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(72) Inventor; and
(71) Applicant : **TUNG, Roger D.** [US/US]; 99 Hayden Ave, #500, Lexington, Massachusetts 02421 (US).

(74) Agents: **IGNATENKO, Vasily A.** et al.; Fish & Richardson P.C., PO Box 1022, Minneapolis, Minnesota 55440-1022 (US).

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(54) Title: DEUTERATED ITI-007

(57) Abstract: This invention relates to novel 2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalines, and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a serotonergic, dopaminergic, and glutamatergic modulator.

DEUTERATED ITI-007

CLAIM OF PRIORITY

[1] This application claims the benefit of U.S. Provisional Application number 62/273,923, filed December 31, 2015. The entire contents of the foregoing are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[2] 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.

[3] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the 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.

[4] 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).

[5] 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.

[6] 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.

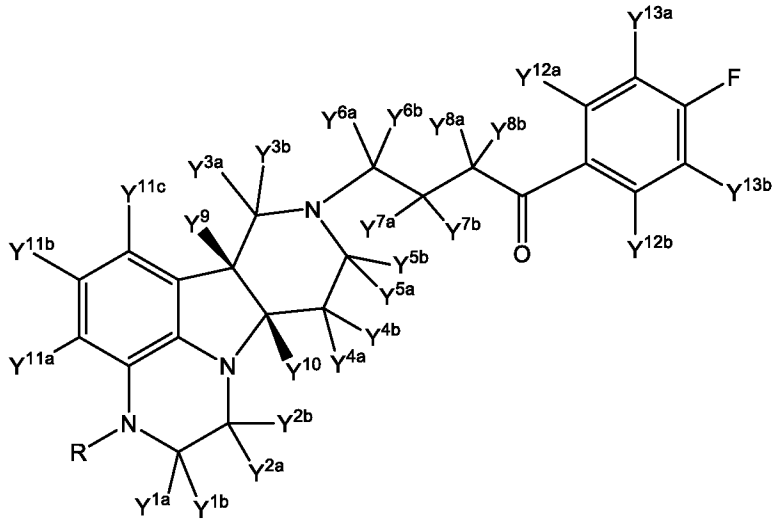
[7] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, MB 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).

[8] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. *See,* for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

SUMMARY OF THE INVENTION

[9] This invention relates to novel 2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalines, and pharmaceutically acceptable salts thereof. Certain aspects of the present invention are directed to compounds of Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein R is CH_3, CH_2D, CHD_2 or CD_3; and 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are independently selected from hydrogen and deuterium; provided

that at least one of R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} comprises deuterium.

[10] Certain aspects of the present invention also provide compositions comprising a compound of this invention, including pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier. Certain aspects of the present invention also provide the use of such compounds and compositions in methods of treating diseases and conditions that are beneficially treated by administering a serotonergic, dopaminergic, and glutamatergic modulator. Some exemplary embodiments include a method of treating a disease or condition selected from schizophrenia, depression, bipolar disorder, agitation, insomnia, dementia, and Alzheimer's Disease, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[11] ITI-007 (CAS Registry numbers 1187020-80-9, 313368-91-1) also known as ITI-722 and 1-(4-fluorophenyl)-4-[(6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl]butan-1-one tosylate, modulates the serotonergic, dopaminergic, and glutamatergic systems.

[12] ITI-007 is currently in phase III clinical trials for the treatment of schizophrenia, depression, bipolar disorder, and agitation; phase II clinical trials for the treatment of insomnia; and phase Ib/II clinical trials for the treatment of Alzheimer's disease; and is currently being tested for safety and efficacy in patients with an acute exacerbation of the aforementioned diseases.

[13] Despite the beneficial activities of ITI-007, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

Definitions

[14] 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.

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

[16] 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.

[17] 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 ITI-007 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, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[18] 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. 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).

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

[20] 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).

[21] 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.

[22] 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.

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

[24] 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 another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[25] 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.

[26] 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, maleate, tartrate, methanesulfonate, 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.

[27] The compounds of the present invention (e.g., compounds of Formula I and/or Formula II), may 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. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. 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.

[28] 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.

[29] 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).

