD_3$
6730	D	H	D	D	$-CD_3$
6731	H	D	D	D	$-CD_3$
6732	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00266] In one embodiment, the compound is a compound of Formula (A-I-x):



(A-I-x)

or a pharmaceutically acceptable form thereof.

[00267] In one embodiment, the compound is a compound of Formula (A-I-x) selected from any one of the compounds in Table 68.

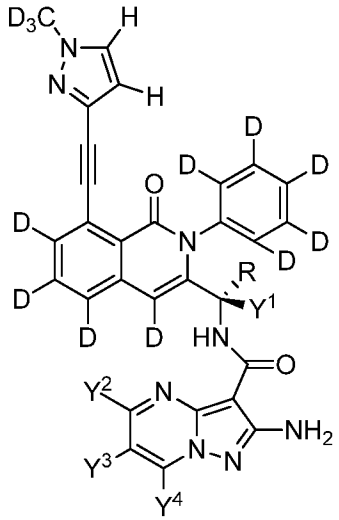
Table 68. Exemplary compounds of Formula (A-I-x)

Compound	Y^1	Y^2	Y^3	Y^4	R
6801	H	H	H	H	$-CH_3$
6802	D	H	H	H	$-CH_3$
6803	H	D	H	H	$-CH_3$
6804	H	H	D	H	$-CH_3$
6805	H	H	H	D	$-CH_3$
6806	D	D	H	H	$-CH_3$
6807	D	H	D	H	$-CH_3$
6808	D	H	H	D	$-CH_3$
6809	H	D	D	H	$-CH_3$
6810	H	D	H	D	$-CH_3$
6811	H	H	D	D	$-CH_3$
6812	D	D	D	H	$-CH_3$
6813	D	D	H	D	$-CH_3$
6814	D	H	D	D	$-CH_3$
6815	H	D	D	D	$-CH_3$
6816	D	D	D	D	$-CH_3$

6817	H	H	H	H	$-CD_3$
6818	D	H	H	H	$-CD_3$
6819	H	D	H	H	$-CD_3$
6820	H	H	D	H	$-CD_3$
6821	H	H	H	D	$-CD_3$
6822	D	D	H	H	$-CD_3$
6823	D	H	D	H	$-CD_3$
6824	D	H	H	D	$-CD_3$
6825	H	D	D	H	$-CD_3$
6826	H	D	H	D	$-CD_3$
6827	H	H	D	D	$-CD_3$
6828	D	D	D	H	$-CD_3$
6829	D	D	H	D	$-CD_3$
6830	D	H	D	D	$-CD_3$
6831	H	D	D	D	$-CD_3$
6832	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00268] In one embodiment, the compound is a compound of Formula (A-II-m):



(A-II-m),

or a pharmaceutically acceptable form thereof.

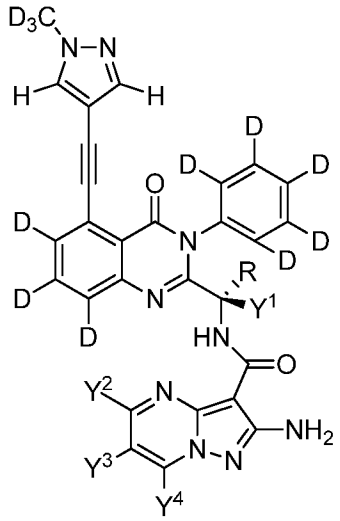
[00269] In one embodiment, the compound is a compound of Formula (A-II-m) selected from any one of the compounds in Table 69.

Table 69. Exemplary compounds of Formula (A-II-m)

Compound	Y^1	Y^2	Y^3	Y^4	R
6901	H	H	H	H	$-CH_3$
6902	D	H	H	H	$-CH_3$
6903	H	D	H	H	$-CH_3$
6904	H	H	D	H	$-CH_3$
6905	H	H	H	D	$-CH_3$
6906	D	D	H	H	$-CH_3$
6907	D	H	D	H	$-CH_3$
6908	D	H	H	D	$-CH_3$
6909	H	D	D	H	$-CH_3$
6910	H	D	H	D	$-CH_3$
6911	H	H	D	D	$-CH_3$
6912	D	D	D	H	$-CH_3$
6913	D	D	H	D	$-CH_3$
6914	D	H	D	D	$-CH_3$
6915	H	D	D	D	$-CH_3$
6916	D	D	D	D	$-CH_3$
6917	H	H	H	H	$-CD_3$
6918	D	H	H	H	$-CD_3$
6919	H	D	H	H	$-CD_3$
6920	H	H	D	H	$-CD_3$
6921	H	H	H	D	$-CD_3$
6922	D	D	H	H	$-CD_3$
6923	D	H	D	H	$-CD_3$
6924	D	H	H	D	$-CD_3$
6925	H	D	D	H	$-CD_3$
6926	H	D	H	D	$-CD_3$
6927	H	H	D	D	$-CD_3$
6928	D	D	D	H	$-CD_3$
6929	D	D	H	D	$-CD_3$
6930	D	H	D	D	$-CD_3$
6931	H	D	D	D	$-CD_3$
6932	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00270] In one embodiment, the compound is a compound of Formula (B-I-w):



(B-I-w),

or a pharmaceutically acceptable form thereof.

[00271] In one embodiment, the compound is a compound of Formula (B-I-w) selected from any one of the compounds in Table 70.

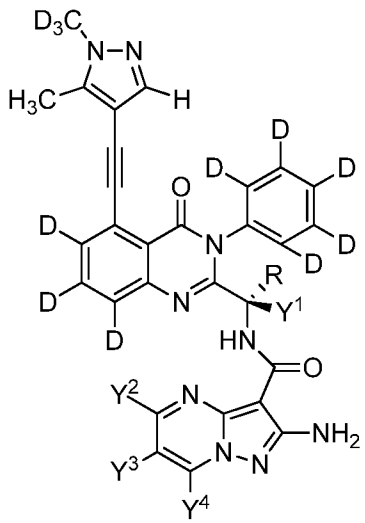
Table 70. Exemplary compounds of Formula (B-I-w)

Compound	Y^1	Y^2	Y^3	Y^4	R
7001	H	H	H	H	$-CH_3$
7002	D	H	H	H	$-CH_3$
7003	H	D	H	H	$-CH_3$
7004	H	H	D	H	$-CH_3$
7005	H	H	H	D	$-CH_3$
7006	D	D	H	H	$-CH_3$
7007	D	H	D	H	$-CH_3$
7008	D	H	H	D	$-CH_3$
7009	H	D	D	H	$-CH_3$
7010	H	D	H	D	$-CH_3$
7011	H	H	D	D	$-CH_3$
7012	D	D	D	H	$-CH_3$
7013	D	D	H	D	$-CH_3$
7014	D	H	D	D	$-CH_3$
7015	H	D	D	D	$-CH_3$
7016	D	D	D	D	$-CH_3$

7017	H	H	H	H	$-CD_3$
7018	D	H	H	H	$-CD_3$
7019	H	D	H	H	$-CD_3$
7020	H	H	D	H	$-CD_3$
7021	H	H	H	D	$-CD_3$
7022	D	D	H	H	$-CD_3$
7023	D	H	D	H	$-CD_3$
7024	D	H	H	D	$-CD_3$
7025	H	D	D	H	$-CD_3$
7026	H	D	H	D	$-CD_3$
7027	H	H	D	D	$-CD_3$
7028	D	D	D	H	$-CD_3$
7029	D	D	H	D	$-CD_3$
7030	D	H	D	D	$-CD_3$
7031	H	D	D	D	$-CD_3$
7032	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00272] In one embodiment, the compound is a compound of Formula (B-I-x):



(B-I-x),

or a pharmaceutically acceptable form thereof.

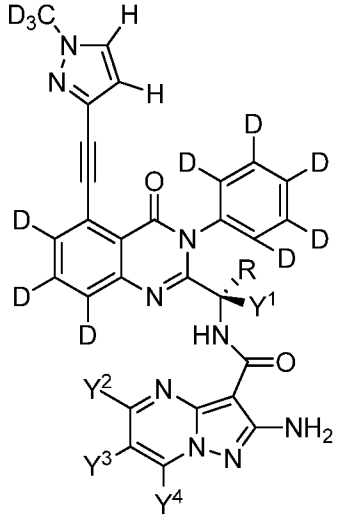
[00273] In one embodiment, the compound is a compound of Formula (B-I-x) selected from any one of the compounds in Table 71.

Table 71. Exemplary compounds of Formula (B-I-x)

Compound	Y^1	Y^2	Y^3	Y^4	R
7101	H	H	H	H	$-CH_3$
7102	D	H	H	H	$-CH_3$
7103	H	D	H	H	$-CH_3$
7104	H	H	D	H	$-CH_3$
7105	H	H	H	D	$-CH_3$
7106	D	D	H	H	$-CH_3$
7107	D	H	D	H	$-CH_3$
7108	D	H	H	D	$-CH_3$
7109	H	D	D	H	$-CH_3$
7110	H	D	H	D	$-CH_3$
7111	H	H	D	D	$-CH_3$
7112	D	D	D	H	$-CH_3$
7113	D	D	H	D	$-CH_3$
7114	D	H	D	D	$-CH_3$
7115	H	D	D	D	$-CH_3$
7116	D	D	D	D	$-CH_3$
7117	H	H	H	H	$-CD_3$
7118	D	H	H	H	$-CD_3$
7119	H	D	H	H	$-CD_3$
7120	H	H	D	H	$-CD_3$
7121	H	H	H	D	$-CD_3$
7122	D	D	H	H	$-CD_3$
7123	D	H	D	H	$-CD_3$
7124	D	H	H	D	$-CD_3$
7125	H	D	D	H	$-CD_3$
7126	H	D	H	D	$-CD_3$
7127	H	H	D	D	$-CD_3$
7128	D	D	D	H	$-CD_3$
7129	D	D	H	D	$-CD_3$
7130	D	H	D	D	$-CD_3$
7131	H	D	D	D	$-CD_3$
7132	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00274] In one embodiment, the compound is a compound of Formula (B-II-m):



(B-II-m),

or a pharmaceutically acceptable form thereof.

[00275] In one embodiment, the compound is a compound of Formula (B-II-m) selected from any one of the compounds in Table 72.

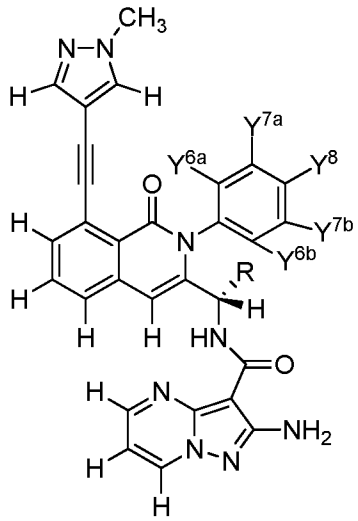
Table 72. Exemplary compounds of Formula (B-II-m)

Compound	Y^1	Y^2	Y^3	Y^4	R
7201	H	H	H	H	$-CH_3$
7202	D	H	H	H	$-CH_3$
7203	H	D	H	H	$-CH_3$
7204	H	H	D	H	$-CH_3$
7205	H	H	H	D	$-CH_3$
7206	D	D	H	H	$-CH_3$
7207	D	H	D	H	$-CH_3$
7208	D	H	H	D	$-CH_3$
7209	H	D	D	H	$-CH_3$
7210	H	D	H	D	$-CH_3$
7211	H	H	D	D	$-CH_3$
7212	D	D	D	H	$-CH_3$
7213	D	D	H	D	$-CH_3$
7214	D	H	D	D	$-CH_3$
7215	H	D	D	D	$-CH_3$
7216	D	D	D	D	$-CH_3$

7217	H	H	H	H	$-CD_3$
7218	D	H	H	H	$-CD_3$
7219	H	D	H	H	$-CD_3$
7220	H	H	D	H	$-CD_3$
7221	H	H	H	D	$-CD_3$
7222	D	D	H	H	$-CD_3$
7223	D	H	D	H	$-CD_3$
7224	D	H	H	D	$-CD_3$
7225	H	D	D	H	$-CD_3$
7226	H	D	H	D	$-CD_3$
7227	H	H	D	D	$-CD_3$
7228	D	D	D	H	$-CD_3$
7229	D	D	H	D	$-CD_3$
7230	D	H	D	D	$-CD_3$
7231	H	D	D	D	$-CD_3$
7232	D	D	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00276] In one embodiment, the compound is a compound of Formula (A-I-y):



(A-I-y)

or a pharmaceutically acceptable form thereof.

[00277] In one embodiment, the compound is a compound of Formula (A-I-y) selected from any one of the compounds in Table 73.

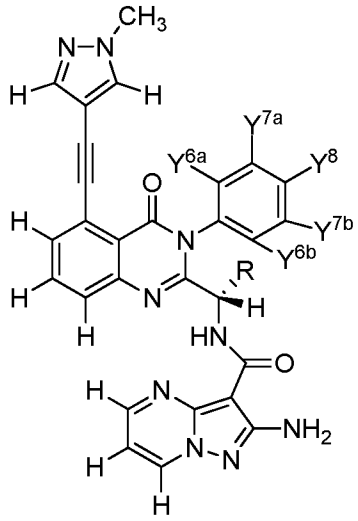
Table 73. Exemplary compounds of Formula (A-I-y)

Compound	Y^{6a}	Y^{7a}	Y^{8}	Y^{7b}	Y^{6b}	R
7301	D	H	H	H	H	$-CH_3$
7302	H	D	H	H	H	$-CH_3$
7303	H	H	D	H	H	$-CH_3$
7304	D	D	H	H	H	$-CH_3$
7305	D	H	D	H	H	$-CH_3$
7306	D	H	H	D	H	$-CH_3$
7307	D	H	H	H	D	$-CH_3$
7308	H	D	D	H	H	$-CH_3$
7309	H	D	H	D	H	$-CH_3$
7310	D	D	D	H	H	$-CH_3$
7311	D	D	H	D	H	$-CH_3$
7312	D	D	H	H	D	$-CH_3$
7313	D	H	D	D	H	$-CH_3$
7314	D	H	D	H	D	$-CH_3$
7315	H	D	D	D	H	$-CH_3$
7316	D	D	D	D	H	$-CH_3$
7317	D	D	D	H	D	$-CH_3$
7318	D	D	H	D	D	$-CH_3$
7319	D	H	H	H	H	$-CD_3$
7320	H	D	H	H	H	$-CD_3$
7321	H	H	D	H	H	$-CD_3$
7322	D	D	H	H	H	$-CD_3$
7323	D	H	D	H	H	$-CD_3$
7324	D	H	H	D	H	$-CD_3$
7325	D	H	H	H	D	$-CD_3$
7326	H	D	D	H	H	$-CD_3$
7327	H	D	H	D	H	$-CD_3$
7328	D	D	D	H	H	$-CD_3$
7329	D	D	H	D	H	$-CD_3$
7330	D	D	H	H	D	$-CD_3$
7331	D	H	D	D	H	$-CD_3$
7332	D	H	D	H	D	$-CD_3$
7333	H	D	D	D	H	$-CD_3$

7334	D	D	D	D	H	$-CD_3$
7335	D	D	D	H	D	$-CD_3$
7336	D	D	H	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00278] In one embodiment, the compound is a compound of Formula (B-I-y):



(B-I-y)

or a pharmaceutically acceptable form thereof.

