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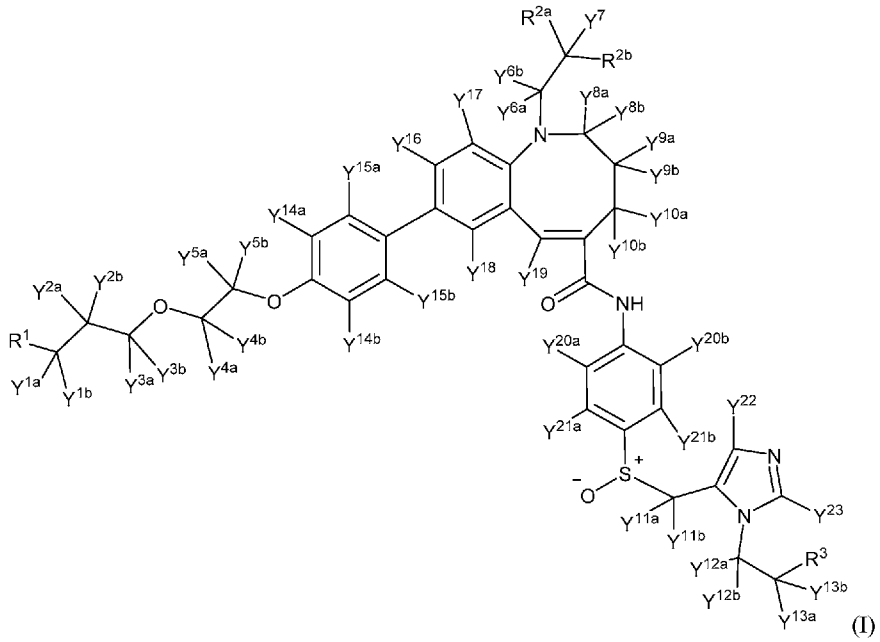
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(54) Title: DEUTERATED CENICRIVIROC



(I)

(57) Abstract: This invention relates to deuterated forms of cenicriviroc, racemic and (*R*) forms thereof, free base forms of any of the foregoing and pharmaceutically acceptable salts of the free base forms. In one aspect, the invention provides a compound of Formula I:or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein each Y and each R is as defined in the application.

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DEUTERATED CENICRIVIROC

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/379,899, filed August 26, 2016, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

[0003] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving a drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

[0004] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically

responsible for their metabolism (see Kempf, D.J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L. et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

[0005] In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

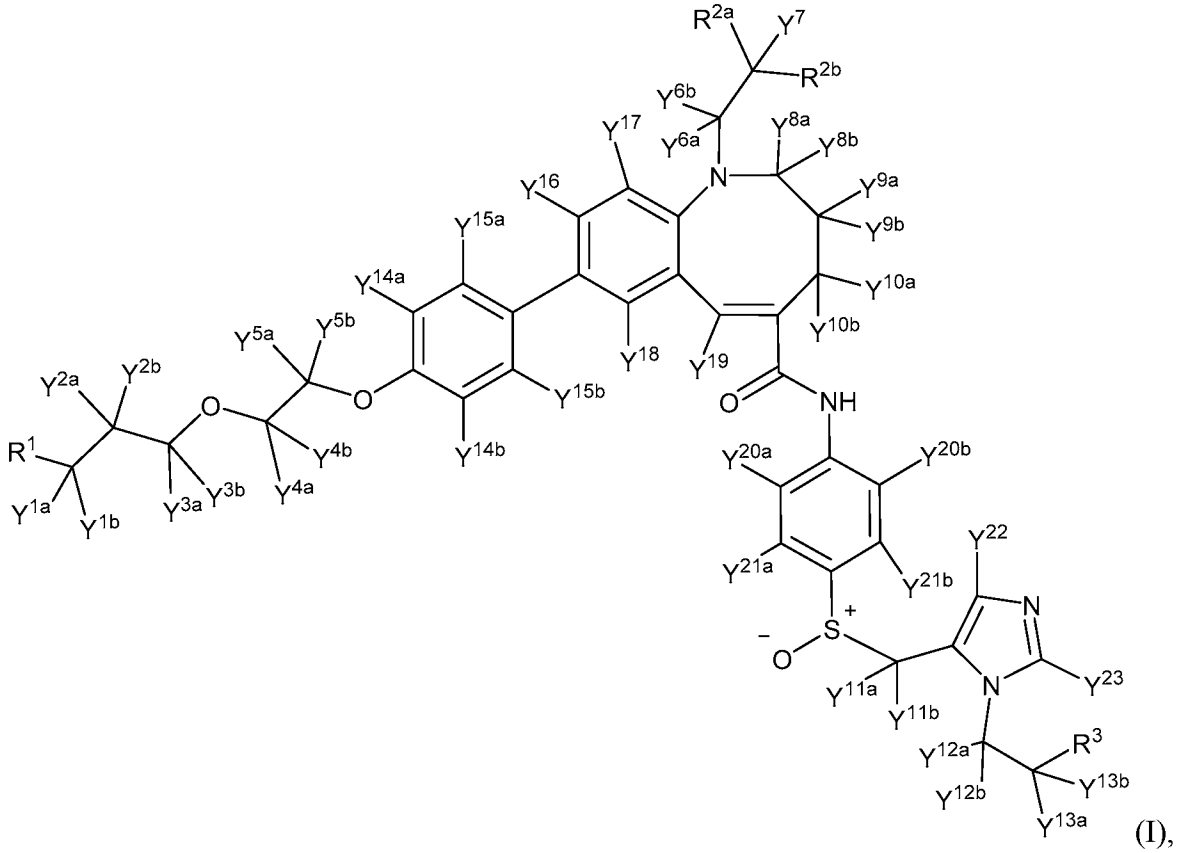
[0006] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[0007] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, M.I. et al., J. Pharm. Sci., 1975, 64:367-91; Foster, A.B., Adv. Drug Res. 1985, 14:1-40 ("Foster"); Kushner, D.J. et al., Can. J. Physiol. Pharmacol. 1999, 79-88; Fisher, M.B. et al., Curr. Opin. Drug Discov. Devel., 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance *in vivo*. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to

question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

SUMMARY OF THE INVENTION

[0008] This invention relates to deuterated forms of cenicriviroc, also known as TAK-652, and by the chemical name (-)-(*S*)-8-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-N-[4-(1-propyl-1H-imidazol-5-ylmethylsulfinyl)phenyl]-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide methanesulfonate, the racemic and (*R*) forms thereof, free base forms of any of the foregoing and pharmaceutically acceptable salts of the free base forms. In one aspect, the invention provides a compound of Formula I:



(I),

or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein:

each of R^1, R^{2a}, R^{2b} and R^3 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$, and $-CD_3$;

each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{7}, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a},

Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is independently selected from hydrogen and deuterium; and

when each of R^1, R^{2a}, R^{2b} and R^3 is $-CH_3$, at least one of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^7, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, or Y^{23} is deuterium.

[0009] This invention also provides compositions comprising a compound of this invention, including pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier. This invention also provides the use of such compounds and compositions in methods of treating diseases and conditions that are beneficially treated by administering a CCR5 antagonist, a CCR2 antagonist, or a dual CCR2/CCR5 antagonist. Some exemplary embodiments include a method of treating a disease or condition selected from HIV infection, non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis, and obesity, the method comprising the step of administering to a subject in need thereof a compound, a pharmaceutically acceptable salt or pharmaceutically acceptable composition of the present invention. Some exemplary embodiments include a method of treating cancer, comprising the step of administering to the subject an effective amount of a compound, a pharmaceutically acceptable salt or a pharmaceutically acceptable composition of the present invention, in combination with one or more immune checkpoint inhibitors. Some exemplary embodiments include a method of treating cancer, comprising the step of administering to the subject an effective amount of a compound, a pharmaceutically acceptable salt or a pharmaceutically acceptable composition of the present invention, in combination with one or more focal adhesion kinase (FAK) antagonists. Some exemplary embodiments include a method of treating cancer, comprising the step of administering to the subject an effective amount of a compound, a pharmaceutically acceptable salt or a pharmaceutically acceptable composition of the present invention, in combination with one or more immune checkpoint inhibitors and one or more focal adhesion kinase (FAK) antagonists.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Cenicriviroc, also known as TAK-652, and by the chemical name (-)-(*S*)-8-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-N-[4-(1-propyl-1H-imidazol-5-ylmethylsulfinyl)phenyl]-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide methanesulfonate, is an orally active C-C chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist.

[0011] Cenicriviroc is currently in phase III clinical trials for the treatment of non-alcoholic steatohepatitis (NASH) in adult patients with liver fibrosis, including patients with type 2 diabetes, and in phase II clinical trials for the treatment of HIV infection in antiretroviral treatment naïve patients in combination with TRUVADA® (emtricitabine and tenofovir disoproxil fumarate), the treatment of HIV infection in antiretroviral therapy experienced but CCR5 antagonist naïve patients, the treatment of obesity in patients with prediabetes or type 2 diabetes and suspected non-alcoholic fatty liver disease, and the treatment of primary sclerosing cholangitis (PSC). Cenicriviroc is also in phase I clinical trials for the treatment of non-alcoholic steatohepatitis (NASH) in combination with pioglitazone. Cenicriviroc is in preclinical studies for the treatment of rheumatoid arthritis.

[0012] The receptors CCR2 and CCR5 are known to bind chemokines CCL2, CCL3, CCL4, CCL5 and CCL8 (CCR2 binds CCL2 and CCR5 binds CCL3, CCL4, CCL5 and CCL8). These chemokines are generated by tumors and attract inhibitory immune cells (e.g., regulatory T cells, tumor associated macrophages and myeloid derived suppressor cells). These immune inhibitory cells prevent activated tumoricidal immune cells from efficiently killing cancer cells. While inhibiting either receptor alone may be sufficient for preventing the establishment of an immunosuppressive tumor environment, the combination of the two may more efficiently prevent the accumulation of inhibitor immune cells within the tumor.

[0013] Immune checkpoint inhibitors are designed to facilitate the generation of an immune response against a tumor. However, many immune checkpoint inhibitors are not efficient in generating an immune response due to the immunosuppressive environment found in a tumor. A combination of a compound of this invention with an immune checkpoint inhibitor may prove beneficial for the treatment of cancer.

[0014] Focal adhesion kinase or FAK plays a central role in the development and survival of cancer stem cells and it has been found that FAK expression is greater in some highly invasive and metastatic tumors. However, similar to checkpoint antagonist therapy, patients that benefit from FAK antagonist therapies are part of a relatively small percentage of the patients with cancer. Not all cancers are impacted by these therapies and not all of the responding population experiences complete or optimal therapy. A combination of a compound of this invention with a FAK inhibitor may prove beneficial for the treatment of

cancer. Additionally, a combination of a compound of this invention with an immune checkpoint inhibitor and a FAK inhibitor may prove beneficial for the treatment of cancer.

[0015] Despite the potential beneficial activities of cenicriviroc, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

Definitions

[0016] The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

[0017] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[0018] As used herein, the term "subject" includes humans and non-human mammals. Non-limiting examples of non-human mammals include mice, rats, guinea pigs, rabbits, dogs, cats, monkeys, apes, pigs, cows, sheep, horses, etc.

[0019] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of cenicriviroc will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E. et al., Seikagaku, 1994, 66:15; Gannes, L.Z. et al., Comp. Biochem. Physiol. Mol. Integr. Physiol., 1998, 119:725.

[0020] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. However, in certain embodiments where stated, when a position is designated specifically as "H" or "hydrogen", the position has at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% hydrogen. In some embodiments, when a position is designated specifically as "H" or "hydrogen", the position incorporates ≤20% deuterium, ≤10% deuterium, ≤5% deuterium, ≤4% deuterium, ≤3% deuterium, ≤2% deuterium, or ≤1% deuterium. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least

3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[0021] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[0022] In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), 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).

[0023] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 52.5%.

[0024] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 60%.

[0025] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 67.5%.

[0026] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 75%.

[0027] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 82.5%.

[0028] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 90%.

[0029] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 95%.

[0030] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 97.5%.

[0031] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99%.

[0032] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99.5%.

[0033] The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

[0034] The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound.

[0035] The invention also provides salts of the compounds of the invention.

[0036] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to one embodiment, the compound is a pharmaceutically acceptable acid addition salt. In one embodiment, the acid addition salt may be a deuterated acid addition salt.

[0037] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[0038] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-

bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, tartrate, methanesulfonate (mesylate), propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid. In one embodiment, the acids commonly employed to form pharmaceutically acceptable salts include the above-listed inorganic acids, wherein at least one hydrogen is replaced with deuterium.

[0039] The compounds of the present invention (e.g., compounds of Formula I), contain an asymmetric sulfur atom (i.e., at the sulfoxide moiety). The compounds of the present invention (e.g., compounds of Formula I), may also contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers, individual diastereomers, or mixtures of diastereomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, a mixture of diastereomers, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. "Stereoisomer" refers to both enantiomers and diastereomers. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[0040] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[0041] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

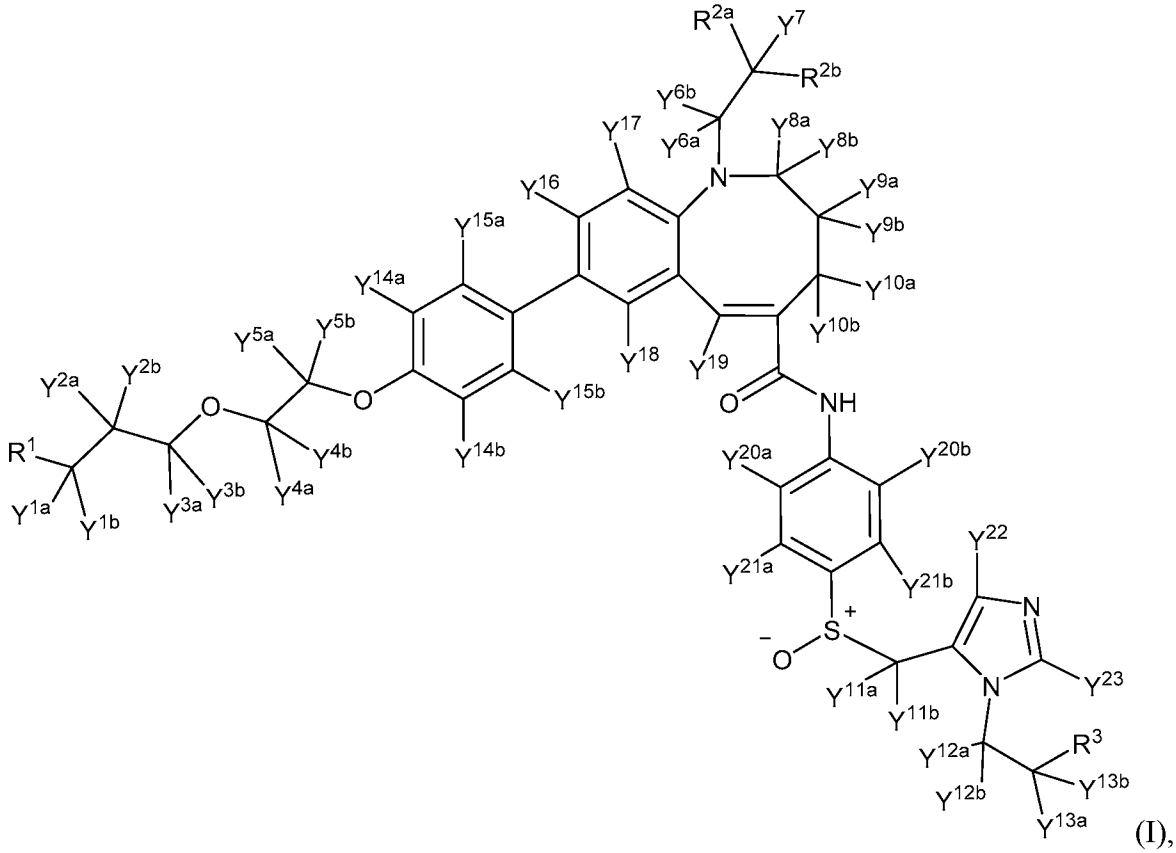
[0042] "D" and "d" both refer to deuterium. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[0043] "Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[0044] Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

[0045] The present invention provides a compound of Formula I:



(I),

or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein:

each of R^1, R^{2a}, R^{2b} and R^3 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$, and $-CD_3$;

each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{7}, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is independently selected from hydrogen and deuterium; and

when each of R^1, R^{2a}, R^{2b} and R^3 is $-CH_3$, at least one of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{7}, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, or Y^{23} is deuterium.