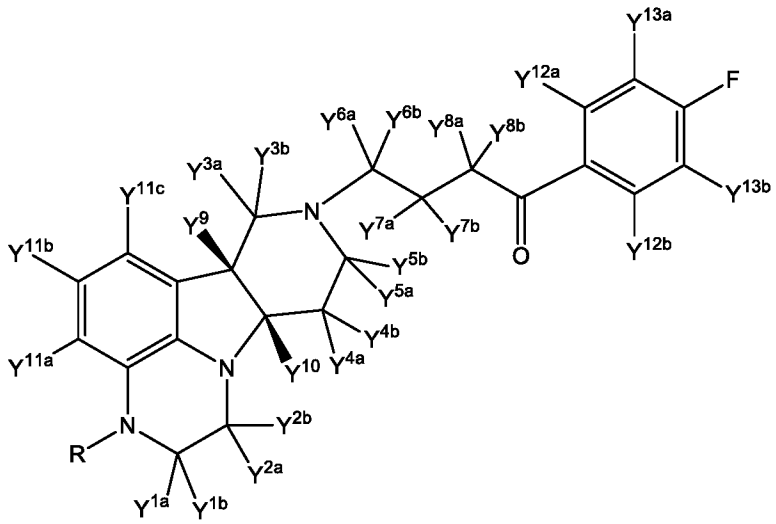
[30] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

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

[32] 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

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



(I)

, or a pharmaceutically acceptable salt thereof,

wherein R is CH_3, CH_2D, CHD_2 or CD_3;

and 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are independently selected from hydrogen and deuterium;

provided that at least one of R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} comprises deuterium.

[34] In some embodiments, R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} together comprise at least two, four, or five atoms of deuterium.

[35] In some embodiments, R is CH_3.

[36] In some embodiments, R is CD_3.

[37] In some embodiments, Y^{1a} and Y^{1b} are the same. In some aspects of these embodiments, Y^{1a} and Y^{1b} are each hydrogen. In other aspects of these embodiments, Y^{1a} and Y^{1b} are each deuterium.

[38] In some embodiments, Y^{2a} and Y^{2b} are the same. In some aspects of these embodiments, Y^{2a} and Y^{2b} are each hydrogen. In other aspects of these embodiments, Y^{2a} and Y^{2b} are each deuterium.

[39] In some embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the same. In some aspects of these embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each hydrogen. In other aspects of these embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each deuterium.

[40] In some embodiments, Y^{3a} and Y^{3b} are the same. In some aspects of these embodiments, Y^{3a} and Y^{3b} are each hydrogen. In other aspects of these embodiments, Y^{3a} and Y^{3b} are each deuterium.

[41] In some embodiments, Y^{4a} and Y^{4b} are the same. In some aspects of these embodiments, Y^{4a} and Y^{4b} are each hydrogen. In other aspects of these embodiments, Y^{4a} and Y^{4b} are each deuterium.

[42] In some embodiments, Y^{5a} and Y^{5b} are the same. In some aspects of these embodiments, Y^{5a} and Y^{5b} are each hydrogen. In other aspects of these embodiments, Y^{5a} and Y^{5b} are each deuterium.

[43] In some embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are the same. In some aspects of these embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each hydrogen. In other aspects of these embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each deuterium.

[44] In some embodiments, Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each hydrogen; and Y^{4a} and Y^{4b} are each deuterium. In other embodiments, Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each deuterium; and Y^{4a} and Y^{4b} are each hydrogen.

[45] In some embodiments, Y^{6a} and Y^{6b} are the same. In some aspects of these embodiments, Y^{6a} and Y^{6b} are each hydrogen. In other aspects of these embodiments, Y^{6a} and Y^{6b} are each deuterium.

[46] In some embodiments, Y^{7a} and Y^{7b} are the same. In some aspects of these embodiments, Y^{7a} and Y^{7b} are each hydrogen. In other aspects of these embodiments, Y^{7a} and Y^{7b} are each deuterium.

[47] In some embodiments, Y^{8a} and Y^{8b} are the same. In some aspects of these embodiments, Y^{8a} and Y^{8b} are each hydrogen. In other aspects of these embodiments, Y^{8a} and Y^{8b} are each deuterium.