[00279] In one embodiment, the compound is a compound of Formula (B-I-y) selected from any one of the compounds in Table 74.

Table 74. Exemplary compounds of Formula (B-I-y)

Compound	Y^{6a}	Y^{7a}	Y^{8}	Y^{7b}	Y^{6b}	R
7401	D	H	H	H	H	$-CH_3$
7402	H	D	H	H	H	$-CH_3$
7403	H	H	D	H	H	$-CH_3$
7404	D	D	H	H	H	$-CH_3$
7405	D	H	D	H	H	$-CH_3$
7406	D	H	H	D	H	$-CH_3$
7407	D	H	H	H	D	$-CH_3$
7408	H	D	D	H	H	$-CH_3$
7409	H	D	H	D	H	$-CH_3$
7410	D	D	D	H	H	$-CH_3$
7411	D	D	H	D	H	$-CH_3$

7412	D	D	H	H	D	$-CH_3$
7413	D	H	D	D	H	$-CH_3$
7414	D	H	D	H	D	$-CH_3$
7415	H	D	D	D	H	$-CH_3$
7416	D	D	D	D	H	$-CH_3$
7417	D	D	D	H	D	$-CH_3$
7418	D	D	H	D	D	$-CH_3$
7419	D	H	H	H	H	$-CD_3$
7420	H	D	H	H	H	$-CD_3$
7421	H	H	D	H	H	$-CD_3$
7422	D	D	H	H	H	$-CD_3$
7423	D	H	D	H	H	$-CD_3$
7424	D	H	H	D	H	$-CD_3$
7425	D	H	H	H	D	$-CD_3$
7426	H	D	D	H	H	$-CD_3$
7427	H	D	H	D	H	$-CD_3$
7428	D	D	D	H	H	$-CD_3$
7429	D	D	H	D	H	$-CD_3$
7430	D	D	H	H	D	$-CD_3$
7431	D	H	D	D	H	$-CD_3$
7432	D	H	D	H	D	$-CD_3$
7433	H	D	D	D	H	$-CD_3$
7434	D	D	D	D	H	$-CD_3$
7435	D	D	D	H	D	$-CD_3$
7436	D	D	H	D	D	$-CD_3$

or a pharmaceutically acceptable form thereof.

[00280] In some embodiments, the compounds provided herein, including any compound specifically provided in the tables above, have an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99%. In one embodiment, the enantiomeric excess is at least 50%. In one embodiment, the enantiomeric excess is at least 75%. In one embodiment, the enantiomeric excess is at least 90%. In one embodiment, the enantiomeric excess is at least 95%. In one embodiment, the enantiomeric excess is at least 99%. In one embodiment, the compound is Coompound 101. In one embodiment, the compound is Coompound 201. In one embodiment, the compound is Coompound 301. In one embodiment, the compound is

Coompound 401. In one embodiment, the compound is Coompound 501. In one embodiment, the compound is Coompound 601.

[00281] In another set of embodiments, provided herein are the corresponding *R*-enantiomers of the *S*-enantiomer compounds provided herein, including any compound specifically provided in the tables above.

[00282] In another set of embodiments, provided herein are the corresponding racemic mixtures of the *S*-enantiomer compounds provided herein, including any compound specifically provided in the tables above.

[00283] In some embodiments, for the compounds provided herein, including any compound specifically provided in the tables above, each position designated as deuterium independently has a minimum isotopic enrichment factor of at least 1000 (15% deuterium incorporation), at least 2000 (30% deuterium incorporation), at least 3000 (45% deuterium incorporation), at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium atom.

[00284] In one embodiment, for the compounds provided herein, including any compound specifically provided in the tables above, wherein Y^1 is designated as deuterium, Y^1 has a minimum isotopic enrichment factor of at least 1000 (15% deuterium incorporation), at least 2000 (30% deuterium incorporation), at least 3000 (45% deuterium incorporation), at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium atom. In one embodiment, the deuterium incorporation at Y^1 is at least 52.5%. In one embodiment, the deuterium incorporation at Y^1 is at least 75%. In one embodiment, the deuterium incorporation at Y^1 is at least 90%. In one embodiment, the deuterium incorporation at Y^1 is at least 95%. In one embodiment, the deuterium incorporation at Y^1 is at least 99%. In one embodiment, the compound is Coompound 101. In one embodiment, the compound is Coompound 201. In one embodiment, the compound is Coompound 301. In one embodiment, the compound is Coompound 401. In one embodiment, the compound is Coompound 501. In one embodiment, the compound is Coompound 601.

[00285] The synthetis of the compounds provided herein may be readily achieved by synthetic chemists of oridinary skill by reference to the exemplary synthesis and examples provided herein. Analogous procedures used for the preparation of certain non-deuterium enriched isoquinolinone and quinazolinone compounds are provided in International Application Publication Nos. WO 2015/051244 and WO 2015/143012, the entireties of which are incorporated herein by reference.

METHODS OF TREATMENT, PREVENTION AND/OR MANAGEMENT

[00286] In certain embodiments, provided herein is a composition (*e.g.*, a pharmaceutical composition) comprising a compound described herein and a pharmaceutically acceptable excipient. In some embodiments, provided herein is a method of inhibiting a PI3 kinase, comprising contacting the PI3 kinase with an effective amount of a compound or a pharmaceutical composition described herein. In certain embodiments, a method is provided for inhibiting a PI3 kinase wherein said PI3 kinase is present in a cell. The inhibition can take place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, among others. In certain embodiments, a second therapeutic agent is administered to the subject.

[00287] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods provided herein can comprise contacting PI3 kinase gamma isoform with an effective amount of a compound or a pharmaceutical composition provided herein. In an embodiment, such contact can occur in a cell.

[00288] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform.

[00289] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase delta isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods provided herein can comprise contacting PI3 kinase delta isoform with an effective amount of a compound or a pharmaceutical composition provided herein. In an embodiment, such contact can occur in a cell.

[00290] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase delta isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase delta isoform over PI3 kinase alpha or beta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase delta isoform over PI3 kinase alpha or beta isoform.

[00291] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase delta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods provided herein can comprise contacting PI3 kinase gamma isoform with an effective amount of a compound or a pharmaceutical composition provided herein. In an embodiment, such contact can occur in a cell.

[00292] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase delta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or a pharmaceutical composition provided herein to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with PI3 kinase, said method comprising selectively modulating the PI3 kinase gamma isoform over PI3 kinase delta isoform by administering an amount of a compound or a pharmaceutical composition provided herein to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase gamma isoform over PI3 kinase delta isoform.

[00293] In certain embodiments, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from a disease or disorder, comprising administering to the subject an effective amount of a compound provided herein.

[00294] In certain embodiments, provided herein is a method of treating or preventing a PI3K mediated disease or disorder in a subject, comprising administering to the subject an effective amount of a compound provided herein. In certain embodiments, provided herein is a method of treating a PI3K mediated disease or disorder in a subject, comprising administering to the subject an effective amount of a compound provided herein.

[00295] In some embodiments, the disease or disorder is an inflammatory disease, an immune disease, or a respiratory disease, In certain embodiments, provided herein is a method of treating an inflammatory disease, an immune disease, or a respiratory disease, comprising administering to the subject an effective amount of a compound provided herein.

[00296] In some embodiments, the disorder treated by the methods or compounds provided herein is a cancer. In some embodiments, the cancer is a solid or soft tissue tumor (*e.g.*, a carcinoid, carcinoma or sarcoma), a hematopoietic tissue tumor (*e.g.*, a heme malignancy), or a metastatic lesion, *e.g.*, a metastatic lesion of any of the cancers or tumors provided herein. In one embodiment, the cancer is metastatic cancer to the bone.

[00297] In one embodiment, the cancer treated by the methods or compounds provided herein is a a soft tissue tumor, a heme malignancy, or a hematological cancer. In one embodiment, the cancer is acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), myeloproliferative disorders, mast cell cancer, Hodgkin disease, non-Hodgkin lymphomas, diffuse large B-cell lymphoma, human lymphotrophic virus type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or multiple myeloma (MM). In one embodiment, the cancer is leukemia or lymphoma. In one embodiment, the leukemia is B-cell acute lymphoblastic leukemia (B-ALL), acute myeloid leukemia (AML), acute lymphoblastic leukemia, chronic myeloid leukemia, hairy cell leukemia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), myelodysplastic syndrome (MDS), or mast cell cancer. In one embodiment, the lymphoma is diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell or Burkitt lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, Hodgkin disease, or non-Hodgkin lymphomas, or a metastatic lesion thereof.

[00298] In one embodiment, the cancer treated by the methods or compounds provided herein is a solid tumor (*e.g.*, a carcinoid, carcinoma or sarcoma), or a metastatic lesion thereof. In one embodiment, the cancer is a lung cancer (*e.g.*, non-small cell lung cancer or small cell lung cancer); a skin cancer; a melanoma; a prostate cancer; a glioblastoma; an endometrial cancer; a pancreatic cancer (*e.g.*, pancreatic adenocarcinoma (*e.g.*, pancreatic ductal adenocarcinoma (PDA)); a renal cell carcinoma; a colorectal cancer; a breast cancer (*e.g.*, triple negative breast cancer); a thyroid cancer; a sarcoma, a liver or hepatocellular cancer (HCC), a head and neck cancer, a cervical or vulvar cancer, an esophageal cancer, a gastric cancer, an adrenal cancer, or an ovarian cancer, or a metastatic lesion thereof. In one embodiment, the solid tumor is prostate cancer, breast cancer, or a glioblastoma, or a metastatic lesion thereof.

[00299] In some embodiments, the cancer or tumor treated is a solid, fibrotic tumor chosen from one or more of pancreatic (*e.g.*, pancreatic adenocarcinoma or pancreatic ductal adenocarcinoma), breast, colorectal, colon, lung (*e.g.*, a small or non-small cell lung cancer), skin, ovarian, prostate, cervix, gastrointestinal (*e.g.*, carcinoid or stromal), stomach, head and neck, kidney, brain cancer, or a metastatic lesion thereof.

[00300] In some embodiments, the cancer or tumor treated using the methods or compounds provided herein is a cancer or tumor chosen from one or more of the head, neck, nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, salivary glands, paragangliomas, pancreas, stomach, skin, esophagus, endometrium, liver and biliary tree, bone, intestine, colon, rectum, ovaries, prostate, lung, breast, lymphatic system, blood, bone marrow central nervous system, brain, or a metastatic lesion thereof.

[00301] In some embodiments, the disorder treated by the methods or compounds provided herein is an inflammatory disease or an immune disease. In one embodiment, the inflammatory disease or the immune disease is asthma, emphysema, allergy, dermatitis, arthritis (*e.g.*, rheumatoid arthritis), psoriasis, lupus erythematosus, graft versus host disease, inflammatory bowel disease, eczema, scleroderma, Crohn's disease, or multiple sclerosis. In one embodiment, the disorder is rheumatoid arthritis. In one embodiment, the disorder is rheumatoid arthritis, and the amount of the compound is effective to ameliorate one or more symptoms associated with rheumatoid arthritis, wherein the symptom associated with rheumatoid arthritis is independently a reduction in the swelling of the joints, a reduction in serum anti collagen levels, a reduction in bone resorption, a reduction in cartilage damage, a reduction in pannus, or a reduction in inflammation.

[00302] In some embodiments, the disorder treated by the methods or compounds provided herein is a respiratory disease. In one embodiment, the respiratory disease is asthma, chronic obstructive pulmonary

disease (COPD), chronic bronchitis, emphysema, or bronchiectasis. In one embodiment, the disorder is asthma.

[00303] In certain embodiments, a method is provided for selectively inhibiting a PI3 kinase gamma isoform over PI3 kinase alpha or beta isoform wherein the inhibition takes place in a subject suffering from a respiratory disease. In one embodiment, the respiratory disease is asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or bronchiectasis. In one embodiment, the respiratory disease is asthma. In one embodiment, the respiratory disease is COPD.

[00304] In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from a cancer, comprising administering to the subject an effective amount of a compound provided herein. In one embodiment, the cancer is selected from acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), myeloproliferative disorders, mast cell cancer, Hodgkin disease, non-Hodgkin lymphomas, diffuse large B-cell lymphoma, human lymphotrophic virus-type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, acute lymphoblastic leukemia (ALL), B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or multiple myeloma (MM). In one embodiment, the cancer is leukemia or lymphoma. In one embodiment, the leukemia is selected from B-cell acute lymphoblastic leukemia (B-ALL), acute lymphocytic leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), myelodysplastic syndrome (MDS), or mast cell cancer. In one embodiment, the lymphoma is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell or Burkitt lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, AIDS-related lymphoma, adult T-cell lymphoma, Hodgkin disease, or non-Hodgkin lymphomas. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

[00305] In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from an inflammatory disease or an immune disease, comprising administering to the subject an effective amount of a compound provided herein. In one embodiment, the inflammatory disease or immune disease is asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, graft versus host disease, inflammatory bowel disease, eczema, scleroderma, Crohn's disease, or multiple sclerosis. In one embodiment, the inflammatory disease or immune disease is rheumatoid arthritis. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

[00306] In one embodiment, provided herein is a method of inhibiting a PI3 kinase in a subject suffering from a respiratory disease, comprising administering to the subject an effective amount of a compound provided herein. In one embodiment, the respiratory disease is asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or bronchiectasis. In one embodiment, the respiratory disease is asthma. In one embodiment, the compound is administered in combination with one or more therapeutic agents provided herein.