[0046] In some embodiments of a compound of Formula I, at least one of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen. In one aspect of these embodiments, each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen.

[0047] In some embodiments of a compound of Formula I, at least one of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen. In one aspect of these

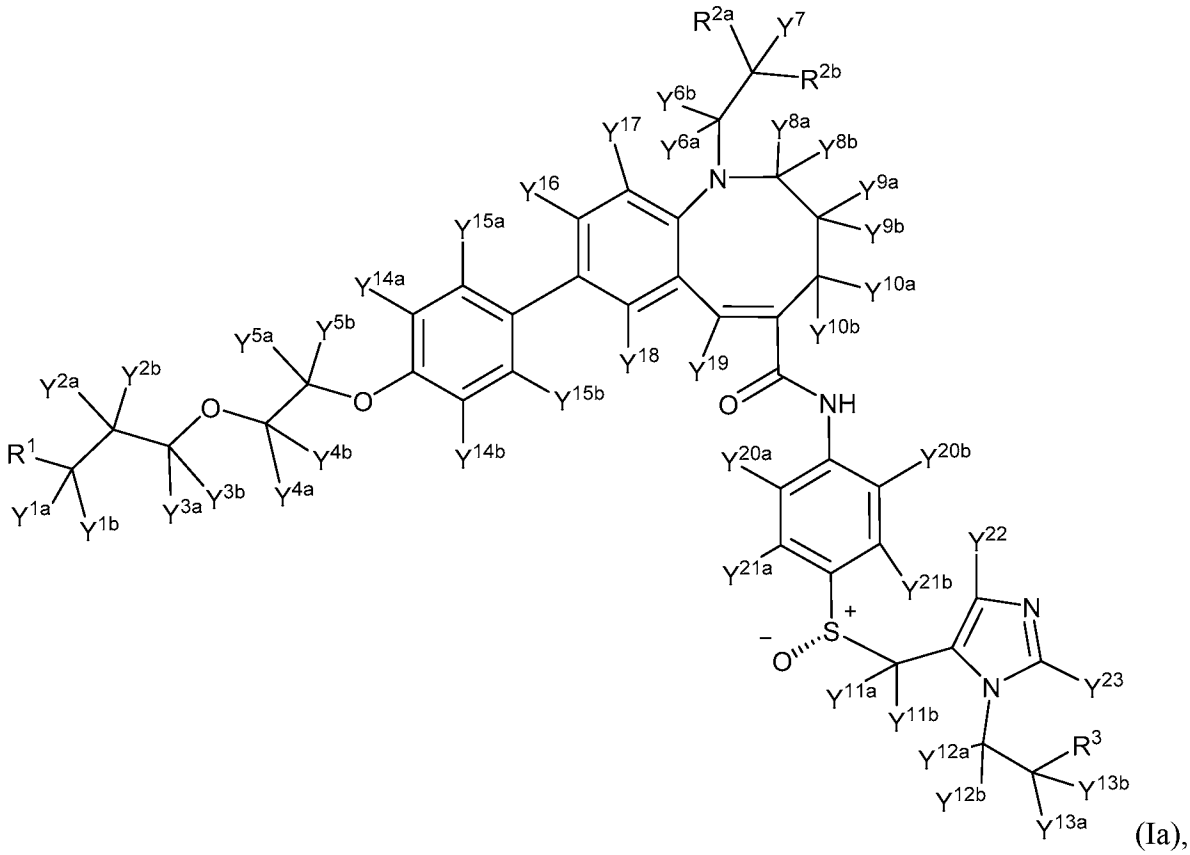
embodiments, each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen.

[0048] In some embodiments of a compound of Formula I, when each of R^1, R^{2a}, R^{2b} and R^3 is $-CD_3$, then at least one of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^7, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b} is hydrogen.

[0049] In some embodiments, each Y bound to a common carbon atom is the same (e.g., Y^{1a} and Y^{1b} are the same; Y^{2a} and Y^{2b} are the same; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same; Y^{6a} and Y^{6b} are the same; Y^{8a} and Y^{8b} are the same; Y^{9a} and Y^{9b} are the same; Y^{10a} and Y^{10b} are the same; Y^{11a} and Y^{11b} are the same; Y^{12a} and Y^{12b} are the same; and Y^{13a} and Y^{13b} are the same). In one aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same. In another aspect of these embodiments, each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same. In still another aspect of these embodiments, each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same. In still another aspect of these embodiments, each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same. In still another aspect of these embodiments, each of Y^{6a}, Y^{6b}, and Y^7 is the same.

[0050] In some embodiments, each of R^1, R^{2a}, R^{2b} and R^3 is independently selected from $-CH_3$ and $-CD_3$. In one aspect of these embodiments, R^{2a} and R^{2b} are the same. In another aspect of these embodiments, each of Y^{1a} and Y^{1b} is deuterium when R^1 is $-CD_3$. In a further aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is deuterium when R^1 is $-CD_3$. In an alternate aspect of these embodiments, each of Y^{1a} and Y^{1b} is hydrogen when R^1 is $-CH_3$. In a further alternate aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is hydrogen when R^1 is $-CH_3$. In another aspect of these embodiments, R^{2a} and R^{2b} are $-CD_3$, and Y^7 is deuterium. In another alternate aspect of these embodiments, R^{2a} and R^{2b} are $-CH_3$, and Y^7 is hydrogen. In a more specific aspect of these embodiments, R^{2a} and R^{2b} are $-CD_3$, Y^7 is deuterium, and each of Y^{6a} and Y^{6b} is deuterium. In another alternate aspect of these embodiments, R^{2a} and R^{2b} are $-CH_3$, Y^7 is hydrogen, and each of Y^{6a} and Y^{6b} is hydrogen. In another aspect of these embodiments, each of Y^{13a} and Y^{13b} is deuterium when R^3 is $-CD_3$. In a further aspect of these embodiments, each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is deuterium when R^3 is $-CD_3$. In an alternate aspect of these embodiments, each of Y^{13a} and Y^{13b} is hydrogen when R^3 is $-CH_3$. In a further alternate aspect of these embodiments, each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is hydrogen when R^3 is $-CH_3$.

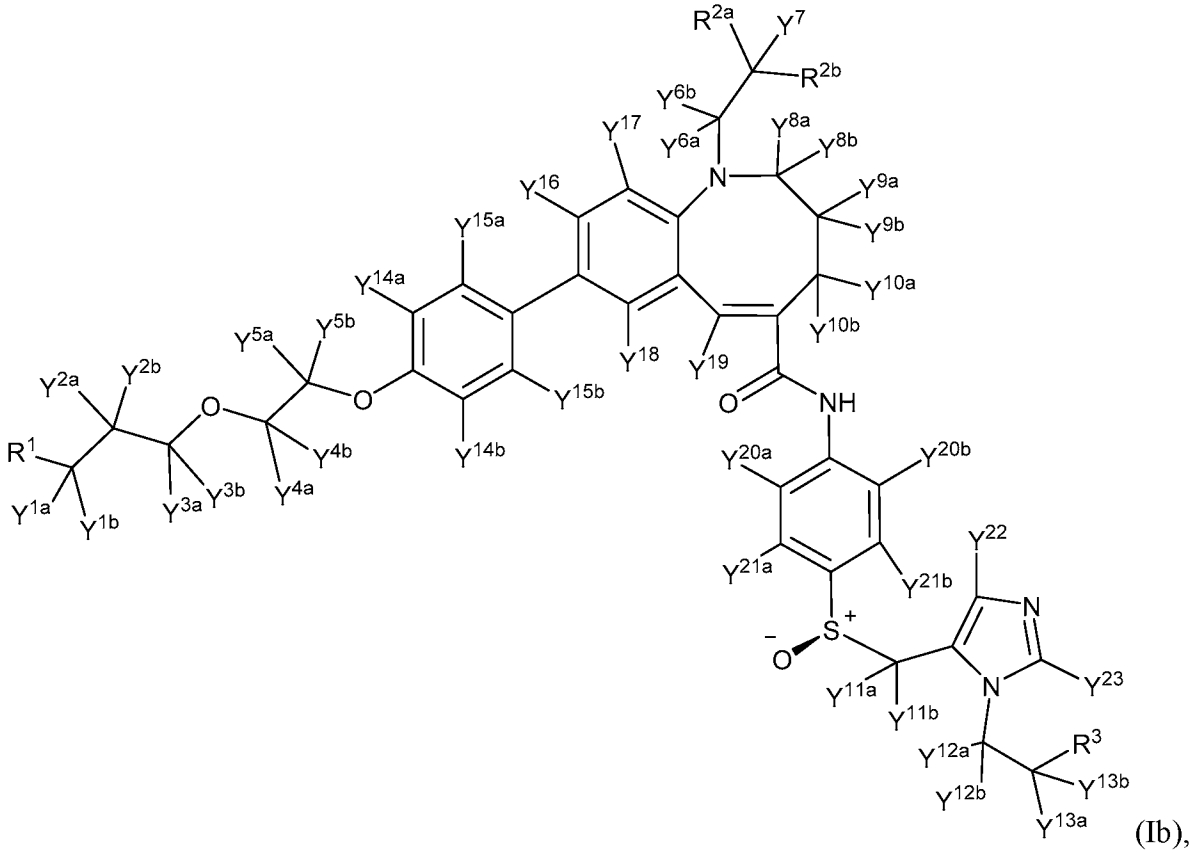
[0051] In some embodiments, the compound is an (*S*) stereoisomer at the sulfoxide moiety having the Formula Ia:



(Ia),

or a pharmaceutically acceptable salt thereof, where all Y and R variables are as defined for Formula I and the various embodiments and aspects thereof.

[0052] In some embodiments, the compound is an (*R*) stereoisomer at the sulfoxide moiety having the Formula Ib:



(Ib),

or a pharmaceutically acceptable salt thereof, where all Y and R variables are as defined for Formula I and the various embodiments and aspects thereof.

[0053] In some embodiments, the compound of Formula I, Ia or Ib is a mesylate salt. In other embodiments, the compound of Formula I, Ia or Ib is an oxalate salt. In still other embodiments, the compound of Formula I, Ia or Ib is a free base.

[0054] In some embodiments of a compound of Formula I, R^{2a} and R^{2b} are the same; each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same (designated $Y^1/Y^2/Y^3$ in Table 1); each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same (designated Y^4/Y^5 in Table 1); each of Y^{6a}, Y^{6b}, and Y^7 is the same (designated Y^6/Y^7 in Table 1); each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same (designated $Y^8/Y^9/Y^{10}$ in Table 1); each of Y^{11a} and Y^{11b} is the same (designated Y^{11} in Table 1); each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same (designated Y^{12}/Y^{13} in Table 1); each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen; and the compound is selected from any one of the compounds (#) set forth in Table 1 (below):

Table 1: Exemplary Embodiments of Formula I

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
100	CD_3	CH_3	CH_3	D	H	H	H	H	H
101	CH_3	CD_3	CH_3	H	H	D	H	H	H

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
102	CH_3	CH_3	CD_3	H	H	H	H	H	D
103	CH_3	CH_3	CH_3	H	D	H	H	H	H
104	CH_3	CH_3	CH_3	H	H	H	D	H	H
105	CD_3	CD_3	CH_3	D	H	D	H	H	H
106	CD_3	CH_3	CD_3	D	H	H	H	H	D
107	CD_3	CH_3	CH_3	D	D	H	H	H	H
108	CD_3	CH_3	CH_3	D	H	H	D	H	H
109	CH_3	CD_3	CD_3	H	H	D	H	H	D
110	CH_3	CD_3	CH_3	H	D	D	H	H	H
111	CH_3	CD_3	CH_3	H	H	D	D	H	H
112	CH_3	CH_3	CD_3	H	D	H	H	H	D
113	CH_3	CH_3	CD_3	H	H	H	D	H	D
114	CH_3	CH_3	CH_3	H	D	H	D	H	H
115	CD_3	CD_3	CD_3	D	H	D	H	H	D
116	CD_3	CD_3	CH_3	D	D	D	H	H	H
117	CD_3	CD_3	CH_3	D	H	D	D	H	H
118	CD_3	CH_3	CD_3	D	D	H	H	H	D
119	CD_3	CH_3	CD_3	D	H	H	D	H	D
120	CD_3	CH_3	CH_3	D	D	H	D	H	H
121	CH_3	CD_3	CD_3	H	D	D	H	H	D
122	CH_3	CD_3	CD_3	H	H	D	D	H	D
123	CH_3	CD_3	CH_3	H	D	D	D	H	H
124	CH_3	CH_3	CD_3	H	D	H	D	H	D
125	CD_3	CD_3	CD_3	D	D	D	H	H	D
126	CD_3	CD_3	CD_3	D	H	D	D	H	D
127	CD_3	CD_3	CH_3	D	D	D	D	H	H
128	CD_3	CH_3	CD_3	D	D	H	D	H	D
129	CH_3	CD_3	CD_3	H	D	D	D	H	D
130	CD_3	CD_3	CD_3	D	D	D	D	H	D
131	CD_3	CH_3	CH_3	D	H	H	H	D	H
132	CH_3	CD_3	CH_3	H	H	D	H	D	H
133	CH_3	CH_3	CD_3	H	H	H	H	D	D
134	CH_3	CH_3	CH_3	H	D	H	H	D	H
135	CH_3	CH_3	CH_3	H	H	H	D	D	H
136	CD_3	CD_3	CH_3	D	H	D	H	D	H
137	CD_3	CH_3	CD_3	D	H	H	H	D	D
138	CD_3	CH_3	CH_3	D	D	H	H	D	H
139	CD_3	CH_3	CH_3	D	H	H	D	D	H
140	CH_3	CD_3	CD_3	H	H	D	H	D	D
141	CH_3	CD_3	CH_3	H	D	D	H	D	H
142	CH_3	CD_3	CH_3	H	H	D	D	D	H
143	CH_3	CH_3	CD_3	H	D	H	H	D	D
144	CH_3	CH_3	CD_3	H	H	H	D	D	D
145	CH_3	CH_3	CH_3	H	D	H	D	D	H
146	CD_3	CD_3	CD_3	D	H	D	H	D	D

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
147	CD_3	CD_3	CH_3	D	D	D	H	D	H
148	CD_3	CD_3	CH_3	D	H	D	D	D	H
149	CD_3	CH_3	CD_3	D	D	H	H	D	D
150	CD_3	CH_3	CD_3	D	H	H	D	D	D
151	CD_3	CH_3	CH_3	D	D	H	D	D	H
152	CH_3	CD_3	CD_3	H	D	D	H	D	D
153	CH_3	CD_3	CD_3	H	H	D	D	D	D
154	CH_3	CD_3	CH_3	H	D	D	D	D	H
155	CH_3	CH_3	CD_3	H	D	H	D	D	D
156	CD_3	CD_3	CD_3	D	D	D	H	D	D
157	CD_3	CD_3	CD_3	D	H	D	D	D	D
158	CD_3	CD_3	CH_3	D	D	D	D	D	H
159	CD_3	CH_3	CD_3	D	D	H	D	D	D
160	CH_3	CD_3	CD_3	H	D	D	D	D	D
161	CD_3	CD_3	CD_3	D	D	D	D	D	D
162	CH_3	CH_3	CH_3	H	H	H	H	D	H

or a pharmaceutically acceptable salt of any of the foregoing.