[48] In some embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are the same. In some aspects of these embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen. In other aspects of these embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium.

[49] In some embodiments, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{6a} and Y^{6b} are each deuterium. In other embodiments, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{6a} and Y^{6b} are each hydrogen.

[50] In some embodiments, Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{7a} and Y^{7b} are each deuterium. In other embodiments, Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{7a} and Y^{7b} are each hydrogen.

[51] In some embodiments, Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each hydrogen; and Y^{8a} and Y^{8b} are each deuterium. In other embodiments, Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each deuterium; and Y^{8a} and Y^{8b} are each hydrogen.

[52] In some embodiments, Y^{9} is deuterium.

[53] In some embodiments, Y^{9} is hydrogen.

[54] In some embodiments, Y^{10} is deuterium.

[55] In some embodiments, Y^{10} is hydrogen.

[56] In some embodiments, Y^{9} and Y^{10} are the same. In some aspects of these embodiments, Y^{9} and Y^{10} are each hydrogen. In other aspects of these embodiments, Y^{9} and Y^{10} are each deuterium.

[57] In some embodiments, the configuration of the carbon atom to which Y^9 is attached is *(R)* according to Cahn-Ingold-Prelog nomenclature. In some embodiments, the configuration of the carbon atom to which Y^{10} is attached is *(S)* according to Cahn-Ingold-Prelog nomenclature. In some embodiments, the configuration of the carbon atom to which Y^9 is attached is *(R)* according to Cahn-Ingold-Prelog nomenclature and the configuration of the carbon atom to which Y^{10} is attached is *(R)* according to Cahn-Ingold-Prelog nomenclature.

[58] In some embodiments, Y^{11a} is deuterium.

[59] In some embodiments, Y^{11a} is hydrogen.

[60] In some embodiments, Y^{11b} is deuterium.

[61] In some embodiments, Y^{11b} is hydrogen.

[62] In some embodiments, Y^{11c} is deuterium.

[63] In some embodiments, Y^{11c} is hydrogen.

[64] In some embodiments, Y^{11b} is hydrogen; and Y^{11a} and Y^{11c} are each deuterium. In other embodiments, Y^{11b} is deuterium; and Y^{11a} and Y^{11c} are each hydrogen.

[65] In some embodiments, Y^{11a}, Y^{11b} and Y^{11c} are the same. In some aspects of these embodiments, Y^{11a}, Y^{11b} and Y^{11c} are each hydrogen. In other aspects of these embodiments, Y^{11a}, Y^{11b} and Y^{11c} are each deuterium.

[66] In some embodiments, Y^{12a} is deuterium.

[67] In some embodiments, Y^{12b} is hydrogen.

[68] In some embodiments, Y^{12a} and Y^{12b} are the same. In some aspects of these embodiments, Y^{12a} and Y^{12b} are each hydrogen. In other aspects of these embodiments, Y^{12a} and Y^{12b} are each deuterium.

[69] In some embodiments, Y^{13a} is deuterium.

[70] In some embodiments, Y^{13b} is hydrogen.

[71] In some embodiments, Y^{13a} and Y^{13b} are the same. In some aspects of these embodiments, Y^{13a} and Y^{13b} are each hydrogen. In other aspects of these embodiments, Y^{13a} and Y^{13b} are each deuterium.

[72] In some embodiments, Y^{12a} and Y^{12b} are each hydrogen; and Y^{13a} and Y^{13b} are each deuterium. In other embodiments, Y^{12a} and Y^{12b} are each hydrogen; and Y^{13a} and Y^{13b} are each deuterium.

[73] In some embodiments, Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are the same. In some aspects of these embodiments, Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each hydrogen. In other aspects of these embodiments, Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each deuterium.

[74] In some embodiments, the compound of Formula I is not a compound in which R is CD_3, and 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are each deuterium.