[00307] In certain embodiments, provided herein is a method of inhibiting PI3K-γ in a subject, comprising administering to the subject an effective amount of a compound provided herein.

[00308] In some embodiments, a method is provided for treating a disease or disorder described herein, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition described herein to a subject.

[00309] In some embodiments, a method is provided for treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition described herein to a subject.

[00310] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a disease or disorder described herein in a subject.

[00311] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a PI3K mediated disorder in a subject.

[00312] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a disease or disorder described herein in a subject.

[00313] In some embodiments, provided herein is use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

[00314] In one embodiment, the methods provided herein further comprise administration of one or more therapeutic agents selected from chemotherapeutic agents, cytotoxic agents, and radiation. In one embodiment, the compound is administered in combination with an mTOR inhibitor. In one embodiment, the compound is administered in combination with one or more of: an agent that inhibits IgE production or activity, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, an mTOR inhibitor, rapamycin, a TORC1 inhibitor, a TORC2 inhibitor, an anti-IgE antibody, prednisone, corticosteroid, a leukotriene inhibitor, XOLAIR, ADVAIR, SINGULAIR, or SPIRIVA. In one embodiment, the

compound is administered in combination with one or more of: a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, an anti-hormone, an angiogenesis inhibitor, an anti-androgen, or an anti-receptor kinase antibody. In one embodiment, the compound is administered in combination with one or more of: Imatinib Mesylate, bortezomib, bicalutamide, gefitinib, ADRIAMYCIN, alkylating agents, alkyl sulfonates, ethylenimines, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, nitrogen mustards, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, nitrosureas, antibiotics, anti-metabolites, denopterin, methotrexate, pteropterin, trimetrexate, 5-fluorouracil (5-FU), fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens, anti-adrenals, folic acid replenisher, arabinoside, cyclophosphamide, thiotepa, taxanes, anti-hormonal agents, anti-estrogens, tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, toremifene, anti-androgens, chlorambucil, gemcitabine, 6-thioguanine; mercaptopurine; cisplatin, carboplatin, vincristine; vinorelbine, vinblastin, ifosfamide, mitomycin C, daunorubicin, doxorubicin, mitoxantrone, HERCEPTIN, AVASTIN, ERBITUX, RITUXAN, TAXOL, ARIMIDEX, TAXOTERE, or an anti-receptor tyrosine kinase antibody selected from cetuximab, panitumumab, trastuzumab, anti CD20 antibody, rituximab, tositumomab, alemtuzumab, bevacizumab, obinutuzumab (GAZYVA), and gemtuzumab. In one embodiment, the compound is administered in combination with one or more of: bortezomib, ADRIAMYCIN, alkylating agents, anti-metabolites, denopterin, pteropterin, trimetrexate, a nitrogen mustard, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, methotrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens, cyclophosphamide, taxanes, anti-hormonal agents, gemcitabine; cisplatin, carboplatin, vincristine, vinorelbine, vinblastin, ifosfamide, mitomycin C, daunorubicin, doxorubicin, mitoxantrone, HERCEPTIN, AVASTIN, ERBITUX, RITUXAN, TAXOL, ARIMIDEX, or TAXOTERE. In one embodiment, the compound is administered in combination with one or more of: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, prednisone, chloroquine, hydroxychloroquine, azathioprine, cyclophosphamide, methotrexate, cyclosporine, anti-CD20 antibodies, ENBREL, REMICADE, HUMIRA, AVONEX, or REBIF.

[00315] In one embodiment, the subject is a mammal. In one embodiment, the mammal is a human. In one embodiment, the subject is a human.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[00316] In some embodiments, provided herein are pharmaceutical compositions comprising a compound as provided herein, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives), and a pharmaceutically acceptable excipient, diluent, or carrier, including inert solid diluents and fillers, sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. In some embodiments, a pharmaceutical composition described herein includes a second active agent such as an additional therapeutic agent, (*e.g.*, a chemotherapeutic).

1. Formulations

[00317] Pharmaceutical compositions can be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (*e.g.*, those targeted for buccal, sublingual, and systemic absorption), capsules, boluses, powders, granules, pastes for application to the tongue, and intraduodenal routes; parenteral administration, including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; intravaginally or intrarectally, for example, as a pessary, cream, stent or foam; sublingually; ocularly; pulmonarily; local delivery by catheter or stent; intrathecally, or nasally.

[00318] Examples of suitable aqueous and nonaqueous carriers which can be employed in pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00319] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents, dispersing agents, lubricants, and/or antioxidants. Prevention of the action of microorganisms upon the compounds described herein can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00320] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein and/or the chemotherapeutic with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound as provided herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00321] Preparations for such pharmaceutical compositions are well-known in the art. *See, e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., *Basic and Clinical Pharmacology*, Twelfth Edition, McGraw Hill, 2011; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; *Remingtons Pharmaceutical Sciences*, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety. Except insofar as any conventional excipient medium is incompatible with the compounds provided herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, the excipient's use is contemplated to be within the scope of this disclosure.

[00322] In some embodiments, the concentration of one or more of the compounds provided in the pharmaceutical compositions provided herein is less than about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v or v/v.

[00323] In some embodiments, the concentration of one or more of the compounds as provided herein is greater than about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19.75%, about 19.50%, about 19.25%, about 19%, about 18.75%, about 18.50%, about 18.25%, about 18%, about 17.75%, about 17.50%, about 17.25%, about 17%, about 16.75%, about 16.50%, about 16.25%, about 16%, about 15.75%, about 15.50%, about 15.25%, about 15%, about 14.75%, about 14.50%, about 14.25%, about 14%, about 13.75%, about 13.50%, about 13.25%, about

13%, about 12.75%, about 12.50%, about 12.25%, about 12%, about 11.75%, about 11.50%, about 11.25%, about 11%, about 10.75%, about 10.50%, about 10.25%, about 10%, about 9.75%, about 9.50%, about 9.25%, about 9%, about 8.75%, about 8.50%, about 8.25%, about 8%, about 7.75%, about 7.50%, about 7.25%, about 7%, about 6.75%, about 6.50%, about 6.25%, about 6%, about 5.75%, about 5.50%, about 5.25%, about 5%, about 4.75%, about 4.50%, about 4.25%, about 4%, about 3.75%, about 3.50%, about 3.25%, about 3%, about 2.75%, about 2.50%, about 2.25%, about 2%, about 1.75%, about 1.50%, about 1.25%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v, or v/v.

[00324] In some embodiments, the concentration of one or more of the compounds as provided herein is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, or approximately 1% to approximately 10%, w/w, w/v or v/v.

[00325] In some embodiments, the concentration of one or more of the compounds as provided herein is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, or approximately 0.1% to approximately 0.9%, w/w, w/v or v/v.

[00326] In some embodiments, the amount of one or more of the compounds as provided herein is equal to or less than about 10 g, about 9.5 g, about 9.0 g, about 8.5 g, about 8.0 g, about 7.5 g, about 7.0 g, about 6.5 g, about 6.0 g, about 5.5 g, about 5.0 g, about 4.5 g, about 4.0 g, about 3.5 g, about 3.0 g, about 2.5 g, about 2.0 g, about 1.5 g, about 1.0 g, about 0.95 g, about 0.9 g, about 0.85 g, about 0.8 g,

about 0.75 g, about 0.7 g, about 0.65 g, about 0.6 g, about 0.55 g, about 0.5 g, about 0.45 g, about 0.4 g, about 0.35 g, about 0.3 g, about 0.25 g, about 0.2 g, about 0.15 g, about 0.1 g, about 0.09 g, about 0.08 g, about 0.07 g, about 0.06 g, about 0.05 g, about 0.04 g, about 0.03 g, about 0.02 g, about 0.01 g, about 0.009 g, about 0.008 g, about 0.007 g, about 0.006 g, about 0.005 g, about 0.004 g, about 0.003 g, about 0.002 g, about 0.001 g, about 0.0009 g, about 0.0008 g, about 0.0007 g, about 0.0006 g, about 0.0005 g, about 0.0004 g, about 0.0003 g, about 0.0002 g, or about 0.0001 g.

[00327] In some embodiments, the amount of one or more of the compounds as provided herein is more than about 0.0001 g, about 0.0002 g, about 0.0003 g, about 0.0004 g, about 0.0005 g, about 0.0006 g, about 0.0007 g, about 0.0008 g, about 0.0009 g, about 0.001 g, about 0.0015 g, about 0.002 g, about 0.0025 g, about 0.003 g, about 0.0035 g, about 0.004 g, about 0.0045 g, about 0.005 g, about 0.0055 g, about 0.006 g, about 0.0065 g, about 0.007 g, about 0.0075 g, about 0.008 g, about 0.0085 g, about 0.009 g, about 0.0095 g, about 0.01 g, about 0.015 g, about 0.02 g, about 0.025 g, about 0.03 g, about 0.035 g, about 0.04 g, about 0.045 g, about 0.05 g, about 0.055 g, about 0.06 g, about 0.065 g, about 0.07 g, about 0.075 g, about 0.08 g, about 0.085 g, about 0.09 g, about 0.095 g, about 0.1 g, about 0.15 g, about 0.2 g, about 0.25 g, about 0.3 g, about 0.35 g, about 0.4 g, about 0.45 g, about 0.5 g, about 0.55 g, about 0.6 g, about 0.65 g, about 0.7 g, about 0.75 g, about 0.8 g, about 0.85 g, about 0.9 g, about 0.95 g, about 1 g, about 1.5 g, about 2 g, about 2.5 g, about 3 g, about 3.5 g, about 4 g, about 4.5 g, about 5 g, about 5.5 g, about 6 g, about 6.5 g, about 7 g, about 7.5 g, about 8 g, about 8.5 g, about 9 g, about 9.5 g, or about 10 g.

[00328] In some embodiments, the amount of one or more of the compounds as provided herein is in the range of about 0.0001 to about 10 g, about 0.0005 to about 9 g, about 0.001 to about 8 g, about 0.005 to about 7 g, about 0.01 to about 6 g, about 0.05 to about 5 g, about 0.1 to about 4 g, about 0.5 to about 4 g, or about 1 to about 3 g.

1A. Formulations for oral administration

[00329] In some embodiments, provided herein are pharmaceutical compositions for oral administration containing a compound as provided herein, and a pharmaceutical excipient suitable for oral administration. In some embodiments, provided herein are pharmaceutical compositions for oral administration containing: (i) an effective amount of a compound provided herein; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for oral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00330] In some embodiments, the pharmaceutical composition can be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions suitable for oral administration

can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00331] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.*, about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00332] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the pharmaceutical compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants,

binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. In some embodiments, tablets can be coated by standard aqueous or nonaqueous techniques.

[00333] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.,* ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00334] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate (*e.g.,* granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00335] Disintegrants can be used in the pharmaceutical compositions as provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant can produce tablets which can disintegrate in the bottle. Too little can be insufficient for disintegration to occur and can thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) can be used to form the dosage forms of the compounds provided herein. The amount of disintegrant used can vary based upon the type of formulation and mode of administration, and can be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00336] Lubricants which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.,* peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants

include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00337] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein can be combined with various sweetening or flavoring agents, coloring matter or dyes and, for example, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00338] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00339] Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

[00340] A suitable hydrophilic surfactant can generally have an HLB value of at least about 10, while suitable lipophilic surfactants can generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.,* hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00341] Hydrophilic surfactants can be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides;

lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00342] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00343] Ionic surfactants can be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00344] Hydrophilic non-ionic surfactants can include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00345] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00346] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, non-limiting examples of lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00347] In one embodiment, the pharmaceutical composition can include a solubilizer to ensure good solubilization and/or dissolution of a compound as provided herein and to minimize precipitation of the compound. This can be especially important for pharmaceutical compositions for non-oral use, *e.g.*, pharmaceutical compositions for injection. A solubilizer can also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the pharmaceutical composition as a stable or homogeneous solution or dispersion.

[00348] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl

isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00349] Mixtures of solubilizers can also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. In some embodiments, solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00350] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer can be limited to a bioacceptable amount, which can be readily determined by one of skill in the art. In some circumstances, it can be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the pharmaceutical composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of about 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer can also be used, such as about 5%, 2%, 1% or even less. Typically, the solubilizer can be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00351] The pharmaceutical composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, oils, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00352] Exemplary preservatives can include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00353] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride,

cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[00354] In addition, an acid or a base can be incorporated into the pharmaceutical composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Examples can include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00355] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

1B. Formulations for Parenteral Administration

[00356] In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing a compound as provided herein, and a pharmaceutical excipient suitable for parenteral administration. In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing: (i) an effective amount of a compound provided herein; optionally

(ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for parenteral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00357] The forms in which the pharmaceutical compositions provided herein can be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00358] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed.

[00359] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00360] Sterile injectable solutions are prepared by incorporating a compound as provided herein in the required amount in the appropriate solvent with various other ingredients as enumerated above, as appropriate, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the appropriate other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional ingredient from a previously sterile-filtered solution thereof.

[00361] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. Injectable compositions can contain from about 0.1 to about 5% w/w of a compound as provided herein.

1C. Formulations for Topical Administration

[00362] In some embodiments, provided herein are pharmaceutical compositions for topical (*e.g.*, transdermal) administration containing a compound as provided herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for topical administration containing: (i) an effective amount of a compound provided herein; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for topical administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00363] Pharmaceutical compositions provided herein can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation can provide more immediate exposure of the active ingredient to the chosen area.

[00364] The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00365] Another exemplary formulation for use in the methods provided herein employs transdermal delivery devices ("patches"). Such transdermal patches can be used to provide continuous or discontinuous infusion of a compound as provided herein in controlled amounts, either with or without another agent.

[00366] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.,* U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00367] Suitable devices for use in delivering intradermal pharmaceutically acceptable compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499;

5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00368] Topically–administrable formulations can, for example, comprise from about 1% to about 10% (w/w) of a compound provided herein relative to the total weight of the formulation, although the concentration of the compound provided herein in the formulation can be as high as the solubility limit of the compound in the solvent. In some embodiments, topically–administrable formulations can, for example, comprise from about 1% to about 9% (w/w) of a compound provided herein, such as from about 1% to about 8% (w/w), further such as from about 1% to about 7% (w/w), further such as from about 1% to about 6% (w/w), further such as from about 1% to about 5% (w/w), further such as from about 1% to about 4% (w/w), further such as from about 1% to about 3% (w/w), and further such as from about 1% to about 2% (w/w) of a compound provided herein. Formulations for topical administration can further comprise one or more of the additional pharmaceutically acceptable excipients described herein.