[0055] In some embodiments of a compound of Formula Ia, R^{2a} and R^{2b} are the same; each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same (designated $Y^1/Y^2/Y^3$ in Table 2); each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same (designated Y^4/Y^5 in Table 2); each of Y^{6a}, Y^{6b}, and Y^7 is the same (designated Y^6/Y^7 in Table 2); each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same (designated $Y^8/Y^9/Y^{10}$ in Table 2); each of Y^{11a} and Y^{11b} is the same (designated Y^{11} in Table 2); each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same ((designated Y^{12}/Y^{13} in Table 2); each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen; and the compound is selected from any one of the compounds (#) set forth in Table 2 (below):

Table 2: Exemplary Embodiments of Formula Ia

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
100a	CD_3	CH_3	CH_3	D	H	H	H	H	H
101a	CH_3	CD_3	CH_3	H	H	D	H	H	H
102a	CH_3	CH_3	CD_3	H	H	H	H	H	D
103a	CH_3	CH_3	CH_3	H	D	H	H	H	H
104a	CH_3	CH_3	CH_3	H	H	H	D	H	H
105a	CD_3	CD_3	CH_3	D	H	D	H	H	H
106a	CD_3	CH_3	CD_3	D	H	H	H	H	D
107a	CD_3	CH_3	CH_3	D	D	H	H	H	H
108a	CD_3	CH_3	CH_3	D	H	H	D	H	H
109a	CH_3	CD_3	CD_3	H	H	D	H	H	D
110a	CH_3	CD_3	CH_3	H	D	D	H	H	H
111a	CH_3	CD_3	CH_3	H	H	D	D	H	H
112a	CH_3	CH_3	CD_3	H	D	H	H	H	D
113a	CH_3	CH_3	CD_3	H	H	H	D	H	D

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
114a	CH_3	CH_3	CH_3	H	D	H	D	H	H
115a	CD_3	CD_3	CD_3	D	H	D	H	H	D
116a	CD_3	CD_3	CH_3	D	D	D	H	H	H
117a	CD_3	CD_3	CH_3	D	H	D	D	H	H
118a	CD_3	CH_3	CD_3	D	D	H	H	H	D
119a	CD_3	CH_3	CD_3	D	H	H	D	H	D
120a	CD_3	CH_3	CH_3	D	D	H	D	H	H
121a	CH_3	CD_3	CD_3	H	D	D	H	H	D
122a	CH_3	CD_3	CD_3	H	H	D	D	H	D
123a	CH_3	CD_3	CH_3	H	D	D	D	H	H
124a	CH_3	CH_3	CD_3	H	D	H	D	H	D
125a	CD_3	CD_3	CD_3	D	D	D	H	H	D
126a	CD_3	CD_3	CD_3	D	H	D	D	H	D
127a	CD_3	CD_3	CH_3	D	D	D	D	H	H
128a	CD_3	CH_3	CD_3	D	D	H	D	H	D
129a	CH_3	CD_3	CD_3	H	D	D	D	H	D
130a	CD_3	CD_3	CD_3	D	D	D	D	H	D
131a	CD_3	CH_3	CH_3	D	H	H	H	D	H
132a	CH_3	CD_3	CH_3	H	H	D	H	D	H
133a	CH_3	CH_3	CD_3	H	H	H	H	D	D
134a	CH_3	CH_3	CH_3	H	D	H	H	D	H
135a	CH_3	CH_3	CH_3	H	H	H	D	D	H
136a	CD_3	CD_3	CH_3	D	H	D	H	D	H
137a	CD_3	CH_3	CD_3	D	H	H	H	D	D
138a	CD_3	CH_3	CH_3	D	D	H	H	D	H
139a	CD_3	CH_3	CH_3	D	H	H	D	D	H
140a	CH_3	CD_3	CD_3	H	H	D	H	D	D
141a	CH_3	CD_3	CH_3	H	D	D	H	D	H
142a	CH_3	CD_3	CH_3	H	H	D	D	D	H
143a	CH_3	CH_3	CD_3	H	D	H	H	D	D
144a	CH_3	CH_3	CD_3	H	H	H	D	D	D
145a	CH_3	CH_3	CH_3	H	D	H	D	D	H
146a	CD_3	CD_3	CD_3	D	H	D	H	D	D
147a	CD_3	CD_3	CH_3	D	D	D	H	D	H
148a	CD_3	CD_3	CH_3	D	H	D	D	D	H
149a	CD_3	CH_3	CD_3	D	D	H	H	D	D
150a	CD_3	CH_3	CD_3	D	H	H	D	D	D
151a	CD_3	CH_3	CH_3	D	D	H	D	D	H
152a	CH_3	CD_3	CD_3	H	D	D	H	D	D
153a	CH_3	CD_3	CD_3	H	H	D	D	D	D
154a	CH_3	CD_3	CH_3	H	D	D	D	D	H
155a	CH_3	CH_3	CD_3	H	D	H	D	D	D
156a	CD_3	CD_3	CD_3	D	D	D	H	D	D
157a	CD_3	CD_3	CD_3	D	H	D	D	D	D
158a	CD_3	CD_3	CH_3	D	D	D	D	D	H

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
159a	CD_3	CH_3	CD_3	D	D	H	D	D	D
160a	CH_3	CD_3	CD_3	H	D	D	D	D	D
161a	CD_3	CD_3	CD_3	D	D	D	D	D	D
162a	CH_3	CH_3	CH_3	H	H	H	H	D	H

or a pharmaceutically acceptable salt of any of the foregoing.

[0056] In some embodiments of a compound of Formula Ib, R^{2a} and R^{2b} are the same; each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same (designated $Y^1/Y^2/Y^3$ in Table 3); each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same (designated Y^4/Y^5 in Table 3); each of Y^{6a}, Y^{6b}, and Y^7 is the same (designated Y^6/Y^7 in Table 3); each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same (designated $Y^8/Y^9/Y^{10}$ in Table 3); each of Y^{11a} and Y^{11b} is the same (designated Y^{11} in Table 3); each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same ((designated Y^{12}/Y^{13} in Table 3); each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen; and the compound is selected from any one of the compounds (#) set forth in Table 3 (below):

Table 3: Exemplary Embodiments of Formula Ib

	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
100b	CD_3	CH_3	CH_3	D	H	H	H	H	H
101b	CH_3	CD_3	CH_3	H	H	D	H	H	H
102b	CH_3	CH_3	CD_3	H	H	H	H	H	D
103b	CH_3	CH_3	CH_3	H	D	H	H	H	H
104b	CH_3	CH_3	CH_3	H	H	H	D	H	H
105b	CD_3	CD_3	CH_3	D	H	D	H	H	H
106b	CD_3	CH_3	CD_3	D	H	H	H	H	D
107b	CD_3	CH_3	CH_3	D	D	H	H	H	H
108b	CD_3	CH_3	CH_3	D	H	H	D	H	H
109b	CH_3	CD_3	CD_3	H	H	D	H	H	D
110b	CH_3	CD_3	CH_3	H	D	D	H	H	H
111b	CH_3	CD_3	CH_3	H	H	D	D	H	H
112b	CH_3	CH_3	CD_3	H	D	H	H	H	D
113b	CH_3	CH_3	CD_3	H	H	H	D	H	D
114b	CH_3	CH_3	CH_3	H	D	H	D	H	H
115b	CD_3	CD_3	CD_3	D	H	D	H	H	D
116b	CD_3	CD_3	CH_3	D	D	D	H	H	H
117b	CD_3	CD_3	CH_3	D	H	D	D	H	H
118b	CD_3	CH_3	CD_3	D	D	H	H	H	D
119b	CD_3	CH_3	CD_3	D	H	H	D	H	D
120b	CD_3	CH_3	CH_3	D	D	H	D	H	H
121b	CH_3	CD_3	CD_3	H	D	D	H	H	D
122b	CH_3	CD_3	CD_3	H	H	D	D	H	D
123b	CH_3	CD_3	CH_3	H	D	D	D	H	H
124b	CH_3	CH_3	CD_3	H	D	H	D	H	D
125b	CD_3	CD_3	CD_3	D	D	D	H	H	D

	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
126b	CD_3	CD_3	CD_3	D	H	D	D	H	D
127b	CD_3	CD_3	CH_3	D	D	D	D	H	H
128b	CD_3	CH_3	CD_3	D	D	H	D	H	D
129b	CH_3	CD_3	CD_3	H	D	D	D	H	D
130b	CD_3	CD_3	CD_3	D	D	D	D	H	D
131b	CD_3	CH_3	CH_3	D	H	H	H	D	H
132b	CH_3	CD_3	CH_3	H	H	D	H	D	H
133b	CH_3	CH_3	CD_3	H	H	H	H	D	D
134b	CH_3	CH_3	CH_3	H	D	H	H	D	H
135b	CH_3	CH_3	CH_3	H	H	H	D	D	H
136b	CD_3	CD_3	CH_3	D	H	D	H	D	H
137b	CD_3	CH_3	CD_3	D	H	H	H	D	D
138b	CD_3	CH_3	CH_3	D	D	H	H	D	H
139b	CD_3	CH_3	CH_3	D	H	H	D	D	H
140b	CH_3	CD_3	CD_3	H	H	D	H	D	D
141b	CH_3	CD_3	CH_3	H	D	D	H	D	H
142b	CH_3	CD_3	CH_3	H	H	D	D	D	H
143b	CH_3	CH_3	CD_3	H	D	H	H	D	D
144b	CH_3	CH_3	CD_3	H	H	H	D	D	D
145b	CH_3	CH_3	CH_3	H	D	H	D	D	H
146b	CD_3	CD_3	CD_3	D	H	D	H	D	D
147b	CD_3	CD_3	CH_3	D	D	D	H	D	H
148b	CD_3	CD_3	CH_3	D	H	D	D	D	H
149b	CD_3	CH_3	CD_3	D	D	H	H	D	D
150b	CD_3	CH_3	CD_3	D	H	H	D	D	D
151b	CD_3	CH_3	CH_3	D	D	H	D	D	H
152b	CH_3	CD_3	CD_3	H	D	D	H	D	D
153b	CH_3	CD_3	CD_3	H	H	D	D	D	D
154b	CH_3	CD_3	CH_3	H	D	D	D	D	H
155b	CH_3	CH_3	CD_3	H	D	H	D	D	D
156b	CD_3	CD_3	CD_3	D	D	D	H	D	D
157b	CD_3	CD_3	CD_3	D	H	D	D	D	D
158b	CD_3	CD_3	CH_3	D	D	D	D	D	H
159b	CD_3	CH_3	CD_3	D	D	H	D	D	D
160b	CH_3	CD_3	CD_3	H	D	D	D	D	D
161b	CD_3	CD_3	CD_3	D	D	D	D	D	D
162b	CH_3	CH_3	CH_3	H	H	H	H	D	H

or a pharmaceutically acceptable salt of any of the foregoing.

[0057] In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth herein is present at its natural isotopic abundance.

[0058] In some embodiments of a compound of this invention, deuterium incorporation at each designated deuterium atom is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, or at least 99%.

[0059] In some embodiments of a compound of this invention, when Y^{1a} and Y^{1b} are deuterium, the level of deuterium incorporation at each Y^{1a} and Y^{1b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0060] In some embodiments of a compound of this invention, when Y^{2a} and Y^{2b} are deuterium, the level of deuterium incorporation at each Y^{2a} and Y^{2b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0061] In some embodiments of a compound of this invention, when Y^{3a} and Y^{3b} are deuterium, the level of deuterium incorporation at each Y^{3a} and Y^{3b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0062] In some embodiments of a compound of this invention, when Y^{4a} and Y^{4b} are deuterium, the level of deuterium incorporation at each Y^{4a} and Y^{4b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0063] In some embodiments of a compound of this invention, when Y^{5a} and Y^{5b} are deuterium, the level of deuterium incorporation at each Y^{5a} and Y^{5b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0064] In some embodiments of a compound of this invention, when Y^{6a} and Y^{6b} are deuterium, the level of deuterium incorporation at each Y^{6a} and Y^{6b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0065] In some embodiments of a compound of this invention, when Y^{7} is deuterium, the level of deuterium incorporation at Y^{7} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0066] In some embodiments of a compound of this invention, when Y^{8a} and Y^{8b} are deuterium, the level of deuterium incorporation at each Y^{8a} and Y^{8b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0067] In some embodiments of a compound of this invention, when Y^{9a} and Y^{9b} are deuterium, the level of deuterium incorporation at each Y^{9a} and Y^{9b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0068] In some embodiments of a compound of this invention, when Y^{10a} and Y^{10b} are deuterium, the level of deuterium incorporation at each Y^{10a} and Y^{10b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0069] In some embodiments of a compound of this invention, when Y^{11a} and Y^{11b} are deuterium, the level of deuterium incorporation at each Y^{11a} and Y^{11b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0070] In some embodiments of a compound of this invention, when Y^{12a} and Y^{12b} are deuterium, the level of deuterium incorporation at each Y^{12a} and Y^{12b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0071] In some embodiments of a compound of this invention, when Y^{13a} and Y^{13b} are deuterium, the level of deuterium incorporation at each Y^{13a} and Y^{13b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0072] In some embodiments of a compound of this invention, when R^1 is $-CD_3$, the level of deuterium incorporation at R^1 is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0073] In some embodiments of a compound of this invention, when R^{2a} and R^{2b} are $-CD_3$, the level of deuterium incorporation at each R^{2a} and R^{2b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0074] In some embodiments of a compound of this invention, when R^3 is $-CD_3$, the level of deuterium incorporation at R^3 is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[0075] In some embodiments of a compound of this invention, at least one of R^1, R^{2a}, R^{2b}, R^3, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^7, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} comprises hydrogen.