[75] provided that at least one of R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} comprises deuterium

[76] In one embodiment, 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^{9} and Y^{10} are the same; Y^{11a}, Y^{11b}, and Y^{11c} are the same; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each deuterium, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1a (below):

Table 1a: Exemplary Embodiments of Formula I

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

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
114a	CD_3	H	H	D	D	D	D	D
115a	CD_3	H	D	D	D	D	D	D
116a	CD_3	D	H	D	D	D	D	D
117a	CD_3	H	H	D	D	D	H	H
118a	CD_3	H	D	D	D	D	H	H
119a	CD_3	D	H	D	D	D	H	H
120a	CD_3	D	D	H	H	H	D	H
121a	CD_3	D	H	H	H	H	D	H
122a	CD_3	H	D	H	H	H	D	H
123a	CD_3	D	D	H	H	H	H	D
124a	CD_3	D	H	H	H	H	H	D
125a	CD_3	H	D	H	H	H	H	D
126a	CD_3	D	D	H	H	H	D	D
127a	CD_3	D	H	H	H	H	D	D
128a	CD_3	H	D	H	H	H	D	D
129a	CD_3	D	D	H	H	H	H	H
130a	CD_3	D	H	H	H	H	H	H
131a	CD_3	H	D	H	H	H	H	H
132a	CH_3	D	D	D	D	D	D	H
133a	CH_3	D	H	D	D	D	D	H
134a	CH_3	H	D	D	D	D	D	H
135a	CH_3	D	D	D	D	D	H	D
136a	CH_3	D	H	D	D	D	H	D
137a	CH_3	H	D	D	D	D	H	D
138a	CH_3	D	D	D	D	D	D	D
139a	CH_3	D	H	D	D	D	D	D
140a	CH_3	H	D	D	D	D	D	D
141a	CH_3	D	D	D	D	D	H	H
142a	CH_3	D	H	D	D	D	H	H

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
143a	CH_3	H	D	D	D	D	H	H

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

[77] In one embodiment, 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^{9} and Y^{10} are the same; Y^{11a}, Y^{11b}, and Y^{11c} are the same; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each hydrogen, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1b (below):

Table 1b: Exemplary Embodiments of Formula I

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
100b	CD_3	D	D	D	D	D	D	D
103b	CD_3	D	D	D	D	D	H	D
104b	CD_3	D	D	D	D	D	D	H
105b	CH_3	H	H	H	H	H	D	D
106b	CH_3	H	H	H	H	H	D	H
107b	CH_3	H	H	H	H	H	H	D
108b	CD_3	H	H	D	D	D	D	H
109b	CD_3	H	D	D	D	D	D	H
110b	CD_3	D	H	D	D	D	D	H
111b	CD_3	H	H	D	D	D	H	D
112b	CD_3	H	D	D	D	D	H	D
113b	CD_3	D	H	D	D	D	H	D
114b	CD_3	H	H	D	D	D	D	D
115b	CD_3	H	D	D	D	D	D	D
116b	CD_3	D	H	D	D	D	D	D
120b	CD_3	D	D	H	H	H	D	H
121b	CD_3	D	H	H	H	H	D	H
122b	CD_3	H	D	H	H	H	D	H

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
123b	CD_3	D	D	H	H	H	H	D
124b	CD_3	D	H	H	H	H	H	D
125b	CD_3	H	D	H	H	H	H	D
126b	CD_3	D	D	H	H	H	D	D
127b	CD_3	D	H	H	H	H	D	D
128b	CD_3	H	D	H	H	H	D	D
132b	CH_3	D	D	D	D	D	D	H
133b	CH_3	D	H	D	D	D	D	H
134b	CH_3	H	D	D	D	D	D	H
135b	CH_3	D	D	D	D	D	H	D
136b	CH_3	D	H	D	D	D	H	D
137b	CH_3	H	D	D	D	D	H	D
138b	CH_3	D	D	D	D	D	D	D
139b	CH_3	D	H	D	D	D	D	D
140b	CH_3	H	D	D	D	D	D	D

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

[78] In one embodiment, 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^{9} and Y^{10} are the same; Y^{11a}, Y^{11b}, and Y^{11c} are the same; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each deuterium, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1c (below):

Table 1c: Exemplary Embodiments of Formula I

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
100c	CD_3	D	D	D	D	D	D	D
101c	CH_3	H	H	H	H	H	H	H
102c	CD_3	D	D	D	D	D	H	H
103c	CD_3	D	D	D	D	D	H	D