1D. Formulations for Inhalation Administration

[00369] In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing a compound as provided herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing: (i) an effective amount of a compound provided herein; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for inhalation administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00370] Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid

or solid pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local or systemic effect. Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, *e.g.,* orally or nasally, from devices that deliver the formulation in an appropriate manner.

1E. Formulations for Ocular Administration

[00371] In some embodiments, the disclosure provides a pharmaceutical composition for treating ophthalmic disorders. The pharmaceutical composition can contain an effective amount of a compound as provided herein and a pharmaceutical excipient suitable for ocular administration. Pharmaceutical compositions suitable for ocular administration can be presented as discrete dosage forms, such as drops or sprays each containing a predetermined amount of an active ingredient a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Other administration foms include intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds as provided herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film. It is contemplated that all local routes to the eye can be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtascleral and suprachoroidal administration. Systemic or parenteral administration can be feasible including, but not limited to intravenous, subcutaneous, and oral delivery. An exemplary method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtascleral administration of a gel or cream formulation.

[00372] Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including, but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethyene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. In some

embodiments, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (*e.g.,* sodium chloride, etc.), buffer agent (*e.g.,* boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (*e.g.,* benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (*e.g.,* saccharide such as lactose, mannitol, maltose, etc.; *e.g.,* hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; *e.g.,* mucopolysaccharide such as chondroitin sulfate, etc.; *e.g.,* sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[00373] In some cases, the colloid particles include at least one cationic agent and at least one non-ionic sufactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quarternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases, the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, rnyristylalkonium halide, stearalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethenium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising poluoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

1F. Formulations for Controlled Release Administration

[00374] In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing a compound as provided herein, and a pharmaceutical excipient suitable for controlled release administration. In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing: (i) an effective amount of a compound provided herein; optionally (ii) an effective amount of one or more second agents; and (iii) one or more

pharmaceutical excipients suitable for controlled release administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00375] Active agents such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500 each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled release of one or more active agents using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active agents provided herein. Thus, the pharmaceutical compositions provided encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

[00376] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non controlled counterparts. In some embodiments, the use of a controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the disease, disorder, or condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00377] In some embodiments, controlled release formulations are designed to initially release an amount of a compound as provided herein that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of the compound in the body, the compound should be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active agent can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[00378] In certain embodiments, the pharmaceutical composition can be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump can be used (*see*, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al., Surgery* 88:507 (1980); Saudek *et al., N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, *e.g.*, thus requiring only a fraction of the systemic dose (*see*, *e.g.*, Goodson, *Medical Applications of Controlled Release*, 115-138 (vol. 2, 1984). Other controlled release systems are discussed in the review by Langer, *Science* 249:1527-1533 (1990). The one or more active agents can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The one or more active agents then diffuse through the outer polymeric membrane in a release rate controlling step. The percentage of active agent in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

2. Dosage

[00379] A compound described herein can be delivered in the form of pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more compounds described herein and/or one or more additional therapeutic agents such as a chemotherapeutic, formulated together with one or more pharmaceutically acceptable excipients. In some instances, the compound described herein and the additional therapeutic agent are administered in separate pharmaceutical compositions and can (*e.g.*, because of different physical and/or chemical characteristics) be administered by different routes (*e.g.*, one therapeutic is administered orally, while the other is administered intravenously). In other instances, the compound described herein and the additional therapeutic agent can be administered separately, but via the same route (*e.g.*, both orally or both intravenously). In still other instances, the

compound described herein and the additional therapeutic agent can be administered in the same pharmaceutical composition.

[00380] The selected dosage level will depend upon a variety of factors including, for example, the activity of the particular compound employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[00381] In general, a suitable daily dose of a compound described herein and/or a chemotherapeutic will be that amount of the compound which, in some embodiments, can be the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described herein. Generally, doses of the compounds described herein for a patient, when used for the indicated effects, will range from about 0.0001 mg to about 100 mg per day, or about 0.001 mg to about 100 mg per day, or about 0.01 mg to about 100 mg per day, or about 0.1 mg to about 100 mg per day, or about 0.0001 mg to about 500 mg per day, or about 0.001 mg to about 500 mg per day, or about 0.01 mg to 1000 mg, or about 0.01 mg to about 500 mg per day, or about 0.1 mg to about 500 mg per day, or about 1 mg to 50 mg per day, or about 5 mg to 40 mg per day. An exemplary dosage is about 10 to 30 mg per day. In some embodiments, for a 70 kg human, a suitable dose would be about 0.05 to about 7 g/day, such as about 0.05 to about 2.5 g/day. Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. In some instances, dosage levels below the lower limit of the aforesaid range can be more than adequate, while in other cases still larger doses can be employed without causing any harmful side effect, *e.g.,* by dividing such larger doses into several small doses for administration throughout the day.

[00382] In some embodiments, the compounds can be administered daily, every other day, three times a week, twice a week, weekly, or bi-weekly. The dosing schedule can include a "drug holiday," *e.g.*, the drug can be administered for two weeks on, one week off, or three weeks on, one week off, or four weeks on, one week off, etc., or continuously, without a drug holiday. The compounds can be administered orally, intravenously, intraperitoneally, topically, transdermally, intramuscularly, subcutaneously, intranasally, sublingually, or by any other route.

[00383] In some embodiments, a compound as provided herein is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, or more than six times per

day. Dosing can be about once a month, about once every two weeks, about once a week, or about once every other day. In another embodiment, a compound as provided herein and another agent are administered together from about once per day to about 6 times per day. In another embodiment, the administration of a compound as provided herein and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6 days, about 10 days, about 14 days, about 28 days, about two months, about six months, or about one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00384] Administration of the pharmaceutical compositions as provided herein can continue as long as necessary. In some embodiments, an agent as provided herein is administered for more than about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 14, or about 28 days. In some embodiments, an agent as provided herein is administered for less than about 28, about 14, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 day. In some embodiments, an agent as provided herein is administered chronically on an ongoing basis, *e.g.,* for the treatment of chronic effects.

[00385] Since the compounds described herein can be administered in combination with other treatments (such as additional chemotherapeutics, radiation or surgery), the doses of each agent or therapy can be lower than the corresponding dose for single-agent therapy. The dose for single-agent therapy can range from, for example, about 0.0001 to about 200 mg, or about 0.001 to about 100 mg, or about 0.01 to about 100 mg, or about 0.1 to about 100 mg, or about 1 to about 50 mg per kilogram of body weight per day. In some embodiments, the dose is about 1 mg/kg, about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 50 mg/kg, about 75 mg/kg, or about 100 mg/kg per day. In some embodiments, the dose is about 1 mg/kg, about 7.5 mg/kg, about 20 mg/kg, or about 50 mg/kg per day.

[00386] When a compound provided herein, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein unit dose forms of the agent and the compound provided herein can be adjusted accordingly.

3. Kits

[00387] In some embodiments, provided herein are kits. The kits can include a compound or pharmaceutical composition as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the pharmaceutical composition, and/or which describe dosing, administration, side effects,

drug interactions, or other information useful to the health care provider. Such information can be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials.

[00388] In some embodiments, a memory aid is provided with the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

[00389] The kit can further contain another agent. In some embodiments, the compound as provided herein and the agent are provided as separate pharmaceutical compositions in separate containers within the kit. In some embodiments, the compound as provided herein and the agent are provided as a single pharmaceutical composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.,* measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and can be included in the kit. In other embodiments, kits can further comprise devices that are used to administer the active agents. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also, in some embodiments, be marketed directly to the consumer.

[00390] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. The strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00391] Kits can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active agents. For example, if an active agent is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in

which the active agent can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00392] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.,* about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

EXAMPLES

CHEMICAL EXAMPLES

[00393] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art.

[00394] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, *e.g.,* taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period that is, for example, about 1 to about 24 hours; reactions left to run overnight in some embodiments can average a period of about 16 hours.

[00395] The terms "solvent," "organic solvent," and "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

[00396] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure, such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples herein below. However, other equivalent separation or isolation procedures can also be used.

[00397] When desired, the (*R*)- and (*S*)-isomers of the non-limiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Further, atropisomers (i.e., stereoisomers from hindered rotation about single bonds) of compounds provided herein can be resolved or isolated by methods known to those skilled in the art. For example, certain B substituents with ortho or meta substituted phenyl may form atropisomers, where they may be separated and isolated.

[00398] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

[00399] In some embodiments, compounds provided herein can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing

these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, *e.g.*, from Aldrich Chemical Company (Milwaukee, WI) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

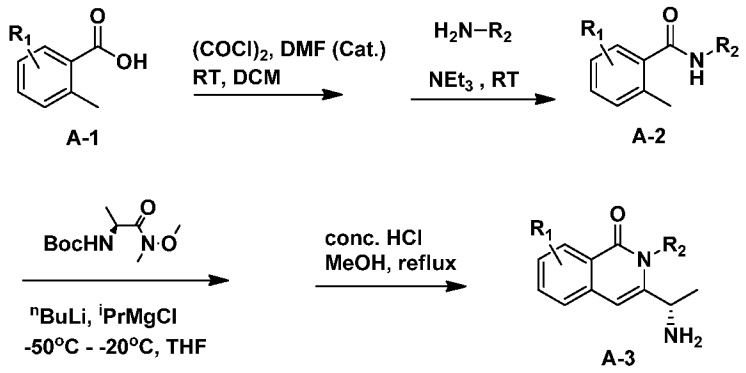
[00400] The discussion below is offered to illustrate certain of the diverse methods available for use in making the compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

GENERAL SYNTHETIC METHODS

[00401] The compounds herein being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments, and are not intended to limit these aspects and embodiments.

[00402] It is to be understood that isotopically enriched compounds provided herein can be prepared by the general methods described herein when corresponding isotopically enriched (*e.g.*, deuterium enriched) starting material, intermediate, and/ro reagents are used.

(i) General method for the synthesis of amine cores:



Method A

[00403] General conditions for the preparation of (*S*)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

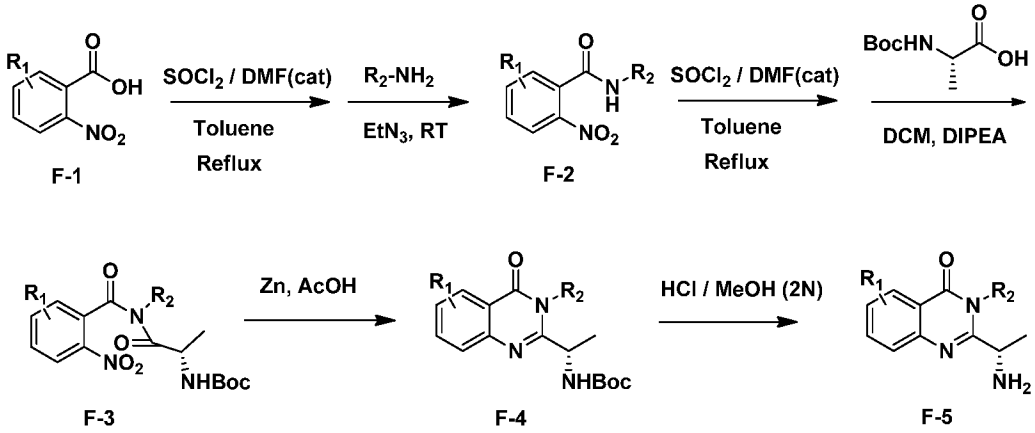
[00404] To a stirred mixture of a given *o*-methylbenzoic acid (**A-1**) (1.5 mol, 1 eq) and DMF (2 mL) in DCM (1275 mL) at RT, oxalyl chloride (1.65 mol, 1.1 eq) is added over 5 min and the resulting mixture is stirred at RT for 2 h. The mixture is then concentrated *in vacuo*. The residue is dissolved in DCM (150 mL) and the resulting solution (solution **A**) is used directly in the next step.

[00405] To a stirred mixture of aniline (1.58 mol, 1.05 eq) and triethylamine (3.15 mol, 2.1 eq) in DCM (1350 mL), the above solution **A** (150 mL) is added dropwise while the reaction temperature is maintained between 25 °C to 40 °C by an ice-water bath. The resulting mixture is stirred at RT for 2 h and

then water (1000 mL) is added. The organic layers are separated and washed with water (2 x 1000 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in *n*-heptanes (1000 mL) and stirred at RT for 30 min. The precipitate is collected by filtration, rinsed with heptanes (500 mL) and further dried *in vacuo* to afford the amide (**A-2**).

[00406] To a stirred mixture of amide (**A-2**) (173 mmol, 1 eq) in anhydrous THF (250 mL) at –30 °C under an argon atmosphere, a solution of *n*-butyllithium in hexanes (432 mol, 2.5 eq) is added dropwise over 30 min while keeping the inner temperature between –30 °C and –10 °C. The resulting mixture is then stirred at –30 °C for 30 min.

[00407] To a stirred mixture of (*S*)-*tert*-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (260 mmol, 1.5 eq) in anhydrous THF (250 mL) at –30 °C under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (286 mmol, 1.65 eq) is added dropwise over 30 min while keeping inner temperature between –30 °C and –10 °C. The resulting mixture is stirred at –30 °C for 30 min. This solution is then slowly added to above reaction mixture while keeping inner temperature between –30 °C and –10 °C. The resulting mixture is stirred at –15 °C for 1 h. The reaction mixture is quenched with water (50 mL) and then acidified with conc. HCl at –10 °C to 0 °C to adjust the pH to 1–3. The mixture is allowed to warm to RT and concentrated *in vacuo*. The residue is dissolved in MeOH (480 mL), and then conc. HCl (240 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo* to reduce the volume to about 450 mL. The residue is extracted with a 2:1 mixture of heptane and ethyl acetate (2 x 500 mL). The aqueous layer is basified with concentrated ammonium hydroxide to adjust the pH value to 9–10 while keeping the inner temperature between –10 °C and 0 °C. The mixture is then extracted with DCM (3 x 300 mL), washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* and the residue is dissolved in MeOH (1200 mL) at RT. To this solution, D-(-)-tartaric acid (21 g, 140 mmol, 0.8 eq) is added in one portion at RT. After stirring at RT for 30 min, a white solid precipitates and the mixture is slurried at RT for 10 h. The solid is collected by filtration and rinsed with MeOH (3 x 50 mL). The collected solid is suspended in water (500 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (3 x 200 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford the (*S*)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones (**A-3**).