[0076] The present invention also provides deuterated intermediates useful, e.g., in the preparation of the compounds of Formula I, Ia, or Ib, and as provided in the Exemplary Schemes.

[0077] The synthesis of compounds of Formula I, Ia, or Ib may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis depicted in Scheme 1 below. Relevant procedures analogous to those of use for the preparation of compounds of Formula I, Ia, or Ib and intermediates thereof are disclosed using well known

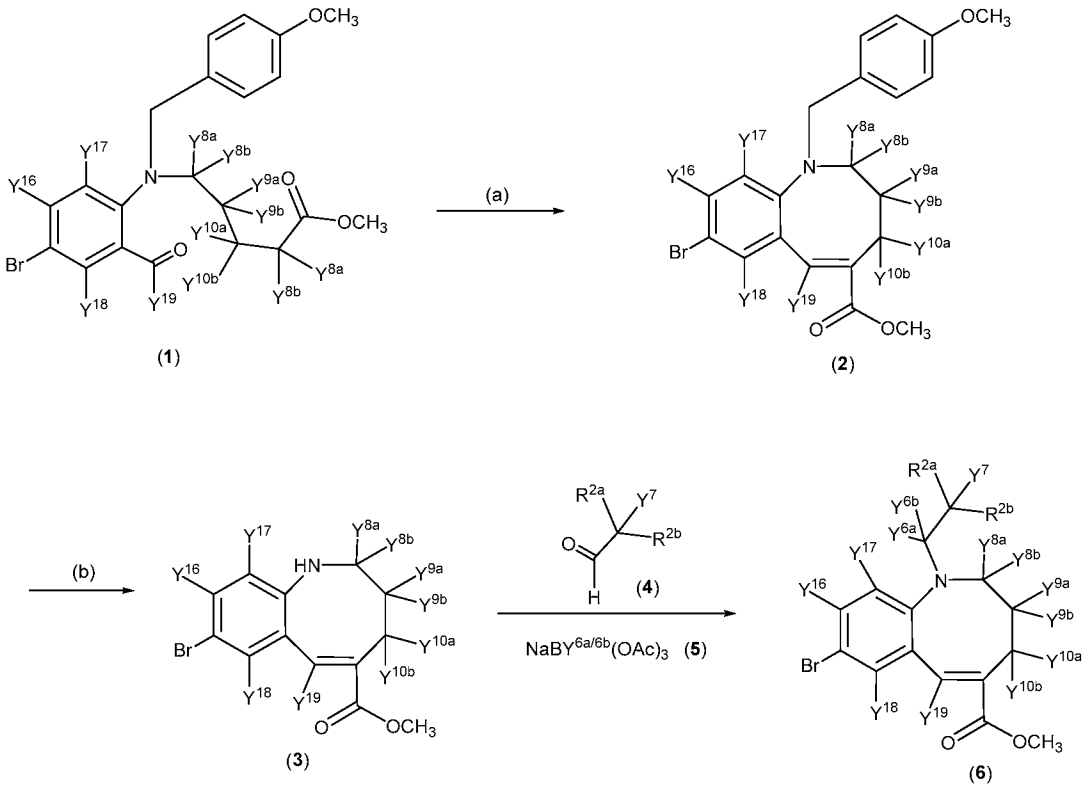
methods in the art disclosed, for instance in WO 2003014105 and Seto, M. et al., Journal of Medicinal Chemistry 49(6), 2037-2048, (2006).

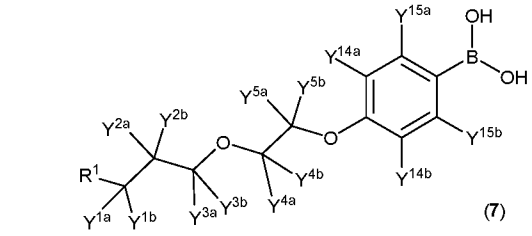
[0078] Such methods can be carried out utilizing corresponding deuterated and, optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

[0079] A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1, below.

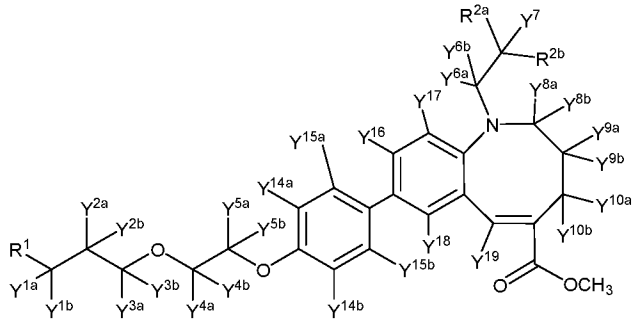
Scheme 1: General Synthesis of Compounds of Formula I





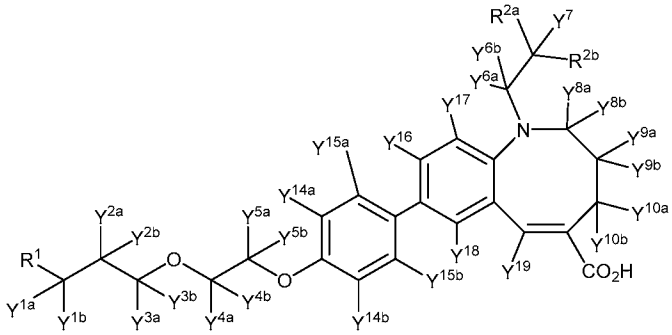
(7)

(c)

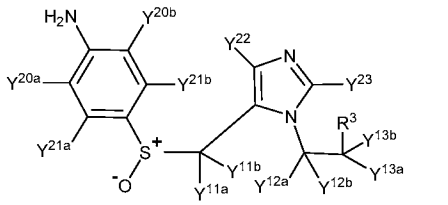


(8)

(d)

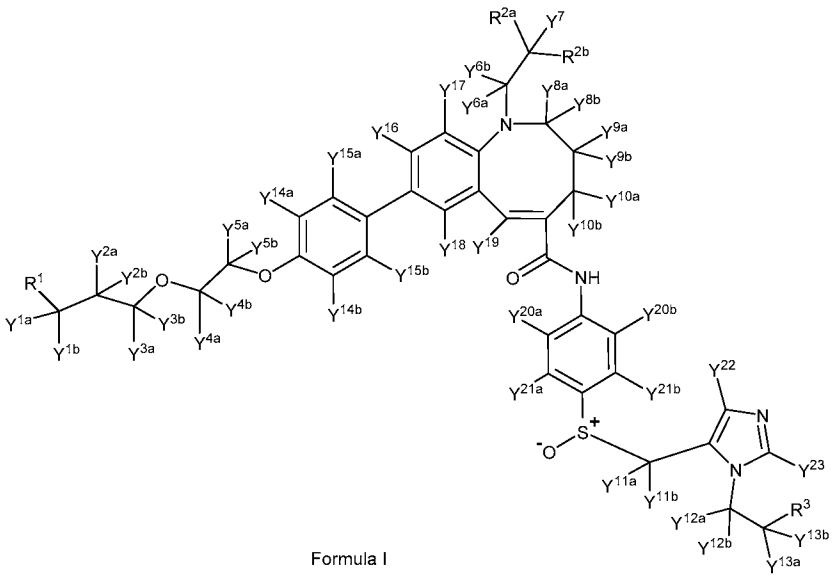


(9)

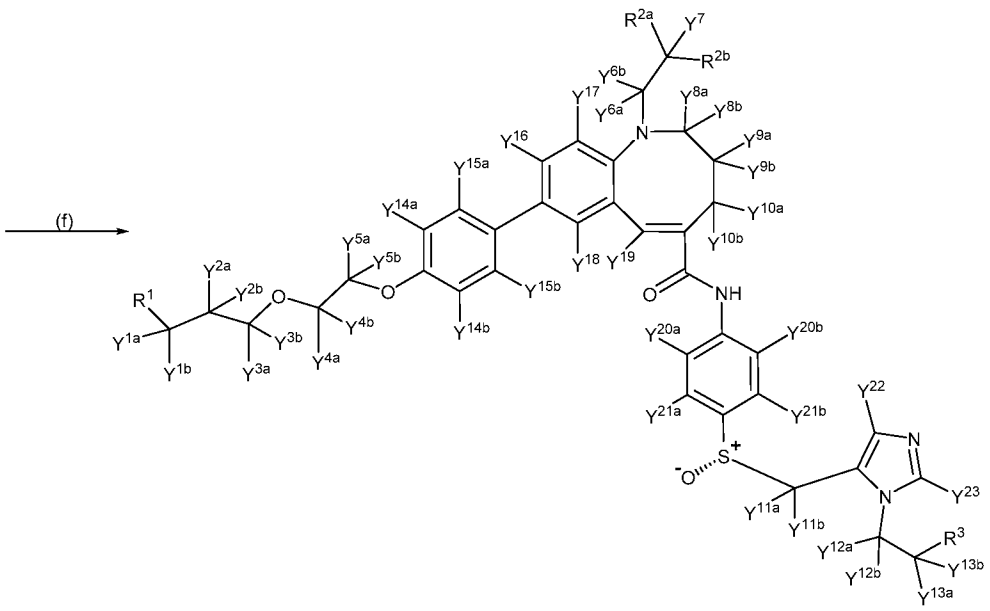


(10)

(e)

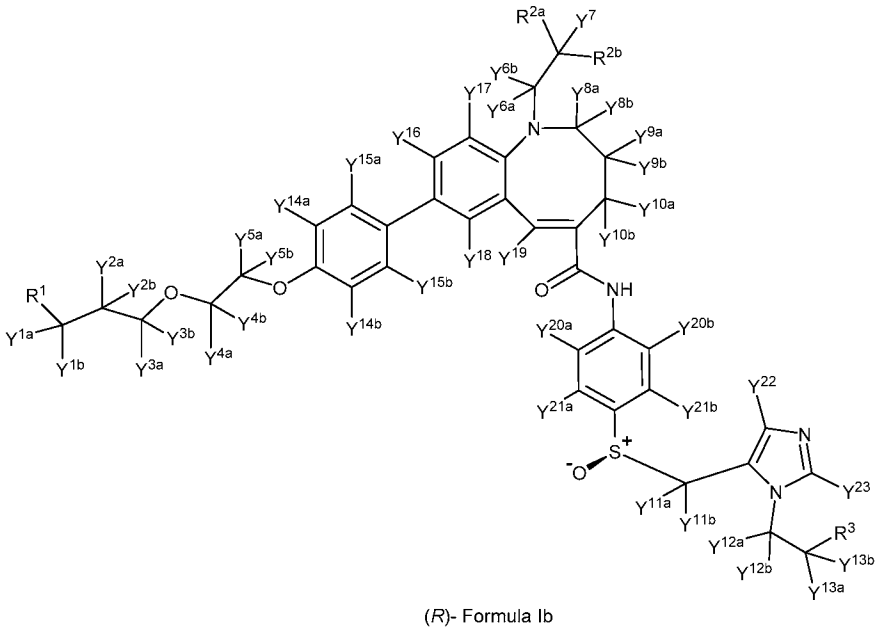


Formula I



(S)- Formula Ia

+



(R)- Formula Ib

Reagents and conditions: (a) $NaOCH_3$, $CO(OCH_3)_2$; (b) TFA; (c) K_2CO_3, $Pd(PPh_3)_4$; (d) NaOH; (e) $SOCl_2$, then Et_3N; (f) Chiral resolution

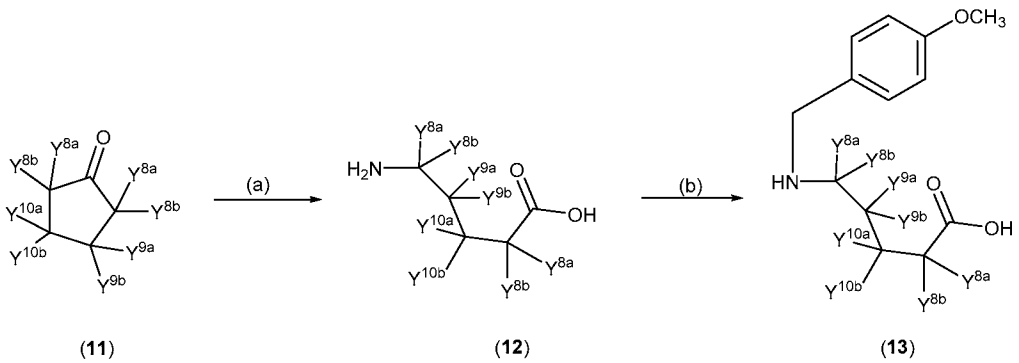
[0080] In a manner analogous to a procedure described in WO 2003014105, and by Seto, M. et al., Journal of Medicinal Chemistry 49(6), 2037-2048, (2006), intramolecular Claisen-Schmidt cyclization of appropriately deuterated intermediate (**1**) containing aldehyde and

ester moieties using dialkylcarbonate such as dimethylcarbonate as solvent in the presence of a base such as sodium methoxide produces appropriately deuterated fused N-benzyl-benzazocine intermediate (**2**). Subsequent removal of the benzyl group in (**2**) using an acid such as trifluoroacetic acid (TFA) affords N-unsubstituted benzazocine intermediate (**3**), and reductive amination with appropriately deuterated aldehyde intermediate (**4**) using appropriately deuterated boron reducing agent such as sodium triacetoxyborohydride or sodium triacetoxyborodeuteride intermediate (**5**) furnishes correspondingly and appropriately deuterated alkyl benzazocine intermediate (**6**). Suzuki cross coupling of the bromide moiety in (**6**) with appropriately deuterated aryl boronic acid intermediate (**7**) provides appropriately deuterated ester intermediate (**8**), and subsequent base hydrolysis produces appropriately deuterated acid intermediate (**9**). Conversion of (**9**) to an acid chloride using thionyl chloride, followed by coupling with appropriately deuterated sulfoxide intermediate (**10**) affords racemic compounds of Formula I. Finally, resolution of a compound of Formula I by chiral HPLC or using other common methods known in the art produces the appropriately deuterated (*S*-) and (*R*-) enantiomers of the compound of Formula I.