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
104c	CD_3	D	D	D	D	D	D	H
105c	CH_3	H	H	H	H	H	D	D
106c	CH_3	H	H	H	H	H	D	H
107c	CH_3	H	H	H	H	H	H	D
108c	CD_3	H	H	D	D	D	D	H
109c	CD_3	H	D	D	D	D	D	H
110c	CD_3	D	H	D	D	D	D	H
111c	CD_3	H	H	D	D	D	H	D
112c	CD_3	H	D	D	D	D	H	D
113c	CD_3	D	H	D	D	D	H	D
114c	CD_3	H	H	D	D	D	D	D
115c	CD_3	H	D	D	D	D	D	D
116c	CD_3	D	H	D	D	D	D	D
117c	CD_3	H	H	D	D	D	H	H
118c	CD_3	H	D	D	D	D	H	H
119c	CD_3	D	H	D	D	D	H	H
120c	CD_3	D	D	H	H	H	D	H
121c	CD_3	D	H	H	H	H	D	H
122c	CD_3	H	D	H	H	H	D	H
123c	CD_3	D	D	H	H	H	H	D
124c	CD_3	D	H	H	H	H	H	D
125c	CD_3	H	D	H	H	H	H	D
126c	CD_3	D	D	H	H	H	D	D
127c	CD_3	D	H	H	H	H	D	D
128c	CD_3	H	D	H	H	H	D	D
129c	CD_3	D	D	H	H	H	H	H
130c	CD_3	D	H	H	H	H	H	H
131c	CD_3	H	D	H	H	H	H	H
132c	CH_3	D	D	D	D	D	D	H

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
133c	CH_3	D	H	D	D	D	D	H
134c	CH_3	H	D	D	D	D	D	H
135c	CH_3	D	D	D	D	D	H	D
136c	CH_3	D	H	D	D	D	H	D
137c	CH_3	H	D	D	D	D	H	D
138c	CH_3	D	D	D	D	D	D	D
139c	CH_3	D	H	D	D	D	D	D
140c	CH_3	H	D	D	D	D	D	D
141c	CH_3	D	D	D	D	D	H	H
142c	CH_3	D	H	D	D	D	H	H
143c	CH_3	H	D	D	D	D	H	H

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

[79] In one embodiment, 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^{9} and Y^{10} are the same; Y^{11a}, Y^{11b}, and Y^{11c} are the same; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each hydrogen, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1d (below):

Table 1d: Exemplary Embodiments of Formula I

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
100d	CD_3	D	D	D	D	D	D	D
103d	CD_3	D	D	D	D	D	H	D
104d	CD_3	D	D	D	D	D	D	H
105d	CH_3	H	H	H	H	H	D	D
106d	CH_3	H	H	H	H	H	D	H
107d	CH_3	H	H	H	H	H	H	D
108d	CD_3	H	H	D	D	D	D	H
109d	CD_3	H	D	D	D	D	D	H

Cmpd	R	Y^{1a}/Y^{1b}	Y^{2a}/Y^{2b}	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{9}/Y^{10}	$Y^{11a}/Y^{11b}/Y^{11c}$
110d	CD_3	D	H	D	D	D	D	H
111d	CD_3	H	H	D	D	D	H	D
112d	CD_3	H	D	D	D	D	H	D
113d	CD_3	D	H	D	D	D	H	D
114d	CD_3	H	H	D	D	D	D	D
115d	CD_3	H	D	D	D	D	D	D
116d	CD_3	D	H	D	D	D	D	D
120d	CD_3	D	D	H	H	H	D	H
121d	CD_3	D	H	H	H	H	D	H
122d	CD_3	H	D	H	H	H	D	H
123d	CD_3	D	D	H	H	H	H	D
124d	CD_3	D	H	H	H	H	H	D
125d	CD_3	H	D	H	H	H	H	D
126d	CD_3	D	D	H	H	H	D	D
127d	CD_3	D	H	H	H	H	D	D
128d	CD_3	H	D	H	H	H	D	D
132d	CH_3	D	D	D	D	D	D	H
133d	CH_3	D	H	D	D	D	D	H
134d	CH_3	H	D	D	D	D	D	H
135d	CH_3	D	D	D	D	D	H	D
136d	CH_3	D	H	D	D	D	H	D
137d	CH_3	H	D	D	D	D	H	D
138d	CH_3	D	D	D	D	D	D	D
139d	CH_3	D	H	D	D	D	D	D
140d	CH_3	H	D	D	D	D	D	D