Method F

[00408] To a stirred mixture of nitrobenzoic acid (**F-1**) (1.0 mol, 1.0 eq) and DMF (2.0 mL) in toluene (800 mL), thionyl chloride (292 mL, 1.0 mol, 4.0 eq) is added dropwise (over 15 min) and the resulting mixture is stirred at reflux for 1.5 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (100 mL) to form solution A, which is used directly in the next step.

[00409] To a stirred mixture of a given amine R_2-NH_2 (102.4 g, 1.1 mol, 1.1 eq) and triethylamine (280 mL, 2.0 mol, 2.0 eq) in DCM (700 mL), solution A is added dropwise while keeping the reaction temperature below 10 °C. The resulting mixture is allowed to warm to RT and then stirred at RT overnight. The reaction mixture is diluted with ice-water (1.0 L) and stirred for 15 min. The precipitate is collected by filtration, rinsed with isopropyl ether (3 x 100 mL) and petroleum ether (3 x 100 mL), and then dried *in vacuo* to afford product amide (**F-2**).

[00410] A mixture of nitro-benzamide (**F-2**) (20.0 mmol, 1.0 eq) and DMF (cat.) in toluene (60 mL) at RT, thionyl chloride (12 mL , 164 mmol, 8.2 eq) is added dropwise (over 5 min) and the resulting mixture is stirred at reflux for 2 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (10 mL) to form solution B, which is used directly in the next step.

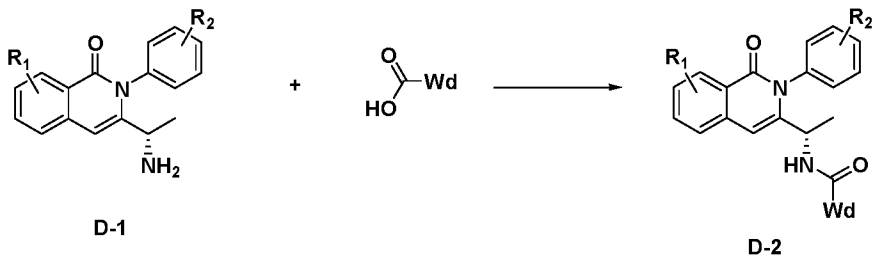
[00411] To a stirred mixture of *N*-(*tert*-butoxycarbonyl)-L-alanine (16.0 mmol, 0.8 eq) and *N,N*-diisopropylethylamine (4.0 g, 31.0 mol, 1.5 eq) in DCM (20 mL), solution B is added dropwise while keeping the reaction temperature between 0–10 °C. The resulting mixture is stirred at this temperature for 1 h and then stirred at RT overnight. The reaction mixture is quenched with ice-water (100 mL). The organic layer is separated and the aqueous layer is extracted with DCM (2 x 80 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in isopropyl ether (100 mL) for 15 min. The solid is collected by filtration and dried *in vacuo* to afford product (**F-3**).

[00412] To a suspension of zinc dust (7.2 g, 110 mmol, 10.0 eq) in glacial acetic acid (40 mL) at 15 °C, a solution of **(F-3)** (11.0 mmol, 1.0 eq) in glacial acetic acid (40 mL) is added and the resulting mixture is stirred at RT for 4 h. The mixture is poured into ice-water (200 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8. The resulting mixture is extracted with DCM (3 x 150 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (7% ethyl acetate-petroleum ether) to afford product **(F-4)**.

[00413] Compound **(F-4)** (0.5 mmol, 1.0 eq) is dissolved in hydrochloric methanol solution (2N, 20 mL) and the resulting mixture is stirred at RT for 2 h. The mixture is concentrated *in vacuo*. The residue is diluted with water (30 mL) and then neutralized with saturated aqueous $NaHCO_3$ to adjust the pH to 8 while keeping the temperature below 5 °C. The resulting mixture is extracted with DCM (3 × 30 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in petroleum ether (10 mL). The solid is collected by filtration and dried *in vacuo* to afford product **(F-5)**.

[00414] The quinazolinone **(F-5)** can be used to synthesize compounds described herein using, for example, Method D to couple the amine to W_d groups.

(ii) General methods for amide synthesis:



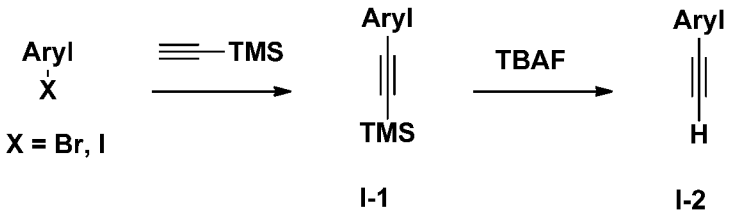
Method D

[00415] To a mixture of amine **(D-1)** (0.5 mmol, 1.0 eq), W_d-COOH carboxylic acid (0.55 mmol, 1.1 eq), and *N,N*-diisopropylethylamine (0.17 mL, 1.0 mmol, 2.0 eq) in anhydrous DMF (5 mL), 1-hydroxybenzotriazole hydrate (0.65 mmol, 1.3 eq) and EDC hydrochloride (0.65 mmol, 1.3 eq) are added sequentially and the resulting mixture is stirred at RT for 2–16 h. Ice-water or saturated sodium carbonate solution is added to the reaction mixture and then stirred for 10 min. The precipitate is collected by filtration, rinsed with water and dried *in vacuo*. The solid collected is further purified by flash column chromatography on silica gel (0–10% MeOH-DCM) to afford the product amide **(D-2)**.

Method E

[00416] A solution of amine (**D-1**) (0.25 mmol, 1 eq), W_d-COOH carboxylic acid (1.1 eq), and 1-hydroxybenzotriazole hydrate (1.3 eq) in dimethylformamide (0.1 M) is treated with diisopropylethylamine (2 eq) and then EDC hydrochloride (63 mg, 1.3 eq). The reaction mixture is stirred at ambient temperature overnight. The reaction mixture is diluted with water (5x solvent) and acetic acid (1.5 eq) is added, then the mixture is stirred in an ice bath for 40 min. The resulting precipitate is collected by filtration, and washed with water (3x 3 mL). The collected solid is dried *in vacuo* to afford amide (**D-2**).

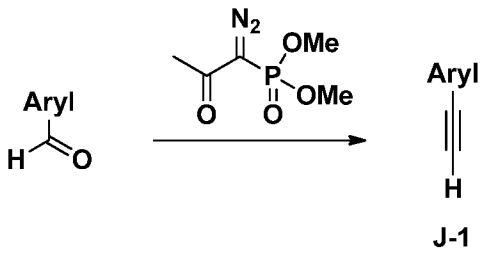
(iii) General methods for alkyne synthesis:



Method I

[00417] A sealed vessled is chared with $PdCl_2(MeCN)_2$ and X-Phos (3:1 ratio of X-Phos to $PdCl_2(MeCN)_2$, 5-15 mol% catalyst), cesium carbonate (1.5-3.0 equiv) and propionitrile (0.5 M). The mixture is stirred for 5 min after which the aryl bromide or aryl iodid substrate is added. After another 5 minutes of stirring TMS-acetylene (3.0 equiv) is added and the flask is sealed and heated at RT for 10 min follwed by 1h of heating at 95 °C. The reaction is allowed to cool after which it is concentrated directly onto silica gel and purified using flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide alkyne **I-1**.

[00418] Alkyne **I-1** (1.0 equiv) is then dissolved in tetrahydrofuran (0.13 M) and charged with TBAF (1.1 equiv, 1.0 M in tetrahydrofuran). The resulting mixture is stirred at RT for 6h after which it is poured into saturated bicarbonate solution and extracted with ethyl acetate. The organic layer is washed with brine and concentrated onto silica gel where it is purifed directly by flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide aryl alkyne **I-2**.

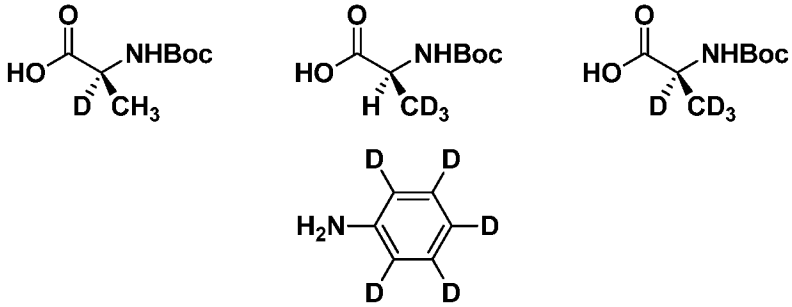


Method J

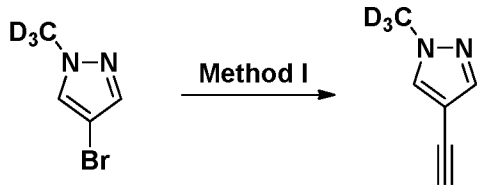
[00419] Aldehyde (1.0 equiv) is a dissolved in anhydrous methanol (0.2-0.5 mM) and charged with cesium carbonate (1.0 equiv) and cooled to 0-5 °C. Dimethyl (1-diazo-2-oxopropyl)phosphonate (1.0 equiv) is added dropwise after which the reaction is allowed to stir for 1-18h after which the crude mixture is concentrated onto silica gel and purified directly by flash silica gel chromatography to provide the desired alkyne **J-1.**

DEUTERIUM INCORPORATION

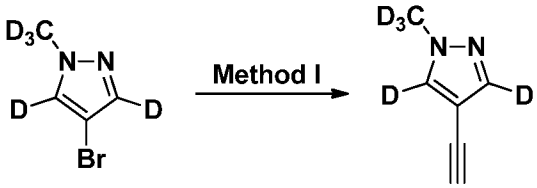
[00420] Deuterium enriched building blocks that are commercially available (*e.g.*, from Sigma-Aldrich or CDN Isotopes, Inc.) include, but are not limited to, the following:



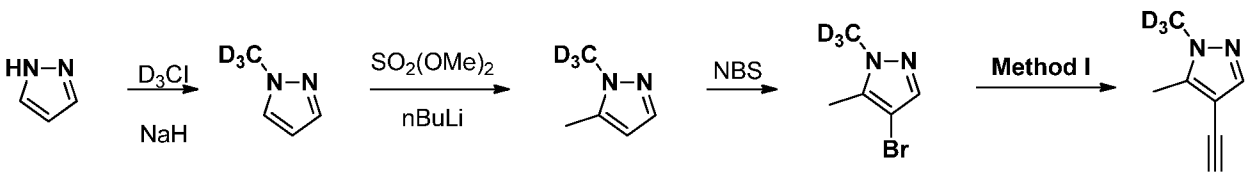
Synthesis of deuterated pyrazoles:



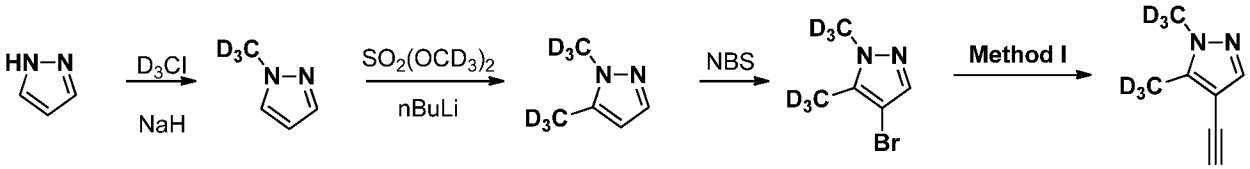
[00421] 4-Ethynyl-1-(methyl-d3)-1H-pyrazole is prepared from 4-bromo-1-(methyl-d3)-1H-pyrazole (commercially available from, *e.g.*, CombiPhos Catalysis, Inc.) based on the routes described in Method I.



[00422] 4-Ethynyl-1-(methyl-d3)-1H-pyrazole-3,5-d2 is prepared from 4-bromo-1-(methyl-d3)-1H-pyrazole-3,5-d2 (commercially available from, *e.g.*, CombiPhos Catalysis, Inc.) based on the routes described in Method I.

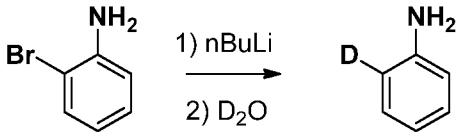


[00423] 4-Bromo-1-(methyl-d3)-5-methyl-1H-pyrazole is prepared from pyrazole in three steps based on the routes described in WO 2015/066188, the entirety of which is incorporated herein by reference. 4-Ethynyl-1-(methyl-d3)-5-methyl-1H-pyrazole is prepared from 4-bromo-1-(methyl-d3)-5-methyl-1H-pyrazole based on the routes described in Method I.

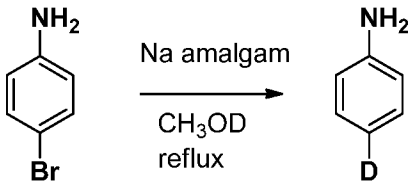


[00424] 4-Bromo-1,5-(dimethyl-d6)-1H-pyrazole is prepared from pyrazole in three steps based on the routes described in WO 2015/066188, the entirety of which is incorporated herein by reference. 4-Ethynyl-1,5-(dimethyl-d6)-1H-pyrazole is prepared from 4-bromo-1,5-(dimethyl-d6)-1H-pyrazole based on the routes described in Method I.