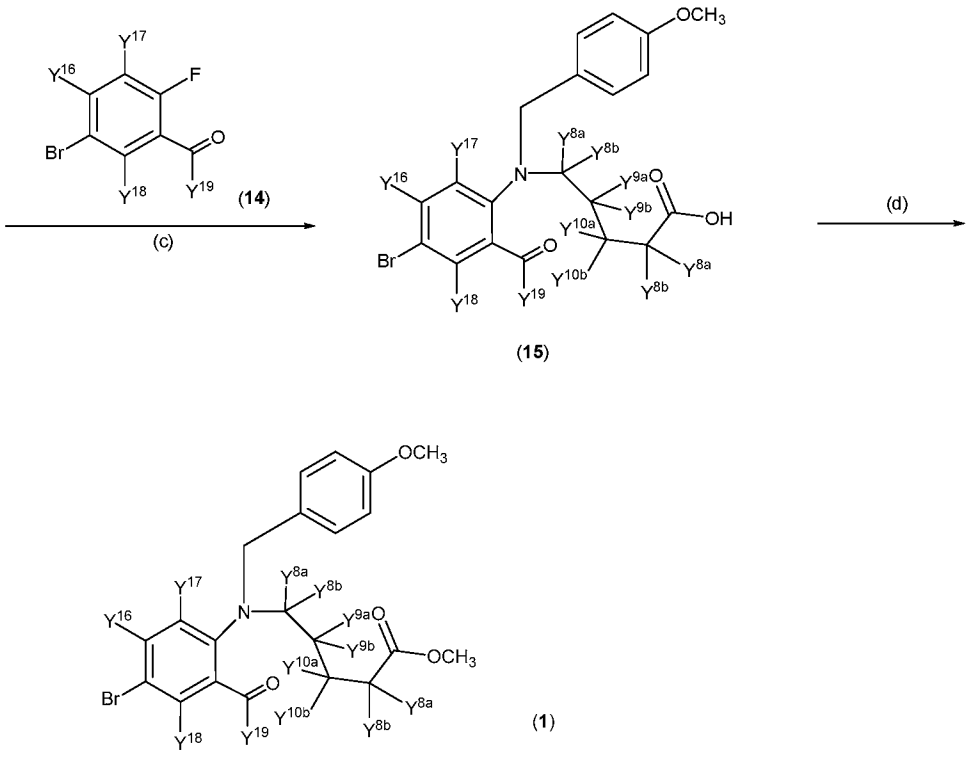
[0081] Using commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I can be prepared with greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% deuterium incorporation at each position designated as D (see below for details).

[0082] Appropriately deuterated intermediate (**1**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 2.

Scheme 2: Preparation of Intermediate (**1**)



(**11**) (**12**) (**13**)



Reagents and conditions: (a) NH_2OH, conc. H_2SO_4, heat; (b) $MgSO_4$, p-anisaldehyde, heat, $NaBH_4$, NaOH; (c) Na_2CO_3; (d) CH_3I, K_2CO_3

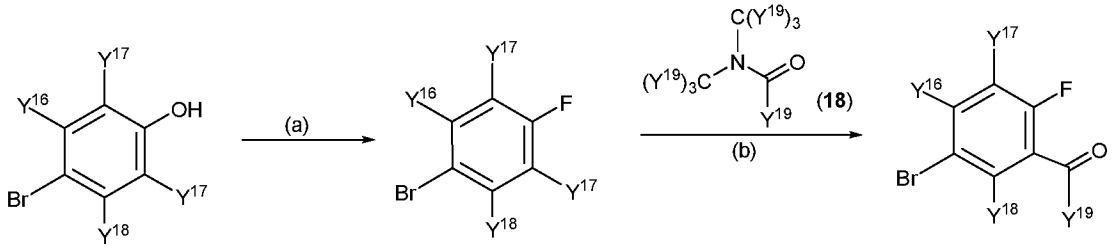
[0083] By analogy to a procedure described by Novotny, A. et al., Chemicke Listy, 52, 718-21,(1958), treatment of appropriately deuterated ketone intermediate (**11**) with hydroxylamine in the presence of sulfuric acid furnishes appropriately deuterated oxime which is not isolated but undergoes Beckmann rearrangement in concentrated sulfuric acid affording a lactam which is ultimately hydrolyzed under acidic conditions at elevated temperature to produce appropriately deuterated amino acid intermediate (**12**). Subsequent reductive amination of (**12**) with p-anisaldehyde using sodium borohydride furnishes appropriately deuterated benzyl amino acid (**13**) in a manner analogous to a procedure described in US2012088761. By analogy to a procedure described by Seto, M. et al., Journal of Medicinal Chemistry 49(6), 2037-2048, (2006), nucleophilic displacement of a fluoride in appropriately deuterated fluorobenzaldehyde intermediate (**14**) with amino moiety in (**13**) affords appropriately deuterated aniline intermediate (**15**) containing aldehyde and carboxylic acid moieties. Esterification of carboxylic acid in (**15**) using iodomethane in the presence of a mild base such as potassium carbonate produces appropriately deuterated intermediate (**1**) containing aldehyde and ester moieties.

[0084] Certain intermediates (**11**) are commercially available: cyclopentanone-d_8 (98 atom %D) (**11a**), cyclopentanone-3,3,4,4-d_4 (98 atom % D) (**11b**), cyclopentanone-2,2,5,5-d_4 (98 atom % D) (**11c**). Cyclopentanone-2,2,3,3,5,5-d_6 (**11d**) and cyclopentanone-*3,3*-d_2 (**11e**) may be prepared according to a procedure described by Leriverend, M. et al., Chemische Berichte 109(10), 3492-5, (1976).

[0085] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{8a, 8b}$, $Y^{9a, 9b}$, $Y^{10a, 10b}$, Y^{16}, Y^{17}, Y^{18} and/or Y^{19} positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[0086] Appropriately deuterated intermediates (**14**), for use in the preparation of intermediate (**1**) according to Scheme 2, which is used to prepare compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 3.

Scheme 3: Preparation of Intermediate (**14**)



Reagents and conditions: (a) PHENOFLUOR™, CsF, Ph_2Zn; (b) LDA

[0087] In a manner analogous to a procedure described in WO 2012142162, deoxyfluorination of appropriately deuterated phenol intermediate (**16**) using 1,3-bis[2,6-bis(1-methylethyl)phenyl]-2,2-difluoro-2,3-dihydro-1H-imidazole (PHENOFLUOR™) in the presence of cesium fluoride and diphenylzinc furnishes appropriately deuterated aryl fluoride intermediate (**17**). Subsequent regioselective deprotonation of (**17**) with lithium diisopropylamide (LDA) and treatment with appropriately deuterated N, N'-dimethylformamide (DMF) intermediate (**18**), by analogy to a procedure described by Boga, S. et al., Tetrahedron Letters 55(32), 4442-4444, (2014) produces appropriately deuterated aryl aldehyde intermediate (**13**).

[0088] Certain intermediates (**16**) may be prepared according to published procedures: 4-bromophenol-3,5-d_2 (**16a**) is prepared according to procedure described by Kirste, B., et al.,

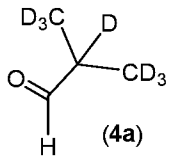
Chemische Berichte 118(5), 1782-97, (1985); 4-bromophenol-2,6-d_2 (**16b**) is prepared in accordance with a procedure described by Zhan, M. et al., European Journal of Organic Chemistry 2015(15), 3370-3373, (2015). 4-Bromophenol-2,3,5,6-d_4 (98 atom %D) (**16c**) is commercially available.

[0089] Intermediate (**18**), N,N-dimethylformamide-d_7 (≥99.5 atom % D) (**18a**) is commercially available.

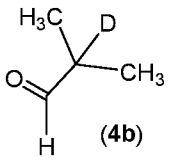
[0090] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^{16}, Y^{17}, Y^{18}, and/or Y^{19} positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[0091] Appropriately deuterated intermediates (**4**), for use in the preparation of compounds of Formula I according to Scheme 1, are commercially available or may be prepared by methods known in the art.

Examples of Intermediates (**4**)



(**4a**) and



(**4b**)

[0092] Intermediate (**4a**) is commercially available: isobutyraldehyde-d_7 (98 atom %D). Intermediate (**4b**), 2-methyl propanal-2-d, may be prepared according to a procedure described by Bowen, R. et al., Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1972-1999), (7), 1041-7, (1992).

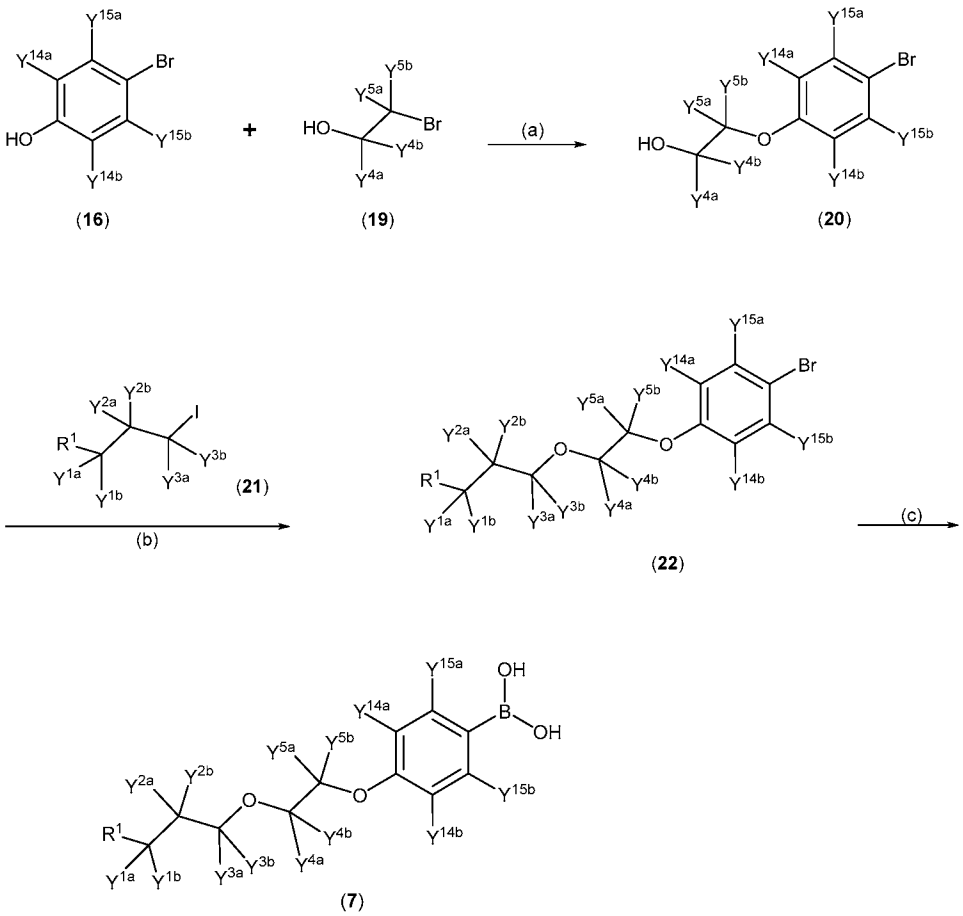
[0093] Use of appropriately deuterated reagents allows deuterium incorporation at the $R^{2a, 2b}$ and/or Y^7 positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[0094] Reagent (**5a**), sodium triacetoxyborodeuteride or $NaBD(OAc)_3$, for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared according to a procedure described in WO2015189413 from sodium borodeuteride (98 atom %D).

[0095] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{6a, 6b}$ positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[0096] Appropriately deuterated intermediates (**7**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 4.

Scheme 4: Preparation of Intermediate (**7**)



Reagents and conditions: (a) K_2CO_3; (b) NaH; (c); Mg, $BrCH_2CH_2Br$ (cat.), $(CH_3O)_3B$, H_2SO_4

[0097] By analogy to a procedure described in WO 2000037455, alkylation of appropriately deuterated bromophenol intermediate (**16**) with appropriately deuterated haloalcohol intermediate (**19**) in the presence of an inorganic base such as potassium carbonate furnishes appropriately deuterated bromophenoxyalcohol intermediate (**20**), which is subsequently alkylated with haloalkane intermediate (**21**) using a base such as sodium hydride to provide appropriately deuterated alkoxybromobenzene intermediate (**22**). Finally, halogen-metal exchange using magnesium metal in the presence of catalytic amounts of 1,2-dibromoethane, affords a Grignard which is treated with trimethylborate followed by hydrolysis to produce appropriately deuterated boronic acid intermediate (**7**).

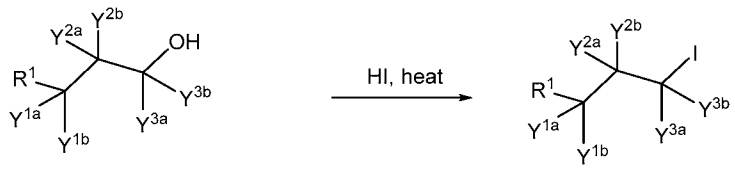
Certain intermediates (**16**) may be prepared according to published procedures described above (**16a, 16b**, see Scheme 3); and (**16c**) is commercially available as previously indicated.

[0098] Intermediate (**19a**), 2-bromoethanol-1,1,2,2-d_4 (99 atom %D), is commercially available. Intermediates (**19b**), 2-bromoethanol-2,2-d_2, and(**19c**), 2-bromoethanol-1,1-d_2, may be prepared according to a procedure described by Ramalingam, K. et al., Journal of Labelled Compounds and Radiopharmaceuticals 24(4), 369-76, (1987).

[0099] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{1a, 1b}$, $Y^{2a, 2b}$, $Y^{3a, 3b}$, $Y^{4a, 4b}$, $Y^{5a, 5b}$, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b} and/or R^1 positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[00100] Appropriately deuterated intermediates (**21**), for use in the preparation of intermediate (**7**) according to Scheme 4, which is used to prepare compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 5.

Scheme 5: Preparation of Intermediate (**21**)



(**23**) (**21**)

[00101] By analogy to a procedure described by Chaykovski, M.M. et al., Journal of the American Chem. Soc. 125(51), 15767-15771, (2003), appropriately deuterated alkyl iodide intermediate (**21**) may be prepared by treating appropriately deuterated alcohol intermediate (**23**) with hydriodic acid (HI) at elevated temperature.