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

[80] In one embodiment, Y^{6a} and Y^{6b} are the same; Y^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same; Y^{12a} and Y^{12b} are the same; Y^{13a} and Y^{13b} are the same; Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each deuterium; Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each hydrogen; Y^{9} and Y^{10} are each deuterium, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1e (below):

Table 1e: Exemplary Embodiments of Formula I

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
100e	CD_3	D	D	D	D	D	D	H	D
101e	CD_3	D	D	D	D	D	D	D	H
102e	CD_3	D	D	D	D	D	H	D	D
103e	CD_3	D	D	D	D	H	D	H	D
104e	CD_3	D	D	D	D	H	D	D	H
105e	CD_3	D	D	D	D	H	H	D	D
106e	CD_3	D	D	D	D	H	D	D	D
107e	CD_3	D	D	D	D	H	H	H	H
108e	CD_3	D	D	D	H	D	D	H	D
109e	CD_3	D	D	D	H	D	D	D	H
110e	CD_3	D	D	D	H	D	H	D	D
111e	CD_3	D	D	D	H	D	D	D	D
112e	CD_3	D	D	D	H	D	H	H	H
113e	CD_3	D	D	D	H	H	D	H	D
114e	CD_3	D	D	D	H	H	D	D	H
115e	CD_3	D	D	D	H	H	H	D	D
116e	CH_3	D	D	D	D	D	D	H	D
117e	CH_3	D	D	D	D	D	D	D	H
118e	CH_3	D	D	D	D	D	H	D	D
119e	CH_3	D	D	D	D	H	D	H	D
120e	CH_3	D	D	D	D	H	D	D	H
121e	CH_3	D	D	D	D	H	H	D	D
122e	CH_3	D	D	D	D	H	D	D	D

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
123e	CH_3	D	D	D	D	H	H	H	H
124e	CH_3	D	D	D	H	D	D	H	D
125e	CH_3	D	D	D	H	D	D	D	H
126e	CH_3	D	D	D	H	D	H	D	D
127e	CH_3	D	D	D	H	D	D	D	D
128e	CH_3	D	D	D	H	D	H	H	H
129e	CH_3	D	D	D	H	H	D	H	D
130e	CH_3	D	D	D	H	H	D	D	H
131e	CH_3	D	D	D	H	H	H	D	D
132e	CD_3	D	H	D	D	D	D	D	D
133e	CD_3	D	D	H	D	D	D	D	D
134e	CD_3	H	D	D	D	D	D	D	D
135e	CD_3	D	H	D	D	D	H	H	H
136e	CD_3	D	D	H	D	D	H	H	H
137e	CD_3	H	D	D	D	D	H	H	H
138e	CD_3	D	H	D	D	D	D	H	D
139e	CD_3	D	D	H	D	D	D	D	H
140e	CD_3	H	D	D	D	D	H	D	D
141e	CD_3	D	H	D	H	H	D	H	D
142e	CD_3	D	D	H	H	H	D	D	H
143e	CD_3	H	D	D	H	H	H	D	D
144e	CH_3	D	H	D	D	D	D	D	D
145e	CH_3	D	D	H	D	D	D	D	D
146e	CH_3	H	D	D	D	D	D	D	D
147e	CH_3	D	H	D	D	D	H	H	H
148e	CH_3	D	D	H	D	D	H	H	H
149e	CH_3	H	D	D	D	D	H	H	H
150e	CH_3	D	H	D	D	D	D	H	D
151e	CH_3	D	D	H	D	D	D	D	H

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
152e	CH_3	H	D	D	D	D	H	D	D
153e	CH_3	D	H	D	H	H	D	H	D
154e	CH_3	D	D	H	H	H	D	D	H
155e	CH_3	H	D	D	H	H	H	D	D