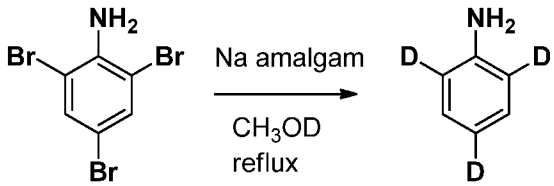
Synthesis of mono, bi, tri and tetra-substituted deuterated anilines:



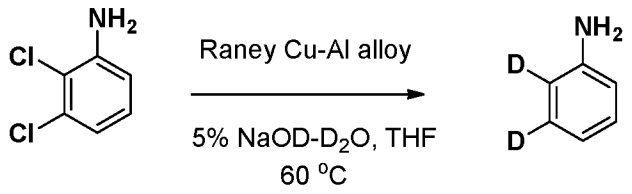
[00425] Aniline-2-d is prepared from 2-bromoaniline based on the routes described in Chi *et. al.*, *Organic Letters*, 2014, 16, 6274-6277, the entirety of which is incorporated herein by reference.



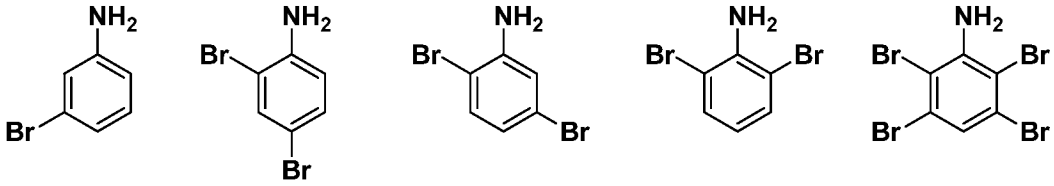
[00426] Aniline-4-d is prepared from 4-bromoaniline based on the routes described in Miura *et. al.*, *J. Org. Chem.* 1997, 62, 1188-1190, the entirety of which is incorporated herein by reference.



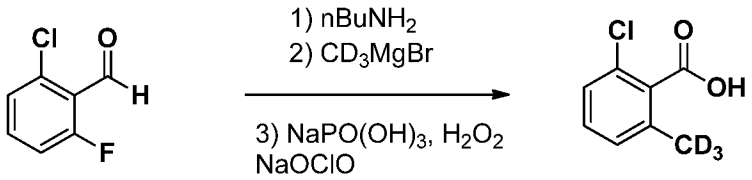
[00427] Aniline-2,4,6-d3 is prepared from 2,4,6-tribromoaniline based on the routes described in Miura *et. al.*, *J. Org. Chem.* 1997, 62, 1188-1190, the entirety of which is incorporated herein by reference.



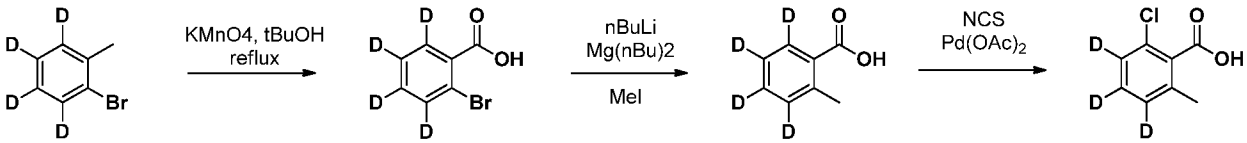
[00428] Aniline-2,3-d2 is prepared from 2,3-dichloroaniline based on the routes described in Tashiro *et al.*, *Journal of Labelled Compounds and Radiopharmaceuticals*, 1990, 28, 703-712, the entirety of which is incorporated herein by reference. Additional deuterated anilines are prepared from the following halogenated aniline using this method:



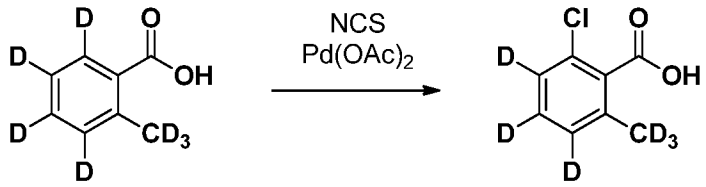
Incorporation of deuterium into quinoline:



[00429] 2-Chloro-6-(methyl-d3)benzoic acid is prepared from 2-chloro-6-fluorobenzaldehyde based on the routes described in Andrzej *et. al.*, *Org. Process Research & Development*, 2002, 6, 220-224, the entirety of which is incorporated herein by reference. Synthesis of CD_3MgBr is described in Al-Afyouni *et al.*, *J. Am. Chem. Soc.*, 2014, 136, 15457-15460, the entirety of which is incorporated herein by reference.

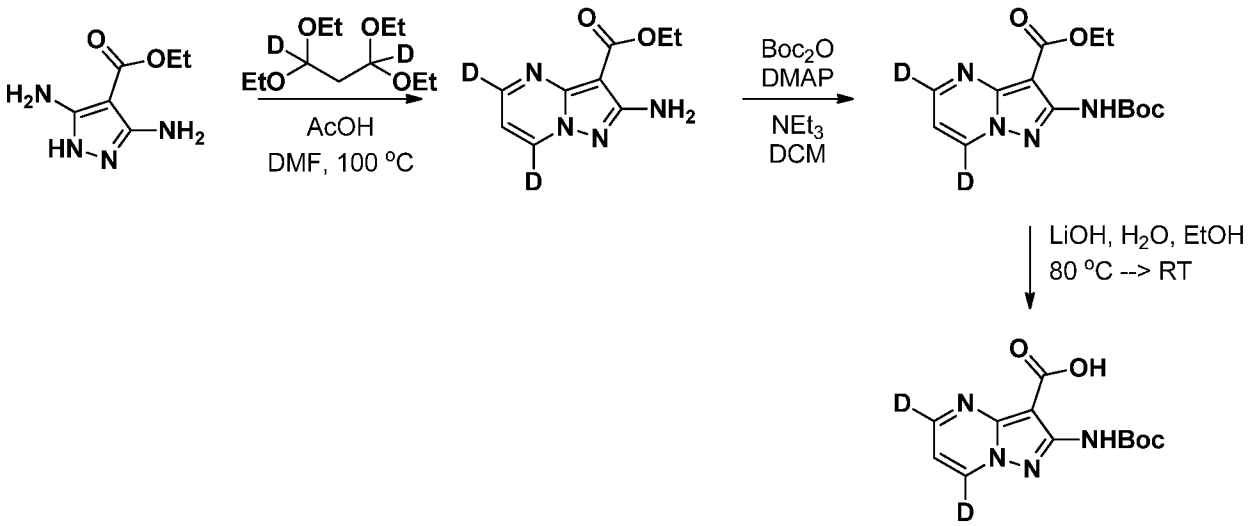


[00430] 2-Chloro-6-methylbenzoic acid-3,4,5-d3 is prepared from 1-bromo-2-methylbenzene-3,4,5,6-d4 (commercially available from, *e.g.*, CDN Isotopes, Inc.) based on the general routes described in (1) Courchay, *et al.*, Organometallics, 2006, 25, 6074-6086, (2) WO 2003/101916, and (3) WO 2001/083421, the entirety of each of which is incorporated herein by reference.



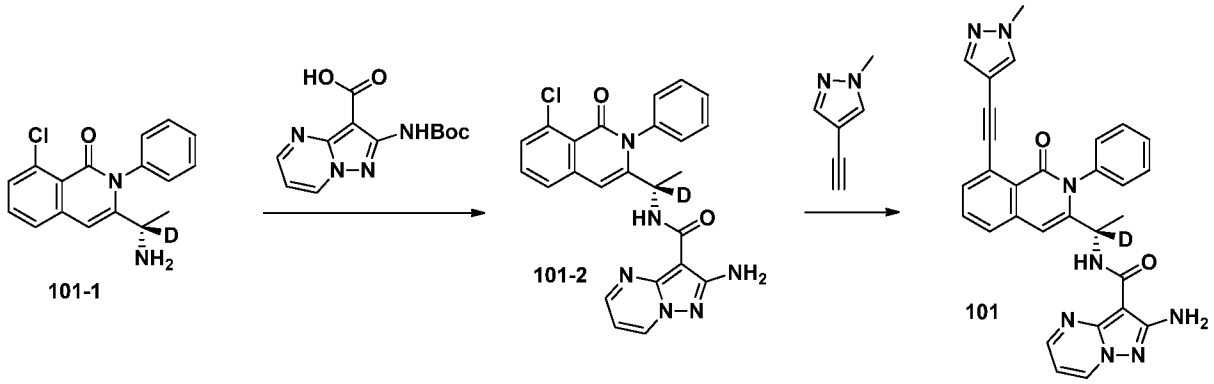
[00431] 2-Chloro-6-(methyl-d3)-benzoic acid-3,4,5-d3 is prepared from 2-(methyl-d3)benzoic acid-3,4,5,6-d4 (commercially available from, *e.g.*, CDN Isotopes, Inc.) based on the general routes described in WO 2001/083421, the entirety of which is incorporated herein by reference.

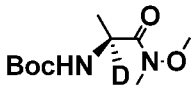
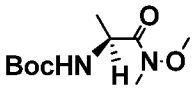
Incorporation of deuterium into pyrazolo[1,5-a]pyrimidine moiety:



[00432] Synthesis of deuterated 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid from commercially available starting materials is accomplished using the analogous procedure from WO 2015/073267, the entirety of each of which is incorporated herein by reference, except that malonaldehyde-1,3-d_2 bis(diethyl acetal) (CDN Isotopes, Inc.) is used in place of 1,1,3,3-tetramethoxy propane.

Example 1: Synthesis of Compound 101



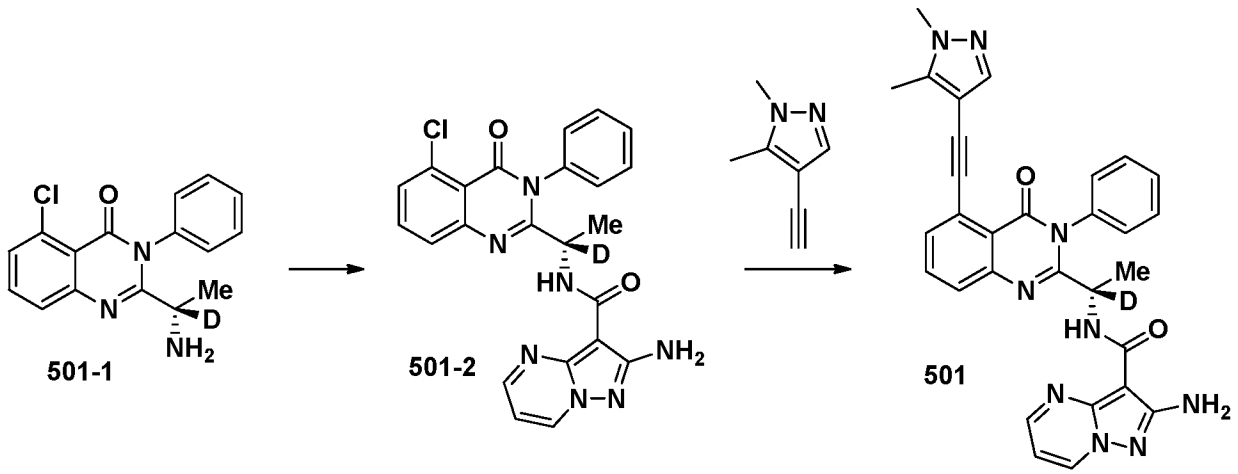
[00433] Compound 101-1 is prepared from 2-chloro-6-methylbenzoic acid based on the routes described in Method A, using  in place of  .

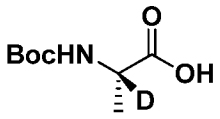
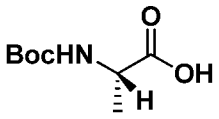
[00434] Compound 101-1 is coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid according to the following procedure: Compound A (27.4 mmol, 1.0 equiv), HOBt hydrate (1.2 equiv), 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (1.05 equiv) and EDC (1.25 equiv) are added to a 200 mL round bottomed flask with a stir bar. N,N-Dimethylforamide (50 mL) is added and the suspension is stirred at RT for 2 min. Hunig's base (4.0 equiv) is added and after which the suspension becomes homogeneous and is stirred for 22h resulting in the formation of a solid cake in the reaction flask. The solid mixture is added to water (600 mL) and stirred for 3h. The resulting cream colored solid is filtered and washed with water (2 x 100 mL) and dried. The solid is then dissolved in methylene chloride (40 mL) after which trifluoroacetic acid (10 equiv, 20 mL) is added and the reaction is stirred for 30 min at RT after which there is no more starting material by LC/MS analysis. The solution is then concentrated and coevaporated with a mixture of methylene choride/ethanol (1:1 v/v) and then dried under high vacuum overnight. The resulting solid is tirturated into 60 mL of ethanol for 1h and then collected via vacuum filtration. The beige solid is then neutralized with sodium carbonate solution (100 mL) and then transferred to a separatory funnel with methylene chloride (350 mL). The water layer is extracted with an additional 100 mL of methylene chloride. The combined organic layers are dried over sodium sulfate, filtered and concentrated under vacuum to provide a crude product that is purified using flash silica gel chromatrography to provide amide 101-2.

[00435] Amide 101-2 is placed in a sealed tube (0.67 mmol, 1.0 equiv) followed by dichlorobis(acetonitrile)palladium (15 mol%), X-Phos (45 mol%), and cesium carbonate (3.0 equiv) Propionitrile (5 mL) is added and the mixture is bubbled with Ar for 1 min. 4-Ethynyl-1-methyl-1H-

pyrazole (1.24 equiv) is added and the resulting orange mixture is sealed and stirred in an oil bath at 85 °C for 1.5h. The resulting mixture is allowed to cool at which point there is no more SM by LC/MS analysis. The mixture is then filtered through a short plug of cotton using acetonitrile and methylene chloride. The combined filtrates are concentrated onto silica gel and purified using flash silica gel chromatography. The resulting material is further purified by reverse phase HPLC to provide the desired compound 101.

Example 2: Synthesis of Compound 501



[00436] Compound 501-1 is prepared from 2-chloro-6-nitrobenzoic acid based on the routes described in Method F, using  in place of  .

[00437] Compound 501-1 is converted to compound 501-2 using the analogous procedure for compound 101-2 in Example 1.

[00438] A suspension of Compound 501-2 (0.317 mmol), Cesium carbonate (198 mg, 0.608 mmol, 2 eq.), dichlorobis(acetonitrile)palladium (II) (15 mg, 0.058 mmol, 0.2 eq.) and Xphos (87 mg, 0.182 mmol, 0.6 eq.) in propionitrile (2 mL) is bubbled with argon for 5 minutes. The mixture is charged with 4-ethynyl-1,5-dimethyl-1H-pyrazole (73 mg, 0.6 mmol, 2 eq.), heated to 95 °C and stirred for 2 hr. The resulting mixture is cooled to RT, partitioned between Ethyl acetate and water. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. . The residue is purified with silica gel chromatography to provide Compound 501.