[00102] Certain intermediates (**23**) are commercially available: n-butyl-d_9 alcohol (99 atom%D) (**23a**), n-butyl-2,2,3,3,4,4,4-d_7 alcohol (98 atom%D) (**23b**), n-butyl-1,1,2,2,3,3-d_6 alcohol (98 atom%D) (**23c**), n-butyl-1,1,2,2-d_4 alcohol (98 atom%D) (**23d**), n-butyl-4,4,4-d_3 alcohol (99 atom%D) (**23e**), and n-butyl-1,1-d_2 alcohol (99 atom %D) (**23f**). The following intermediates (**23**) may be prepared by published procedures: 1-butan-2,2,3,3-d_4-ol (**23g**) may be prepared according to a procedure described by Olah, G. et al., Angewandte Chemie 93(1), 107, (1981); 1-butan-1,1,2,2,4,4,4-d_7-ol (**23h**) and 1-butan-1,1,4,4,4-d_5-ol (**23i**) may be prepared according to a procedure described by Hudson, H. et al., Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1972-1999) (1), 57-

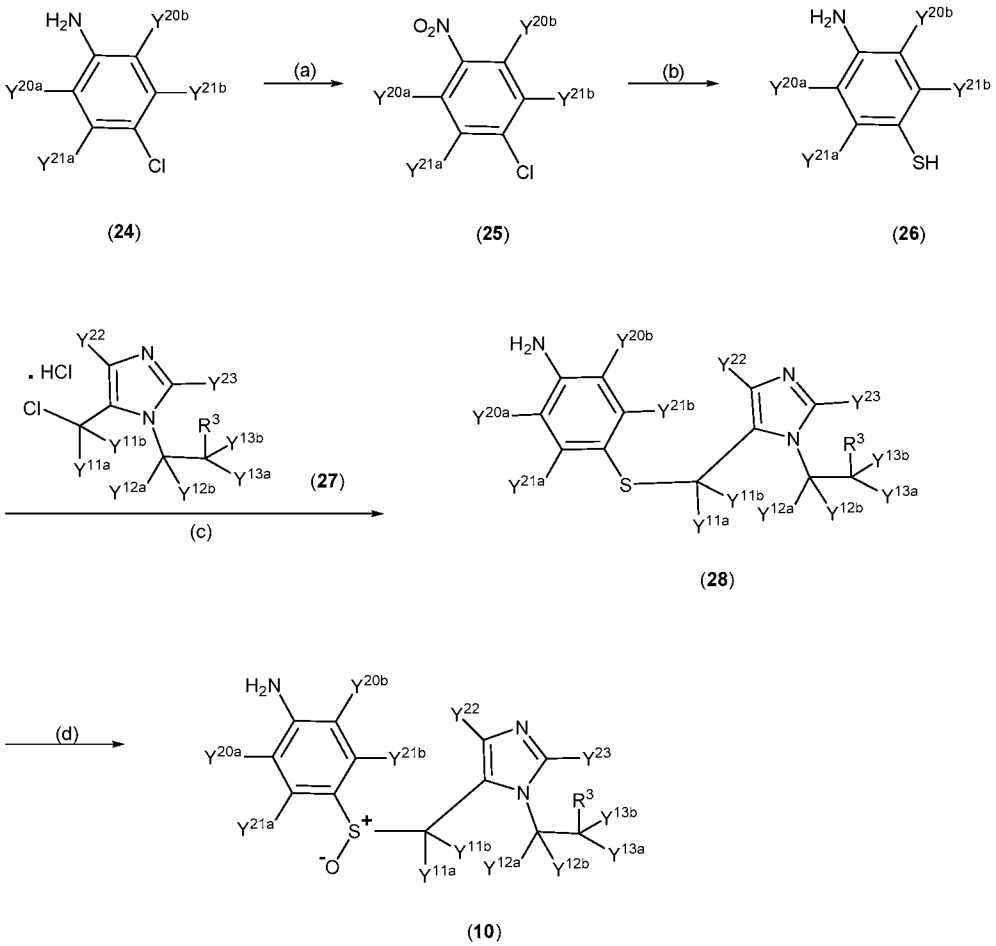
66, (1979); 1-butan-3,3-d_2-ol (**23j**) and 1-butan-2,2-d_2-ol (**23k**) may be prepared according to a procedure described by Khrizman, A. et al., Journal of Labelled Compounds and Radiopharmaceuticals 54(8), 401-407, (2011).

[00103] Additionally, intermediate (**21a**), 1-iodobutane-d_9 (98 atom %D), is commercially available.

[00104] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{1a, 1b}$, $Y^{2a, 2b}$, $Y^{3a, 3b}$ and/or R^1 positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[00105] Appropriately deuterated intermediates (**10**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 6.

Scheme 6: Preparation of Intermediate (**10**)



Reagents and conditions: (a) *m*-CPBA; (b) Na_2S, SDS, AcOH ; (c) Et_3N; (d) H_2O_2, AcOH, NaOH, Na_2SO_3

[00106] By analogy to a procedure described by Liu, J. et al., Tetrahedron Letters 55(9), 1581-1584, (2014), appropriately deuterated aniline intermediate (**24**) is oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) at elevated temperature to furnish appropriately deuterated nitroarene intermediate (**25**), which is subsequently treated with sodium sulfide in aqueous solution containing surfactant such as sodium dodecyl sulfate (SDS) in a manner analogous to a procedure described in JP 07053507, affording appropriately deuterated aminothiophenol intermediate (**26**). By analogy to a procedure described by Ikemoto, T. et al., Tetrahedron 61(21), 5043-5048, (2005), alkylation of thiol (**26**) with a hydrohalide salt such as hydrochloride salt of appropriately deuterated imidazolyl alkyl halide intermediate (**27**) in the presence of a base such as triethylamine furnishes appropriately deuterated sulfide intermediate (**28**). Finally, oxidation with oxidizing agent such as with hydrogen peroxide in acetic acid produces racemic and appropriately deuterated sulfoxide intermediate (**10**).

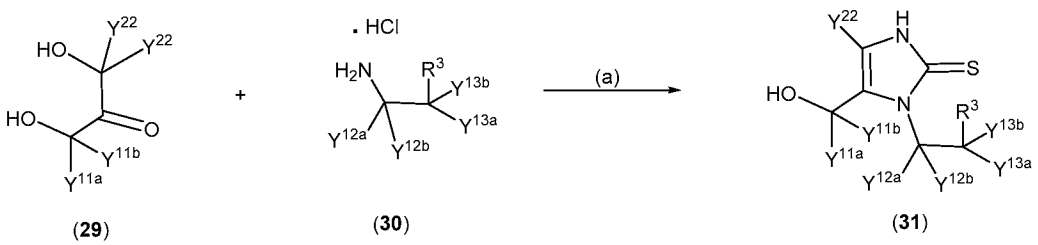
[00107] Certain intermediates (**24**) are commercially available: 4-chloroaniline-2,3,5,6-d_4 (98 atom %D) (**24a**), and 4-chloroaniline-2,6-d_2 (98 atom % D) (**24b**).

[00108] 4-Chloro-benzen-amine-3,5-d_2, (**24c**) may be prepared according to a procedure described by Suehiro, T. et al., Bulletin of the Chemical Society of Japan 60(9), 3321-30, (1987).

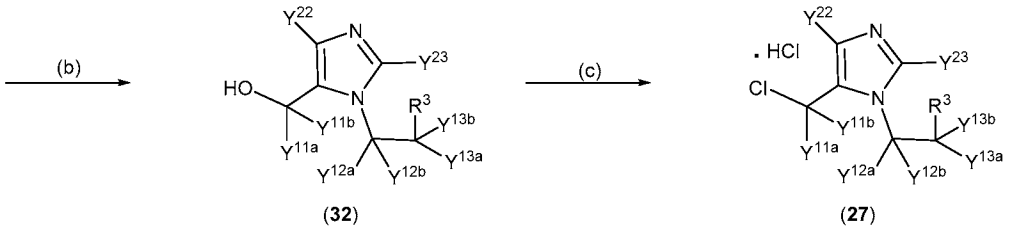
[00109] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{11a, 11b}$, $Y^{12a, 12b}$, $Y^{13a, 13b}$, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, Y^{23} and/or R^3 positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[00110] Appropriately deuterated intermediates (**27**), for use in the preparation of intermediate (**10**) according to Scheme 6, which is used to prepare compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 7.

Scheme 7: Preparation of Intermediate (**27**)



(**29**) (**30**) (**31**)



Reagents and conditions: (a) KSCN; (b) aq. HNO_3, $NaNO_2$, K_2CO_3 or HNO_3/D_2O, $NaNO_2$, K_2CO_3; (c) $SOCl_2$

[00111] In a manner analogous to a procedure described by Seto, M. et al., Bioorganic & Medicinal Chemistry 13(2), 363-386, (2004), appropriately deuterated acetone intermediate (**29**) is treated with hydrohalide salt such as hydrochloride salt of appropriately deuterated alkyl amine intermediate (**30**) in the presence of a thiocyanate such as potassium thiocyanate to furnish appropriately deuterated mercaptoimidazole intermediate (**31**). Oxidative desulfurization of mercapto moiety in (**31**) using aqueous nitric acid and catalytic amount of sodium nitrite or deuterated nitric acid in deuterium dioxide and catalytic amount of sodium nitrite followed by basification with inorganic base such as potassium carbonate affords correspondingly and appropriately deuterated imidazole (**32**). Finally, chlorination of hydroxyl moiety in (**32**) using thionyl chloride at elevated temperature produces hydrochloride salt of appropriately deuterated imidazolyl alkyl halide intermediate (**27**).

[00112] Intermediate (**29a**), 1,3-dihydroxy-2-Propanone-1,1,3,3-d_4, may be prepared according to a procedure described by Yi, J. et al., ChemSusChem 5, 1401–1404, (2012).

[00113] 1,3-Dihydroxy-2-propanone-1,1,-d_2 (**28b**) may be prepared from 1,2,3-propane-1, 1-d_2-triol by analogy to an oxidation procedure described in WO 2014102840. 1,2,3-Propane-1,1-d_2-triol may be prepared, in turn, according to a procedure described by Hill, A. et al., Chemical Communications (Cambridge) (21), 2361-2362, (1998).

[00114] Certain intermediates (**30**) are commercially available: n-propyl-d_7-amine HCl (98 atom %D) (**30a**); n-propyl-2,2,3,3,3-d_5-amine HCl (98 atom % D) (**30b**); and n-propyl-3,3,3-d_3-amine HCl (99 atom %D) (**30c**).

[00115] Use of appropriately deuterated reagents allows deuterium incorporation at the $Y^{11a, 11b}$, $Y^{12a, 12b}$, $Y^{13a, 13b}$, Y^{22}, Y^{23} and/or R^3 positions of a compound of Formula I or any appropriate intermediate herein at levels, e.g., greater than about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%.

[00116] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[00117] Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[00118] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Pharmaceutical Compositions

[00119] The invention also provides pharmaceutical compositions comprising an effective amount of a compound of Formula I, Ia, or Ib (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

[00120] Pharmaceutically acceptable carriers, adjuvants, excipients and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates (e.g., phosphate-buffered saline, etc.), glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate,

potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00121] If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[00122] Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ or PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Patent No. 7,014,866; and United States Patent Appln. Publication Nos. 20060094744 and 20060079502.

[00123] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

[00124] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00125] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such

as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[00126] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[00127] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[00128] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[00129] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or

suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[00130] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00131] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz J.D. and Zaffaroni A.C., U.S. Patent No. 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[00132] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[00133] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[1] Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patent Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics to the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

[00134] According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

[00135] According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[00136] According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

[00137] According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

[00138] Where an organ or tissue is accessible because of removal from the subject, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

[00139] In another embodiment, a composition of this invention further comprises one or more additional therapeutic agents. The additional therapeutic agent(s) may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as cenicriviroc (e.g., a CCR5 antagonist). Such agents include, but are not limited to, those described in PCT publications WO2016040860, WO2015187663, WO2015143367, and WO2003014105.

[00140] Preferably, the additional therapeutic agent is an agent useful in the treatment of a disease or condition selected from HIV infection, hepatic impairment, NASH, primary sclerosing cholangitis, pre-diabetes, non-alcoholic fatty liver disease and type 2 diabetes.

[00141] In some embodiments, the additional therapeutic agent is selected from a farnesoid X receptor (FXR) agonist, high dose vitamin E (> 400 iU/d), a peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, a PPAR-γ agonist, a PPAR-δ agonist, and a chemokine antagonist. In one aspect of these embodiments, the second agent is selected from obeticholic acid, pioglitazone, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(l-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]benzoic acid (GW4064), 2-methyl-2-[[4-[2- [[(cyclohexylamino)carbonyl](4-cyclohexylbutyl)amino]ethyl]phenyl]thio]-propanoic acid (GW7647), 2-[2,6 dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-l(E)-propenyl]phenoxyl]-2-methylpropanoic acid (GFT505), and BX471.

[00142] In some embodiments, the additional therapeutic agent is an antiretroviral agent selected from entry inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, maturation inhibitors (e.g., GSK2838232), and combinations thereof. In one aspect of these embodiments, the one or more additional antiretroviral agents include, but are not limited to, lamivudine, efavirenz, raltegravir, vivecon, bevirimat, alpha interferon, zidovudine, abacavir, lopinavir, ritonavir, tenofovir, tenofovir disoproxil or its fumarate salt, tenofovir alafenamide or its fumarate salt, emtricitabine, elvitegravir, cobicistat, darunavir, atazanavir, rilpivirine, dolutegravir, and combinations thereof.

[00143] In one embodiment, the additional therapeutic agent is selected from dolutegravir, midazolam, TRUVADA® (emtricitabine and tenofovir disoproxil fumarate), efavirenz, evogliptin, pioglitazone, a statin (e.g., rosuvastatin, atorvastatin, simvastatin), or evogliptin.

[00144] In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described additional therapeutic agents, wherein the compound and additional therapeutic agent are associated with one another. The term "associated with one another," as used herein, means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[00145] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

[00146] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., Cancer Chemother. Rep, 1966, 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[00147] An effective amount of a compound of this invention can range from about 1 mg/day to about 2000 mg/day, from about 5 mg/day to about 1000 mg/day, from about 10 mg/day to about 500 mg/day, or from about 25 mg/day to about 200 mg/day.

[00148] An effective amount of a compound of this invention can range from about 10 mg/day to about 200 mg/day, from about 10 mg/day to about 100 mg/day, from about 25 mg/day to about 150 mg/day, or from about 25 mg/day to about 100 mg/day.

[00149] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for cenicriviroc.

[00150] For pharmaceutical compositions that comprise one or more additional therapeutic agents, an effective amount of the additional therapeutic agent is between about 20% and

100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these additional therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[00151] Some of the additional therapeutic agents referenced above may act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the additional therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantages of minimizing toxic side effects of either the additional therapeutic agent or the compound of this invention, synergistically improving efficacy, improving ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

[00152] Certain aspects of the invention provide a method of antagonizing the activity of CCR2 in a cell, comprising contacting a cell with one or more compounds of Formula I, Ia or Ib herein, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the cell is contacted *in vitro*. In some embodiments, the cell is contacted *in vivo*. In some embodiments, the cell is contacted *ex vivo*.

[00153] Certain aspects of the invention provide a method of treating a disease that is beneficially treated by cenicriviroc in a subject in need thereof, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention. In certain embodiments the subject is a patient in need of such treatment. In certain embodiments the subject is a human.

[00154] Certain aspects of the invention provide a method of antagonizing the activity of CCR5 in a cell, comprising contacting a cell with one or more compounds of Formula I, Ia or Ib herein, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[00155] Certain aspects of the invention provide a method of antagonizing the activity of both CCR2 and CCR5 in a cell, comprising contacting a cell with one or more compounds of Formula I, Ia or Ib herein, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[00156] Certain aspects of the invention provide a method of treating a disease that is beneficially treated by administration of a CCR2 antagonist, a CCR5 antagonist, or a dual CCR2/CCR5 antagonist to a subject in need thereof, comprising administering to the subject an effective amount of a compound, a pharmaceutically acceptable salt or a composition of this invention. In one embodiment, the subject is a patient in need of such treatment. Such diseases are well known in the art and are disclosed in, but not limited to the following published applications: WO2016040860, WO2015187663, WO2015143367, WO2014186581, WO2005116013, WO2003076411 and WO2003014105. Such diseases include, but are not limited to, cirrhosis, hepatic fibrosis, kidney fibrosis, hepatic non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), emerging cirrhosis, graft-versus-host disease, HIV infection, rheumatoid arthritis, autoimmune disease, allergies, ischemic brain cell disorder, cardiac infarction, chronic nephritis, arteriosclerosis, alcoholic liver disease, HIV/HCV co-infection, HBV infection, HCV infection, metabolic syndrome, obesity, type 2 diabetes, and prediabetes.

[00157] In one particular embodiment, the method of this invention is used to treat a disease or condition selected from HIV infection, non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), and obesity in a subject in need thereof.

[00158] Certain aspects of this invention provide a method of treating cancer, comprising administering to a subject in need thereof an effective amount of a compound, a pharmaceutically acceptable salt or a composition of this invention in combination with one or more immune checkpoint inhibitors. Such checkpoint inhibitors include, but are not limited to, inhibitors of programmed cell death protein 1 (PD-1), programed cell death-ligand 1 (PD-L1), programed cell death 1-ligand 2 (PD-L2), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and cluster of differentiation 276 gene (CD276 also known as B7-H3). Examples of such inhibitors include, but are not limited to, PD-1inhibitors: nivolumab, pembrolizumab and AMP-224; PD-L1 inhibitors: MDX-1105, atezolizumab, and durvalumab; CTLA-4 inhibitors: ipilimumab and tremelimumab; LAG-3 protein or fusion protein: IMP-321; CD276 inhibitor: enoblituzumab; pidilizumab and MGD009.

[00159] Certain aspects of this invention provide a method of treating cancer, comprising administering to a subject in need thereof an effective amount of a compound, a

pharmaceutically acceptable salt or a composition of this invention in combination with one or more FAK inhibitors. Such FAK inhibitors include, but are not limited to, BI 853529, GSK2256098, NVP-226, PF-573,228, PF-562,271 (VS-6062), VS-4718, VS-6063, VS-5095, Y15, CFAK-C4, INT2-31, M13, and R2.

[00160] Certain aspects of this invention provide a method of treating cancer, comprising administering to a subject in need thereof an effective amount of a compound, a pharmaceutically acceptable salt or a composition of this invention in combination with one or more checkpoint inhibitors and one or more FAK inhibitors.

[00161] In some embodiments, the invention provides a method of treating a cancer selected from skin cancer, basal cell carcinoma, melanoma, renal carcinoma, urothelial cancer, bladder cancer, pancreatic cancer, colorectal cancer, breast cancer, prostate cancer, head and neck cancer, digestive/gastrointestinal cancer, esophageal cancer, gastric cancer, respiratory/thoracic cancer, laryngeal cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, genitourinary cancer, female reproductive system cancer, ovarian cancer, thyroid cancer, endometrial cancer, cervical cancer, glioblastoma multiforme, malignant pleural mesothelioma, squamous cell carcinoma, myelodysplastic syndrome, multiple myeloma, myeloid leukemia, lymphoma, lymphocytic leukemia, non-Hodgkin's lymphoma, endocrine cancer, neurologic cancer, sarcoma, osteosarcoma, liver cancer, astrocytoma, glioma, hematological cancer and solid tumors. In one embodiment, the cancer is selected from pancreatic cancer, colorectal cancer, breast cancer, head and neck cancer, melanoma, renal carcinoma, non-small cell lung cancer, Hodgkin's lymphoma and bladder cancer. In one embodiment, the cancer is selected from head and neck cancer, melanoma, renal carcinoma, non-small cell lung cancer, Hodgkin's lymphoma and bladder cancer.

[00162] Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[00163] In another embodiment, any of the above methods of treatment further comprises co-administering to the subject in need thereof one or more additional therapeutic agents. The choice of additional therapeutic agent may be made from any additional therapeutic agent set forth above for use in combination compositions comprising a compound of this invention and an additional therapeutic agent.

[00164] In some embodiments, the combination therapies of this invention include co-administering a compound of Formula I, or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent selected from dolutegravir, midazolam, TRUVADA® (emtricitabine and tenofovir disoproxil fumarate), evogliptin, pioglitazone, a statin (e.g., rosuvastatin, atorvastatin, simvastatin), and evogliptin.

[00165] The term "co-administered," as used herein, means that the additional therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an additional therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the additional therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention comprising both a compound of the invention and an additional therapeutic agent to a subject does not preclude the separate administration of that same therapeutic agent, any other additional therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[00166] Effective amounts of these additional therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the additional therapeutic agent's optimal effective-amount range.

[00167] In one embodiment of the invention, where an additional therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the additional therapeutic agent is not administered. In another embodiment, the effective amount of the additional therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[00168] In yet another aspect, the invention provides the use of a compound of Formula I, Ia or Ib, or a pharmaceutically acceptable salt of any of the foregoing, alone or together with one or more of the above-described additional therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I, Ia or Ib, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment in a subject of a disease, disorder or symptom thereof delineated herein.

Example 1. Evaluation of Metabolic Stability

[00169] ***Microsomal Assay:*** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[00170] ***Determination of Metabolic Stability:*** 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

[00171] ***Data analysis:*** The *in vitro* $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

in vitro $t_{½}$ = 0.693/k

k = -[slope of linear regression of % parent remaining (ln) vs incubation time]

[00172] Data analysis is performed using Microsoft Excel Software.

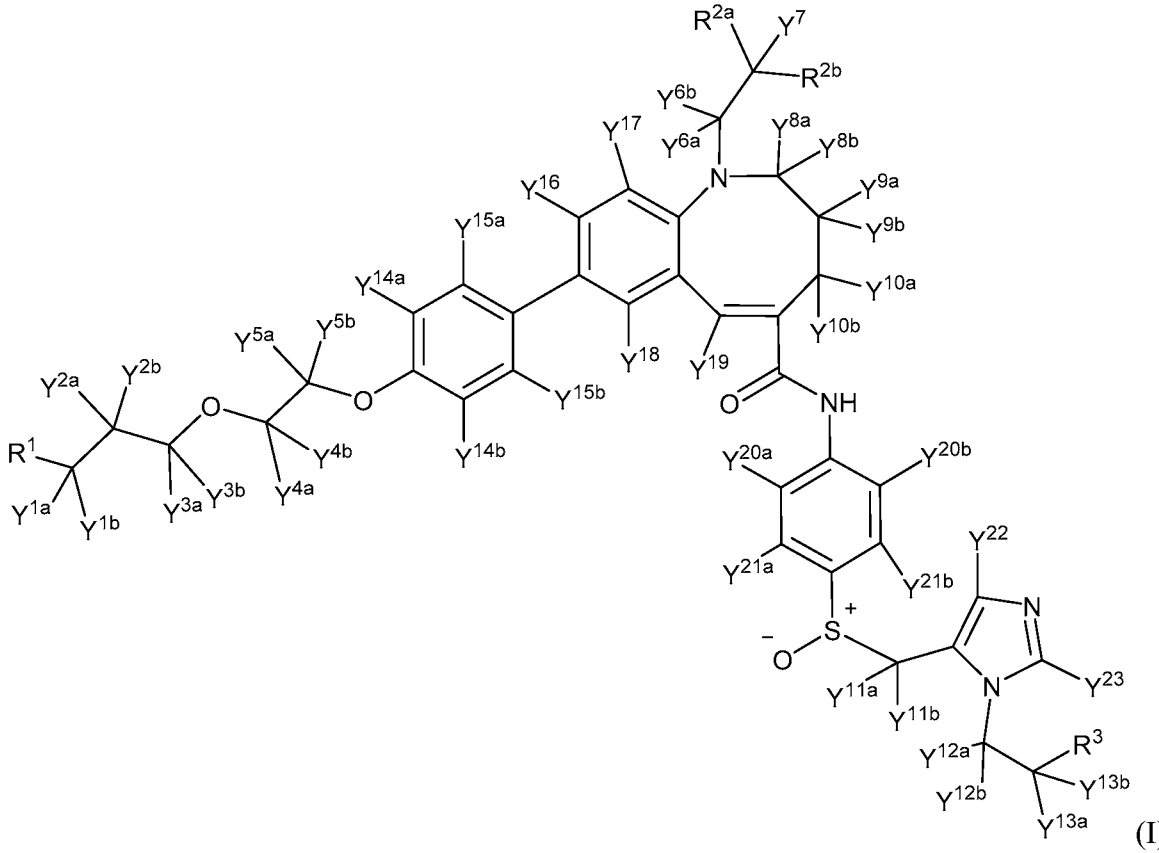
[00173] The relevant teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

[00174] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A compound of Formula I:



(I),

or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein:

each of R^1, R^{2a}, R^{2b} and R^3 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$, and $-CD_3$;

each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^7, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is independently selected from hydrogen and deuterium; and

when each of R^1, R^{2a}, R^{2b} and R^3 is $-CH_3$, at least one of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^7, Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a}, Y^{10b}, Y^{11a}, Y^{11b}, Y^{12a}, Y^{12b}, Y^{13a}, Y^{13b}, Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, or Y^{23} is deuterium.

2. The compound of claim 1, wherein each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen.

3. The compound of claim 1 or 2, wherein Y^{1a} and Y^{1b} are the same; Y^{2a} and Y^{2b} are the same; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same; Y^{6a} and Y^{6b} are the same; Y^{8a} and Y^{8b} are the same; Y^{9a} and Y^{9b} are the same; Y^{10a} and Y^{10b} are the same; Y^{11a} and Y^{11b} are the same; Y^{12a} and Y^{12b} are the same; and Y^{13a} and Y^{13b} are the same.

4. The compound of any one of claims 1-3, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same.

5. The compound of any one of claims 1-4, wherein each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same.

6. The compound of any one of claims 1-5, wherein each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same.

7. The compound of any one of claims 1-6, wherein each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same.

8. The compound of any one of claims 1-7, wherein each of Y^{6a}, Y^{6b}, and Y^{7} is the same.

9. The compound of any one of claims 1-8, wherein each of R^{1}, R^{2a}, R^{2b} and R^{3} is independently selected from $-CH_3$ and $-CD_3$.

10. The compound of any one of claims 1-9, wherein R^{2a} and R^{2b} are the same.

11. The compound of any one of claims 1-10, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is deuterium; and R^{1} is $-CD_3$.

12. The compound of any one of claims 1-10, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is hydrogen; and R^1 is $-CH_3$.

13. The compound of any one of claims 1-12, wherein Y^7 is deuterium; and R^{2a} and R^{2b} are $-CD_3$.

14. The compound of claim 13, wherein each of Y^{6a} and Y^{6b} is deuterium.

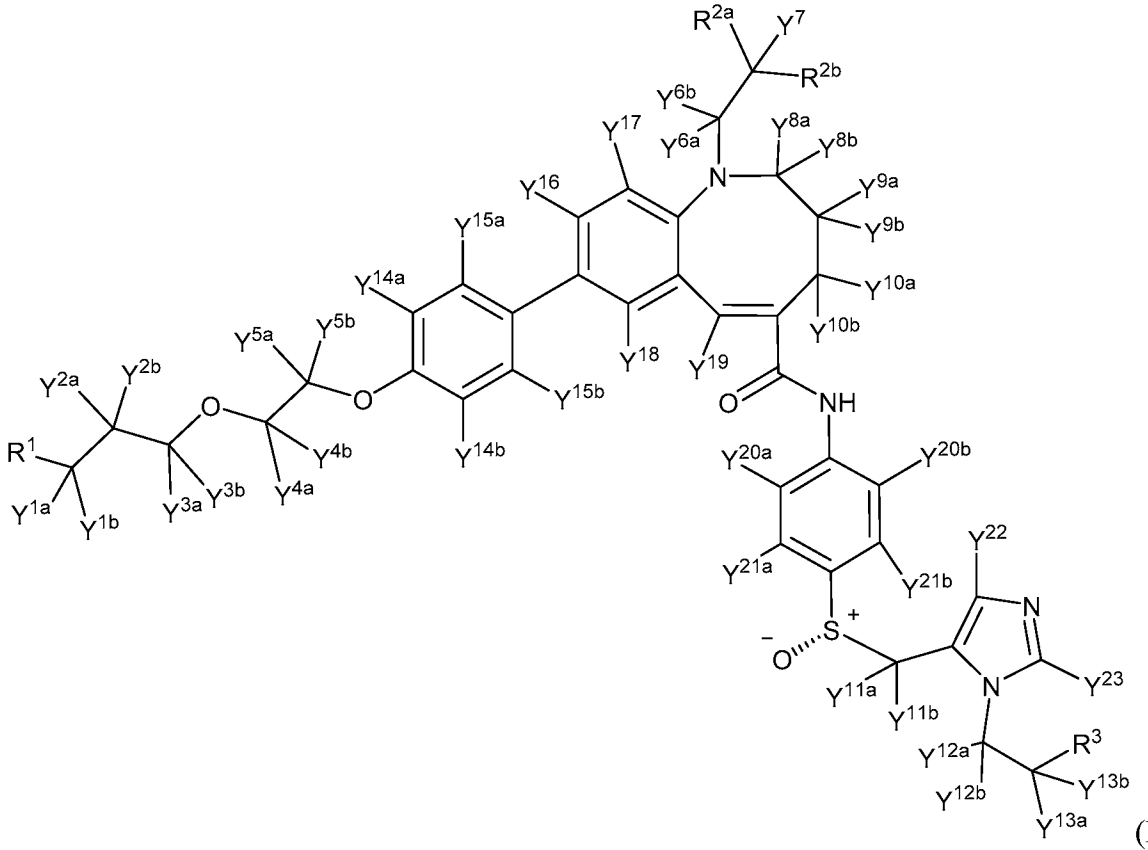
15. The compound of any one of claims 1-12, wherein Y^7 is hydrogen, and R^{2a} and R^{2b} are $-CH_3$.

16. The compound of claim 15, wherein each of Y^{6a} and Y^{6b} is hydrogen.

17. The compound of any one of claims 1-16, wherein each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is deuterium; and R^3 is $-CD_3$.

18. The compound of any one of claims 1-16, wherein each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is hydrogen; and R^3 is $-CH_3$.