Example 3: PI3-Kinase HTRF™ Assay

[00439] A PI3-Kinase HTRF® assay kit (cat No. 33-016) purchased from Millipore Corporation is used to screen compounds provided herein. This assay uses specific, high affinity binding of the GRP1 pleckstrin homology (PH) domain to PIP3, the product of a Class 1A or 1B PI3 Kinase acting on its physiological substrate PIP2. During the detection phase of the assay, a complex is generated between the GST-tagged PH domain and biotinylated short chain PIP3. The biotinylated PIP3 and the GST-tagged PH domain recruite fluorophores (Streptavidin-Allophycocyanin and Europium-labeled anti-GST respectively) to form the fluorescence resonance energy transfer (FRET) architecture, generating a stable time-resolved FRET signal. The FRET complex is disrupted in a competitive manner by non-biotinylated PIP3, a product formed in the PI3 Kinase assay.

[00440] PI3 Kinase α, β, γ or δ activity is assayed using the PI3 Kinase HTRF® assay kit (catalogue No. 33-016) purchased from Millipore Corporation. Purified recombinant PI3Kα (catalogue No. 14-602-K), PI3Kβ (catalogue No. 14-603-K), PI3Kγ (catalogue No. 14-558-K), and PI3Kδ (catalogue No. 14-604-K) are obtained from Millipore Corporation. Purified recombinant PI3K enzyme is used to catalyze the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2 at 10 μM) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the presence of 10 μM ATP. The assay is carried out in 384-well format and detected using a Perkin Elmer EnVision Xcite Multilabel Reader. Emission ratios are converted into percent inhibitions and imported into GraphPad Prism software. The concentration necessary to achieve inhibition of enzyme activity by 50% (IC_{50}) is calculated using concentrations ranging from 20 μM to 0.1 nM (12-point curve). IC_{50} values are determined using a nonlinear regression model available in GraphPad Prism 5.

Example 4: Chemical Stability

[00441] The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μM stock solution to an aliquot of PBS (in duplicate) to give a final assay volume of 400 μL, containing 5 μM test compound and 1% DMSO (for half-life determination a total sample volume of 700 μL is prepared). Reactions are incubated, with shaking, for 24 hours at 37 °C; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μL of the incubation mixture to 100 μL of acetonitrile and vortexing for 5 minutes. The samples are then stored at –20 °C until analysis by HPLC-MS/MS. Where desired, a control compound or a reference compound such as chlorambucil (5 μM) is tested simultaneously with a subject compound of interest, as

this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 5: Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ:

[00442] Class I PI3-Ks can be either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight *et al.*, 2004). IC_{50} values are measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM $MgCl_2$), and freshly sonicated phosphatidylinositol (100 μg/ml). Reactions are initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration of 10 or 100 μM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 μL 1N HCl followed by 160 μL $CHCl_3$:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract is spotted on TLC plates and developed for 3–4 hours in a 65:35 solution of *n*-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10–12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC_{50} determinations are repeated two to four times, and the reported value is the average of these independent measurements.

[00443] Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including, but not limited to, PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (*e.g.*, a 384 well microtiter plate). The total reaction volume is approximately 20 μL per well. In the first step, each well receives 2 μL of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration.

Next, approximately 14.5 μL of a kinase/PIP2 mixture (diluted in 1X reaction buffer) is added per well for a final concentration of 0.25–0.3 μg/mL kinase and 10 μM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start the reaction, 3.5 μL of ATP (diluted in 1X reaction buffer) is added per well for a final concentration of 10 μM ATP. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 5 μL of Stop Solution per well and then 5 μL of Detection Mix is added per well. The plate is sealed, incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC_{50}s are generated using GraphPad Prism 5.

Example 6: B Cell Activation and Proliferation Assay

[00444] The ability of one or more subject compounds to inhibit B cell activation and proliferation is determined according to standard procedures known in the art. For example, an *in vitro* cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90 μL at 50,000 cells/well in B Cell Media (RPMI + 10% FBS + Penn/Strep + 50 μM bME + 5 mM HEPES). A compound provided herein is diluted in B Cell Media and added in a 10 μL volume. Plates are incubated for 30 min at 37 °C and 5% CO_2 (0.2% DMSO final concentration). A 50 μL B cell stimulation cocktail is then added containing either 10 μg/mL LPS or 5 μg/mL F(ab')2 Donkey anti-mouse IgM plus 2 ng/mL recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37 °C and 5% CO_2. A volume of 15 μL of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37 °C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} or EC_{50} values are calculated using GraphPad Prism 5.

Example 7: Tumor Cell Line Proliferation Assay

[00445] The ability of one or more subject compounds to inhibit tumor cell line proliferation can be determined according to standard procedures known in the art. For instance, an *in vitro* cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96-well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC (*e.g.*, MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM + 10%FBS), and plated in 90 μL at 5,000 cells/well in Tumor Cell Media. A compound provided herein is diluted in Tumor Cell Media and added in a 10 μL volume. Plates are incubated for 72 hours at 37 °C and 5% CO_2. A volume of 10 μL of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37 °C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} values are calculated using GraphPad Prism 5.

Example 8: Antitumor Activity *in vivo*

[00446] The compounds described herein can be evaluated in a panel of human and murine tumor models.

Paclitaxel-Refractory Tumor Models

1. *Clinically-Derived Ovarian Carcinoma Model.*

[00447] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient. The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

2. *A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).*

[00448] A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

3. *HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).*

[00449] HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. *In vivo*, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

4. *M5076 Murine Sarcoma Model*

[00450] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel *in vivo*. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00451] One or more compounds as provided herein can be used in combination with other therapeutic agents *in vivo* in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

[00452] In one aspect, compounds provided herein may be evaluated in the following models according to methods known in the art. The dosage and schedule of administration may be varied

depending on the model. The results may be evaluated with those of selective delta inhibitors, and combinations of delta and gamma inhibitors, and/or with antibodies that block specific inhibitory receptors.

Pancreatic Models

[00453] KPC model is a transgenic mouse model of pancreatic ductal adenocarcinoma (PDA), in which there is conditional expression of both mutant KrasG12D and p53R172H alleles in pancreatic cells. Tumors develop spontaneously in this mouse over a period of 3 -6 months, and can be used to study prophylactic, as well as therapeutic efficacy with novel agents. Cells from these KPC tumors can also be adoptively transferred into syngeneic B6.129 hybrid mice, creating a model with a shorter latency period and allowing large number of animals with tumors to be synchronously established. See e.g., Cancer Cell 7:468 (2005).

[00454] Pan02 model: The murine pancreatic adenocarcinoma cell line Pan02 is a nonmetastatic tumor line, syngeneic to C57BL/6. It can be studied following s.c. injection into flank, or orthotopically following injection directly into the pancreas. See e.g., Cancer Res. 44: 717–726 (1984).

Lung Models

[00455] LLC Lewis Lung Adenocarcinoma model: LLC cells are derived from a spontaneous lung tumor from a C57BL/6 mouse and can be studied as a s.c. tumor when injected in the flank, or as an orthotopic tumor if injected i.v., following which it localizes to the lung.

[00456] LLC cells have also been modified to express a peptide from ovalbumin (LL2-OVA cells). Use of these cells, following either s.c. or i.v. injection, allows the tracking of OVA-specific CD8+ lymphocyctes and measurement of effects of therapy on the adaptive immune response against the tumor. See e.g., Science 330:827 (2010).

Breast Model

[00457] The 4T1 mammary carcinoma is a transplantable tumor cell line that grows in syngeneic BALB/c mice. It is highly tumorigenic and invasive and, unlike most tumor models, can spontaneously metastasize from the primary tumor in the mammary gland to multiple distant sites including lymph nodes, blood, liver, lung, brain, and bone. See *e.g.*, Current Protocols in Immunology Unit 20.2 (2000).

Lymphoma Model

[00458] EL4 is a C57BL/6 T thymoma and EG7 is an OVA-expressing subclone of EL4. The parental EL4 line has been modified to constitutively express luciferase, which allows non-invasive imaging of tumor growth throughout the animal using the Xenogen imaging platform.

Melanoma Model

[00459] B16 murine melanoma cells are syngeneic with C57BL/6 mice and can be studied after s.c. or i.v. injection. Placement at either site will result in metastases to lung and other organs. This model has been extensively studied in terms of the role that inhibitory receptors play in the anti-tumor immune response. See e.g., PNAS 107:4275 (2010).

Example 9: Microsome Stability Assay

[00460] The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an *in vitro* assay. For example, an *in vitro* microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf tube. Each tube contains 0.1 μL of 10.0 mg/mL NADPH; 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 425 μL of ddH_2O. Negative control (without NADPH) tube contains 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 525 μL of ddH_2O. The reaction is started by adding 1.0 μL of 10.0 mM tested compound. The reaction tubes are incubated at 37 °C. 100 μL sample is collected into new Eppendorf tube containing 300 μL cold methanol at 0, 5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 10: Plasma Stability Assay

[00461] The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. *See, e.g., Rapid Commun. Mass Spectrom.*, 10: 1019–1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4 °C prior to use. A subject compound is added from a 400 μM stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 μL (or 800 μL for half-life determination), containing 5 μM test compound and 0.5 % DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 C, or for 0, 15, 30, 45 and 60 minutes at 37 C for half life determination. Reactions are stopped by transferring 50 μL of the incubation mixture to 200 μL of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000 x g for 15

minutes at 4 °C and 120 μL of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

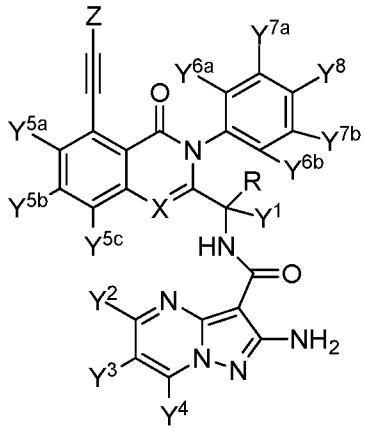
[00462] In one embodiment, one or more control or reference compounds (5 μM) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

[00463] Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

[00464] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims. Various publications, patents and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A compound of Formula (AB'):



(AB'),

or a pharmaceutically acceptable form thereof, wherein

R is C_1-C_3 alkyl optionally substituted with one or more deuterium or halogen;

X is CY^{5d} or N;

Y^1 is hydrogen or deuterium;

Y^2, Y^3, and Y^4 are each independently hydrogen or deuterium;

Y^{5a}, Y^{5b}, Y^{5c}, and Y^{5d} are each independently hydrogen or deuterium;

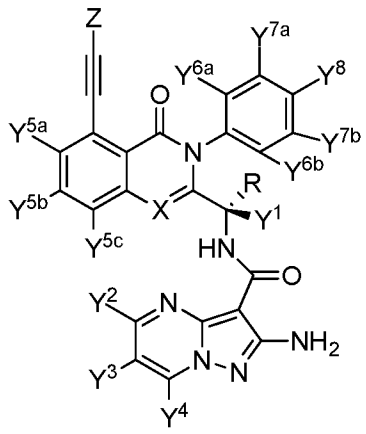
Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are each independently hydrogen, deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen;

Z is a 5- to 10-membered heteroaryl optionally substituted with one or more deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^8, and Z is or comprises a deuterium;

provided that, when Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^8 are all deuterium, at least one of R, Y^1, Y^2, Y^3, Y^4, Y^{5a}, Y^{5b}, Y^{5c}, Y^{5d}, and Z is or comprises a deuterium.

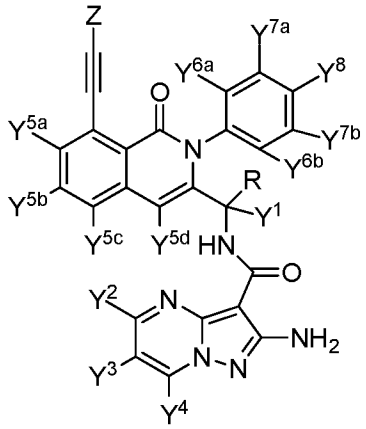
2. The compound of claim 1, wherein the compound is a compound of Formula (AB):



(AB),

or a pharmaceutically acceptable form thereof.

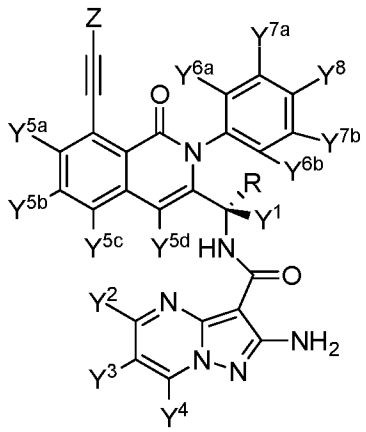
3. The compound of claim 1, wherein the compound is a compound of Formula (A'):



(A'),

or a pharmaceutically acceptable form thereof.

4. The compound of claim 1, wherein the compound is a compound of Formula (A):

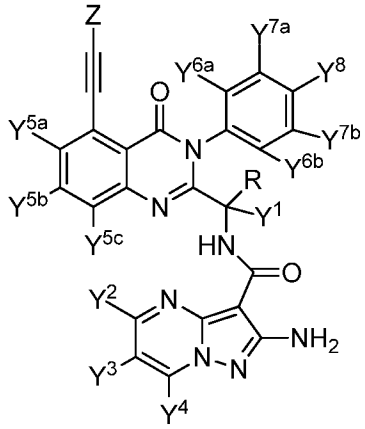


(A),

or a pharmaceutically acceptable form thereof.

5. The compound of claim 3 or 4, wherein Y^{5d} is deuterium.

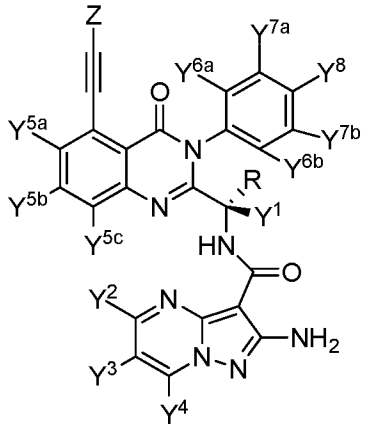
6. The compound of claim 1, wherein the compound is a compound of Formula (B'):



(B'),

or a pharmaceutically acceptable form thereof.