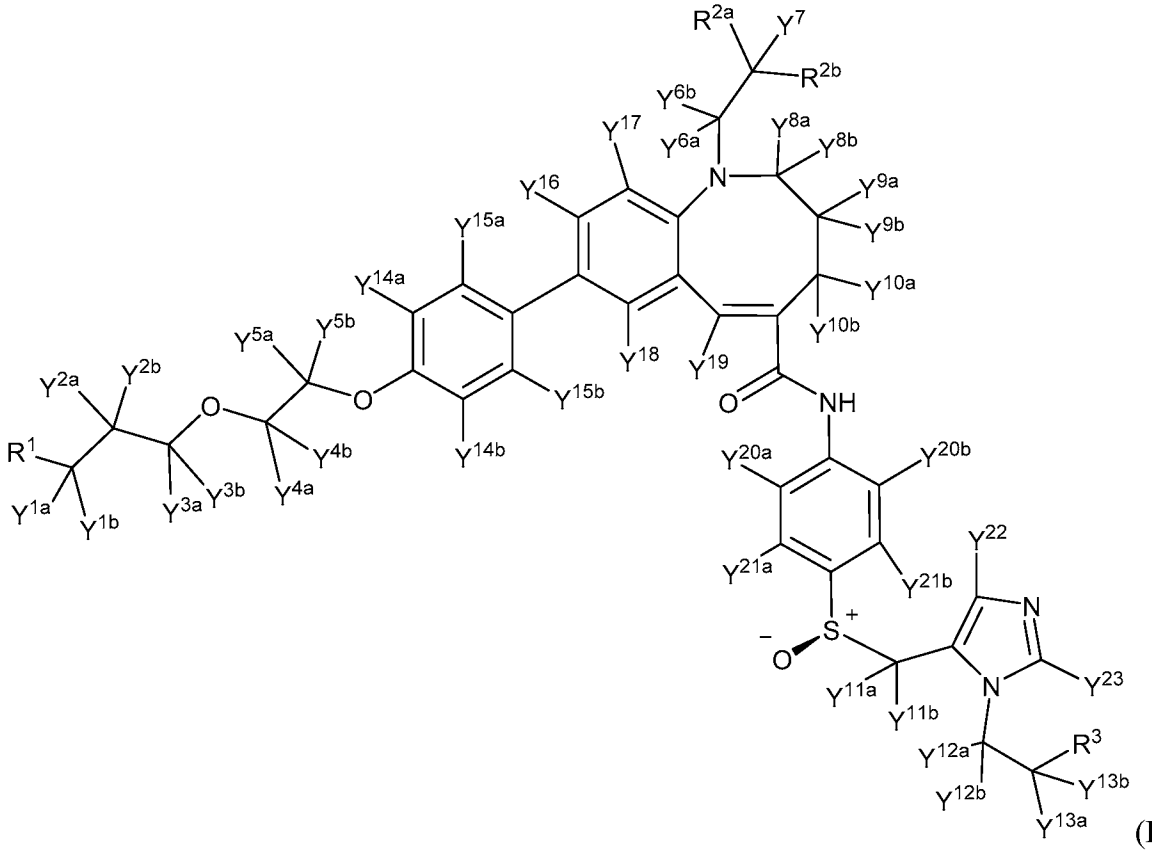
19. The compound of any one of claims 1-18, wherein the compound is an (*S*) stereoisomer at the sulfoxide moiety having the Formula Ia:



(Ia),

or a pharmaceutically acceptable salt thereof.

20. The compound of any one of claims 1-18, wherein the compound is an (*R*) stereoisomer at the sulfoxide moiety having the Formula Ib:



(Ib),

or a pharmaceutically acceptable salt thereof.

21. The compound of any one of claims 1-20, wherein the compound is a mesylate salt.

22. The compound of any one of claims 1-21, wherein any atom not specifically designated as deuterium is present at its natural isotopic abundance.

23. The compound of claim 19, wherein R^{2a} and R^{2b} are the same; each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a} and Y^{3b} is the same; each of Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} is the same; each of Y^{6a}, Y^{6b}, and Y^{7} is the same; each of Y^{8a}, Y^{8b}, Y^{9a}, Y^{9b}, Y^{10a} and Y^{10b} is the same; each of Y^{11a} and Y^{11b} is the same; each of Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} is the same; each of Y^{14a}, Y^{14b}, Y^{15a}, Y^{15b}, Y^{16}, Y^{17}, Y^{18}, Y^{19}, Y^{20a}, Y^{20b}, Y^{21a}, Y^{21b}, Y^{22}, and Y^{23} is hydrogen; and the compound is selected from any one of the compounds set forth in table below:

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
100a	CD_3	CH_3	CH_3	D	H	H	H	H	H
101a	CH_3	CD_3	CH_3	H	H	D	H	H	H
102a	CH_3	CH_3	CD_3	H	H	H	H	H	D

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
103a	CH_3	CH_3	CH_3	H	D	H	H	H	H
104a	CH_3	CH_3	CH_3	H	H	H	D	H	H
105a	CD_3	CD_3	CH_3	D	H	D	H	H	H
106a	CD_3	CH_3	CD_3	D	H	H	H	H	D
107a	CD_3	CH_3	CH_3	D	D	H	H	H	H
108a	CD_3	CH_3	CH_3	D	H	H	D	H	H
109a	CH_3	CD_3	CD_3	H	H	D	H	H	D
110a	CH_3	CD_3	CH_3	H	D	D	H	H	H
111a	CH_3	CD_3	CH_3	H	H	D	D	H	H
112a	CH_3	CH_3	CD_3	H	D	H	H	H	D
113a	CH_3	CH_3	CD_3	H	H	H	D	H	D
114a	CH_3	CH_3	CH_3	H	D	H	D	H	H
115a	CD_3	CD_3	CD_3	D	H	D	H	H	D
116a	CD_3	CD_3	CH_3	D	D	D	H	H	H
117a	CD_3	CD_3	CH_3	D	H	D	D	H	H
118a	CD_3	CH_3	CD_3	D	D	H	H	H	D
119a	CD_3	CH_3	CD_3	D	H	H	D	H	D
120a	CD_3	CH_3	CH_3	D	D	H	D	H	H
121a	CH_3	CD_3	CD_3	H	D	D	H	H	D
122a	CH_3	CD_3	CD_3	H	H	D	D	H	D
123a	CH_3	CD_3	CH_3	H	D	D	D	H	H
124a	CH_3	CH_3	CD_3	H	D	H	D	H	D
125a	CD_3	CD_3	CD_3	D	D	D	H	H	D
126a	CD_3	CD_3	CD_3	D	H	D	D	H	D
127a	CD_3	CD_3	CH_3	D	D	D	D	H	H
128a	CD_3	CH_3	CD_3	D	D	H	D	H	D
129a	CH_3	CD_3	CD_3	H	D	D	D	H	D
130a	CD_3	CD_3	CD_3	D	D	D	D	H	D
131a	CD_3	CH_3	CH_3	D	H	H	H	D	H
132a	CH_3	CD_3	CH_3	H	H	D	H	D	H
133a	CH_3	CH_3	CD_3	H	H	H	H	D	D
134a	CH_3	CH_3	CH_3	H	D	H	H	D	H
135a	CH_3	CH_3	CH_3	H	H	H	D	D	H
136a	CD_3	CD_3	CH_3	D	H	D	H	D	H
137a	CD_3	CH_3	CD_3	D	H	H	H	D	D
138a	CD_3	CH_3	CH_3	D	D	H	H	D	H
139a	CD_3	CH_3	CH_3	D	H	H	D	D	H
140a	CH_3	CD_3	CD_3	H	H	D	H	D	D
141a	CH_3	CD_3	CH_3	H	D	D	H	D	H
142a	CH_3	CD_3	CH_3	H	H	D	D	D	H
143a	CH_3	CH_3	CD_3	H	D	H	H	D	D
144a	CH_3	CH_3	CD_3	H	H	H	D	D	D
145a	CH_3	CH_3	CH_3	H	D	H	D	D	H
146a	CD_3	CD_3	CD_3	D	H	D	H	D	D
147a	CD_3	CD_3	CH_3	D	D	D	H	D	H

#	R^1	R^{2a}/R^{2b}	R^3	$Y^1/Y^2/Y^3$	Y^4/Y^5	Y^6/Y^7	$Y^8/Y^9/Y^{10}$	Y^{11}	Y^{12}/Y^{13}
148a	CD_3	CD_3	CH_3	D	H	D	D	D	H
149a	CD_3	CH_3	CD_3	D	D	H	H	D	D
150a	CD_3	CH_3	CD_3	D	H	H	D	D	D
151a	CD_3	CH_3	CH_3	D	D	H	D	D	H
152a	CH_3	CD_3	CD_3	H	D	D	H	D	D
153a	CH_3	CD_3	CD_3	H	H	D	D	D	D
154a	CH_3	CD_3	CH_3	H	D	D	D	D	H
155a	CH_3	CH_3	CD_3	H	D	H	D	D	D
156a	CD_3	CD_3	CD_3	D	D	D	H	D	D
157a	CD_3	CD_3	CD_3	D	H	D	D	D	D
158a	CD_3	CD_3	CH_3	D	D	D	D	D	H
159a	CD_3	CH_3	CD_3	D	D	H	D	D	D
160a	CH_3	CD_3	CD_3	H	D	D	D	D	D
161a	CD_3	CD_3	CD_3	D	D	D	D	D	D
162a	CH_3	CH_3	CH_3	H	H	H	H	D	H

or a pharmaceutically acceptable salt of any of the foregoing, wherein any atom not specifically designated as deuterium is present at its natural isotopic abundance.

24. A pharmaceutical composition comprising a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

25. A method of antagonizing the activity of CCR5 in a cell, comprising contacting the cell with a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a composition of claim 24.

26. A method of antagonizing the activity of CCR2 in a cell, comprising contacting the cell with a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a composition of claim 24.

27. A method of antagonizing the activity of CCR5 and CCR2 in a cell, comprising contacting the cell with a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a composition of claim 24.

28. A method of treating a disease in a subject, selected from HIV infection, non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), and obesity, comprising administering to a subject in need thereof an effective amount of a compound or

pharmaceutically acceptable salt of any one of claims 1-23, or a composition of claim 24.

29. The method of claim 28, further comprising co-administering to the subject in need thereof one or more additional therapeutic agents selected from dolutegravir, midazolam, emtricitabine, tenofovir disoproxil fumarate, evogliptin, pioglitazone, a statin, and evogliptin.

30. A method of treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a composition of claim 24, in combination with an immune checkpoint inhibitor.

31. The method of claim 30, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, a CTLA-4 inhibitor, a soluble LAG3 and a CD276 inhibitor.

32. The method of claim 30, wherein the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, AMP-224, MDX-1105, atezolizumab, durvalumab, ipilimumab, tremelimumab, pidilizumab, enoblituzumab, IMP321 and MGD009.

33. The method of claim 30, wherein the cancer is selected from skin cancer, basal cell carcinoma, melanoma, renal carcinoma, urothelial cancer, bladder cancer, pancreatic cancer, colorectal cancer, breast cancer, prostate cancer, head and neck cancer, digestive/gastrointestinal cancer, esophageal cancer, gastric cancer, respiratory/thoracic cancer, laryngeal cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, genitourinary cancer, female reproductive system cancer, ovarian cancer, thyroid cancer, endometrial cancer, cervical cancer, glioblastoma multiforme, malignant pleural mesothelioma, squamous cell carcinoma, myelodysplastic syndrome, multiple myeloma, myeloid leukemia, lymphoma, Hodgkin’s lymphoma, lymphocytic leukemia, non-Hodgkin's lymphoma, endocrine cancer, neurologic cancer, sarcoma, osteosarcoma, liver cancer, astrocytoma, glioma, hematological cancer and solid tumors.

34. The method of claim 33, wherein the cancer is selected from head and neck cancer, melanoma, renal carcinoma, non-small cell lung cancer, Hodgkin's lymphoma and bladder cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/048549

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/395; A61K 31/4164; A61K 31/4178; C07D 225/04; C07D 225/06 (2017.01)

CPC - A61K 31/395; A61K 31/4164; A61K 31/4178; C07D 225/00; C07D 225/04; C07D 225/06 (2017.08)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/011316 A1 (CHDI FOUNDATION INC) 21 January 2016 (21.01.2016) entire document	1, 2
A	US 2011/0200592 A1 (OLSON et al) 18 August 2011 (18.08.2011) entire document	1, 2
A	PUBCHEM, Substance Record for SID 223915294, Available Date: 02 February 2015 [retrieved on 26 September 2017]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/223915294#section=Top> entire document	1, 2

☐ 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
05 December 2017	02 JAN 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/048549

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 4-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1 and 2 have been analyzed subject to the restriction that the claims read on a compound of Formula I or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein: each of R1, R2a, R2b, and R3 is independently –CH3; Y1a is deuterium and each of Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Y7, Y8a, Y7b, Y8a, Y8b, Y9a, Y9b, Y10a, Y10b, Y11a, Y11b, Y12a, Y12b, Y13a, Y13b, Y14a, Y14b, Y15a, Y15b, Y16, Y17, Y18, Y19, Y20a, Y20b, Y21a, Y21b, Y22, and Y23 is independently hydrogen.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/048549

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3 are drawn to compounds of Formula I or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing.

The first invention of Group I+ is restricted based on the proviso when each of R1, R2a, R2b and R3 is -CH3, at least one of Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Y7, Y8a, Y7b, Y8a, Y8b, Y9a, Y9b, Y10a, Y10b, Y11a, Y11b, Y12a, Y12b, Y13a, Y13b, Y14a, Y14b, Y15a, Y15b, Y16, Y17, Y18, Y19, Y20a, Y20b, Y21a, Y21b, Y22, and Y23 is deuterium; and is restricted to a compound of Formula I or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein: each of R1, R2a, R2b, and R3 is independently –CH3; Y1a is deuterium and each of Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Y7, Y8a, Y7b, Y8a, Y8b, Y9a, Y9b, Y10a, Y10b, Y11a, Y11b, Y12a, Y12b, Y13a, Y13b, Y14a, Y14b, Y15a, Y15b, Y16, Y17, Y18, Y19, Y20a, Y20b, Y21a, Y21b, Y22, and Y23 is independently hydrogen. It is believed that claims 1 and 2 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing, wherein: R1 is -CD3 and each of R2a, R2b, and R3 is independently –CH3; Y1a is deuterium and each of Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Y7, Y8a, Y7b, Y8a, Y8b, Y9a, Y9b, Y10a, Y10b, Y11a, Y11b, Y12a, Y12b, Y13a, Y13b, Y14a, Y14b, Y15a, Y15b, Y16, Y17, Y18, Y19, Y20a, Y20b, Y21a, Y21b, Y22, and Y23 is independently hydrogen. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2a, R2b R3, Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Y7, Y8a, Y7b, Y8a, Y8b, Y9a, Y9b, Y10a, Y10b, Y11a, Y11b, Y12a, Y12b, Y13a, Y13b, Y14a, Y14b, Y15a, Y15b, Y16, Y17, Y18, Y19, Y20a, Y20b, Y21a, Y21b, Y22, and Y23.

The Groups I+ share the technical features of a compound having the core structure of Formula I or a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing. However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 223915294 to PubChem teaches a compound having the core structure of Formula I (Pg. 3;... see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.