7. The compound of claim 1, wherein the compound is a compound of Formula (B):



(B),

or a pharmaceutically acceptable form thereof.

8. The compound of any one of claims 1–7, wherein Y^{5a} is deuterium.

9. The compound of any one of claims 1–8, wherein Y^{5b} is deuterium.

10. The compound of any one of claims 1–9, wherein Y^{5c} is deuterium.

11. The compound of any one of claims 1–7, wherein Y^{5a}, Y^{5b}, and Y^{5c} are all hydrogen.

12. The compound of any one of claims 1–7, wherein Y^{5a}, Y^{5b}, and Y^{5c} are all deuterium.

13. The compound of any one of claims 1–12, wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are all hydrogen.

14. The compound of any one of claims 1–12, wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are all deuterium.

15. The compound of any one of claims 1–12, wherein one or more of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are halogen.

16. The compound of any one of claims 1–12, wherein one or more of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, and Y^{8} are C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

17. The compound of any one of claims 1–16, wherein Z is a 6-membered heteroaryl.

18. The compound of claim 17, wherein Z is a pyridinyl or pyrimidinyl.

19. The compound of any one of claims 1–16, wherein Z is a 5-membered heteroaryl.

20. The compound of claim 19, wherein Z is a thiazolyl, pyrazolyl, or imidazolyl.

21. The compound of claim 20, wherein Z is a pyrazolyl.

22. The compound of claim 21, wherein Z is a 3-pyrazolyl.

23. The compound of claim 21, wherein Z is a 4-pyrazolyl.

24. The compound of claim 21, wherein Z is a 5-pyrazolyl.

25. The compound of any one of claims 1–24, wherein Z is substituted with one or more deuterium, halogen, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

26. The compound of claim 25, wherein Z is substituted with one or more C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

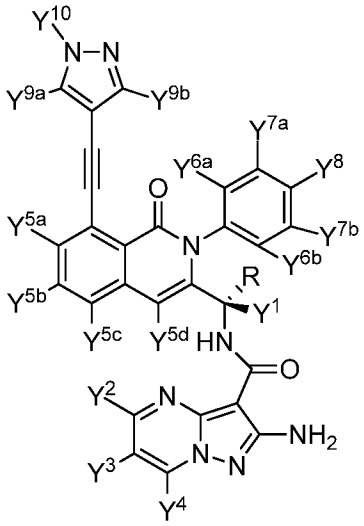
27. The compound of claim 26, wherein Z is substituted with one or two C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

28. The compound of claim 27, wherein Z is substituted with one or two methyl, wherein each instance of the methyl is independently optionally substituted with one or more deuterium or halogen.

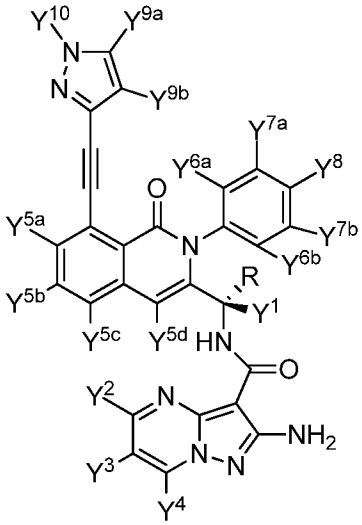
29. The compound of claim 28, wherein Z is substituted with one or two $-CH_3$.

30. The compound of claim 28, wherein Z is substituted with one or two $-CD_3$.

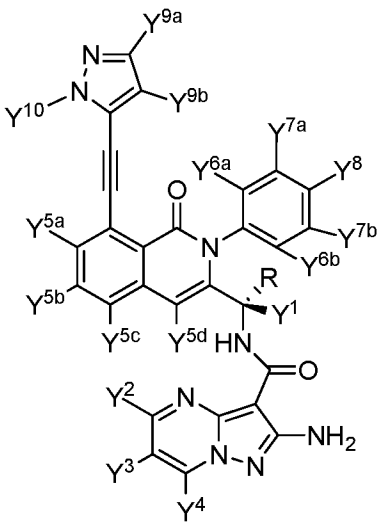
31. The compound of claim 4, wherein the compound is a compound of Formula (A-I), (A-II), or (A-III):



(A-I),



(A-II), or



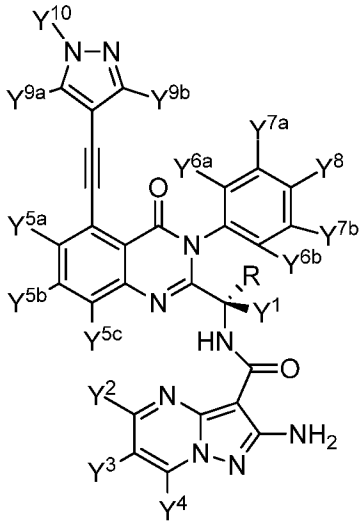
(A-III),

or a pharmaceutically acceptable form thereof, wherein

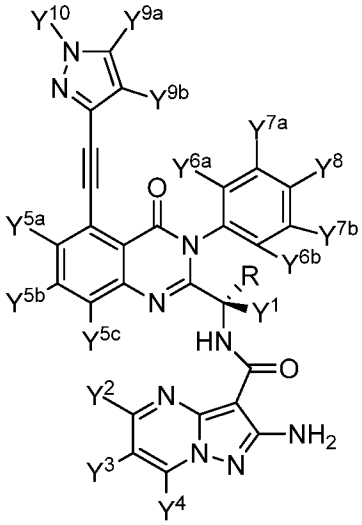
Y^{9a} and Y^{9b} are each independently hydrogen, deuterium, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

Y^{10} is hydrogen or C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

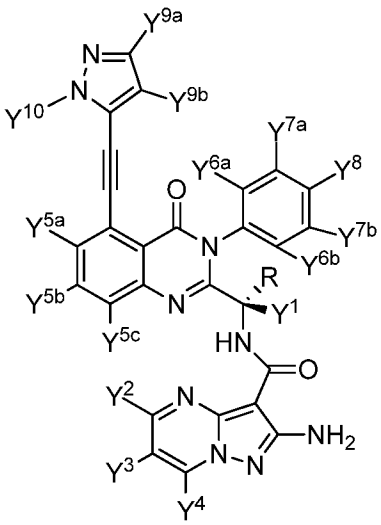
32. The compound of claim 7, wherein the compound is a compound of Formula (B-I), (B-II), or (B-III):



(B-I),



(B-II), or



(B-III),

or a pharmaceutically acceptable form thereof, wherein

Y^{9a} and Y^{9b} are each independently hydrogen, deuterium, or C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen; and

Y^{10} is hydrogen or C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

33. The compound of claim 31 or 32, wherein Y^{9a} and Y^{9b} are each independently hydrogen or deuterium.

34. The compound of claim 31 or 32, wherein one of Y^{9a} and Y^{9b} is hydrogen or deuterium, and the other is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

35. The compound of claim 31 or 32, wherein Y^{9a} and Y^{9b} are both C_1-C_3 alkyl, wherein each instance of the C_1-C_3 alkyl is independently optionally substituted with one or more deuterium or halogen.

36. The compound of any one of claims 31–35, wherein Y^{10} is hydrogen.

37. The compound of any one of claims 31–35, wherein Y^{10} is C_1-C_3 alkyl, wherein the C_1-C_3 alkyl itself is optionally substituted with one or more deuterium or halogen.

38. The compound of claim 37, wherein Y^{10} is $-CH_3$.

39. The compound of claim 37, wherein Y^{10} is $-CD_3$.

40. The compound of any one of claims 1–39, wherein R is C_1-C_3 alkyl optionally substituted with one or more deuterium.

41. The compound of claim 40, wherein R is methyl or ethyl optionally substituted with one or more deuterium.

42. The compound of claim 41, wherein R is methyl optionally substituted with one or more deuterium.

43. The compound of claim 42, wherein R is $–CH_3$.

44. The compound of claim 42, wherein R is $–CD_3$.

45. The compound of any one of claims 1–44, wherein Y^1 is deuterium.

46. The compound of any one of claims 1–45, wherein Y^2 is deuterium.

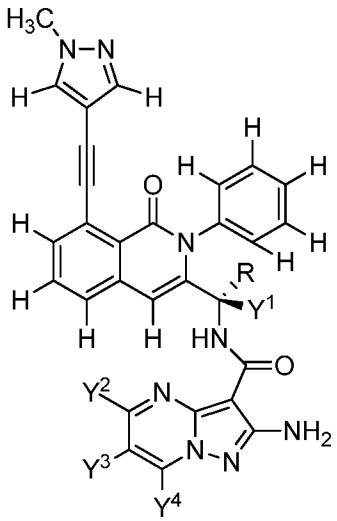
47. The compound of any one of claims 1–46, wherein Y^3 is deuterium.

48. The compound of any one of claims 1–47, wherein Y^4 is deuterium.

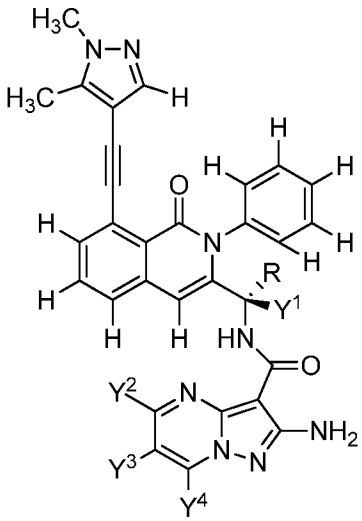
49. The compound of any one of claims 1–45, wherein Y^2, Y^3, and Y^4 are all hydrogen.

50. The compound of any one of claims 1–45, wherein Y^2, Y^3, and Y^4 are all deuterium.

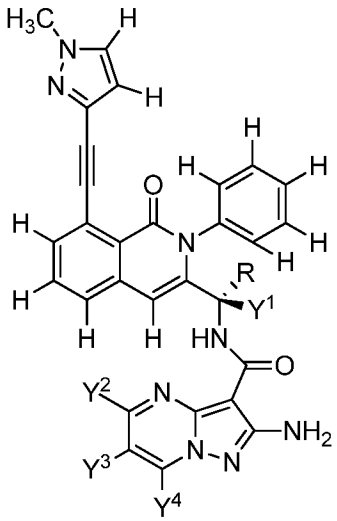
51. The compound of claim 4, wherein the compound is a compound of Formula (A-I-a), (A-I-b), or (A-II-a):



(A-I-a),



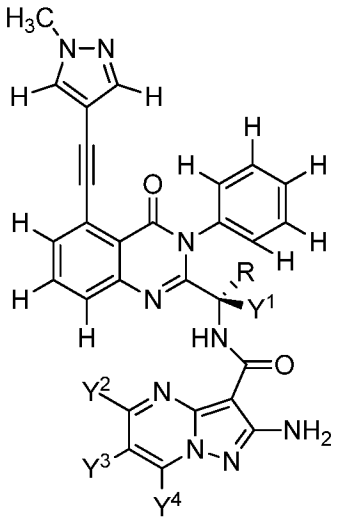
(A-I-b), or



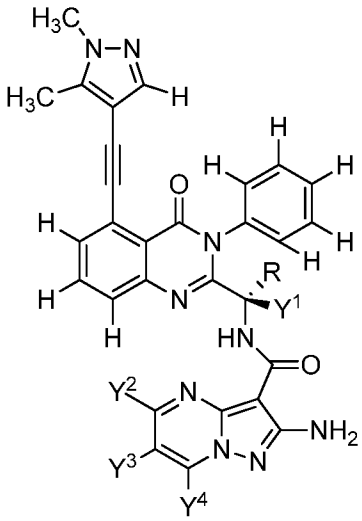
(A-II-a),

or a pharmaceutically acceptable form thereof.

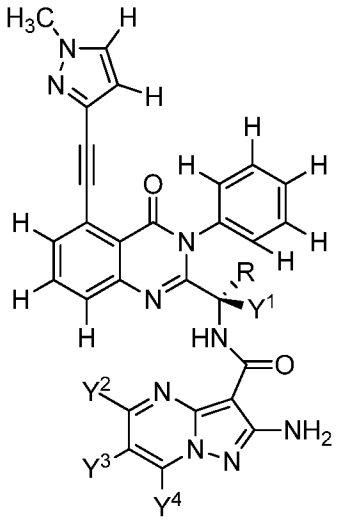
52. The compound of claim 7, wherein the compound is a compound of Formula (B-I-a), (B-I-b), or (B-II-a):



(B-I-a),



(B-I-b), or



(B-II-a),

or a pharmaceutically acceptable form thereof.

53. The compound of claim 1, which is selected from any one of the compounds in Tables 1 to 74, or a pharmaceutically acceptable form thereof.

54. A pharmaceutical composition comprising a compound of any one of claims 1–53, and a pharmaceutically acceptable excipient.

55. A method of treating or preventing a PI3K mediated disorder in a subject having the disorder or in need of the prevention, comprising administering a therapeutically effective amount of a compound of any one of claims 1–53 or a pharmaceutical composition of claim 54 to the subject.

56. The method of claim 55, wherein the PI3K mediated disorder is a PI3K-γ mediated disorder.

57. The method of claim 55, wherein the PI3K mediated disorder is cancer, an inflammatory disease, or an auto-immune disease.

58. The method of claim 57, wherein the cancer is a solid tumor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/022705

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P35/00 A61P37/00 A61P29/00
ADD.

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)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/051244 A1 (INFINITY PHARMACEUTICALS INC [US]) 9 April 2015 (2015-04-09) cited in the application paragraphs [0010]-[0011]; paragraph [0098]; claim 25; tables 3-4; compounds V, VI, VII, VIII -----	1-58

☐ 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2017	10/05/2017

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

Information on patent family members

International application No
PCT/US2017/022705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015051244 A1	09-04-2015	CA 2925944 A1	09-04-2015
		CN 105793255 A	20-07-2016
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		EP 3052485 A1	10-08-2016
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		KR 20160068832 A	15-06-2016
		PH 12016500582 A1	16-05-2016
		SG 11201602445S A	28-04-2016
		TW 201605829 A	16-02-2016
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		US 2015225410 A1	13-08-2015
		WO 2015051244 A1	09-04-2015