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

[81] In one embodiment, Y^{6a} and Y^{6b} are the same; Y^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same; Y^{12a} and Y^{12b} are the same; Y^{13a} and Y^{13b} are the same; Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each hydrogen; Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each deuterium; Y^{9} and Y^{10} are each hydrogen, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1f (below):

Table 1f: Exemplary Embodiments of Formula I

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
100f	CD_3	D	D	D	D	D	D	H	D
101f	CD_3	D	D	D	D	D	D	D	H
102f	CD_3	D	D	D	D	D	H	D	D
103f	CD_3	D	D	D	D	H	D	H	D
104f	CD_3	D	D	D	D	H	D	D	H
105f	CD_3	D	D	D	D	H	H	D	D
106f	CD_3	D	D	D	D	H	D	D	D
107f	CD_3	D	D	D	D	H	H	H	H
108f	CD_3	D	D	D	H	D	D	H	D
109f	CD_3	D	D	D	H	D	D	D	H
110f	CD_3	D	D	D	H	D	H	D	D
111f	CD_3	D	D	D	H	D	D	D	D
112f	CD_3	D	D	D	H	D	H	H	H
113f	CD_3	D	D	D	H	H	D	H	D
114f	CD_3	D	D	D	H	H	D	D	H

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
115f	CD_3	D	D	D	H	H	H	D	D
116f	CH_3	D	D	D	D	D	D	H	D
117f	CH_3	D	D	D	D	D	D	D	H
118f	CH_3	D	D	D	D	D	H	D	D
119f	CH_3	D	D	D	D	H	D	H	D
120f	CH_3	D	D	D	D	H	D	D	H
121f	CH_3	D	D	D	D	H	H	D	D
122f	CH_3	D	D	D	D	H	D	D	D
123f	CH_3	D	D	D	D	H	H	H	H
124f	CH_3	D	D	D	H	D	D	H	D
125f	CH_3	D	D	D	H	D	D	D	H
126f	CH_3	D	D	D	H	D	H	D	D
127f	CH_3	D	D	D	H	D	D	D	D
128f	CH_3	D	D	D	H	D	H	H	H
129f	CH_3	D	D	D	H	H	D	H	D
130f	CH_3	D	D	D	H	H	D	D	H
131f	CH_3	D	D	D	H	H	H	D	D
132f	CD_3	D	H	D	D	D	D	D	D
133f	CD_3	D	D	H	D	D	D	D	D
134f	CD_3	H	D	D	D	D	D	D	D
135f	CD_3	D	H	D	D	D	H	H	H
136f	CD_3	D	D	H	D	D	H	H	H
137f	CD_3	H	D	D	D	D	H	H	H
138f	CD_3	D	H	D	D	D	D	H	D
139f	CD_3	D	D	H	D	D	D	D	H
140f	CD_3	H	D	D	D	D	H	D	D
141f	CD_3	D	H	D	H	H	D	H	D
142f	CD_3	D	D	H	H	H	D	D	H
143f	CD_3	H	D	D	H	H	H	D	D

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
144f	CH_3	D	H	D	D	D	D	D	D
145f	CH_3	D	D	H	D	D	D	D	D
146f	CH_3	H	D	D	D	D	D	D	D
147f	CH_3	D	H	D	D	D	H	H	H
148f	CH_3	D	D	H	D	D	H	H	H
149f	CH_3	H	D	D	D	D	H	H	H
150f	CH_3	D	H	D	D	D	D	H	D
151f	CH_3	D	D	H	D	D	D	D	H
152f	CH_3	H	D	D	D	D	H	D	D
153f	CH_3	D	H	D	H	H	D	H	D
154f	CH_3	D	D	H	H	H	D	D	H
155f	CH_3	H	D	D	H	H	H	D	D

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

[82] In one embodiment, Y^{6a} and Y^{6b} are the same; Y^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same; Y^{12a} and Y^{12b} are the same; Y^{13a} and Y^{13b} are the same; Y^{1a}, Y^{1b}, Y^{2a} Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{9} and Y^{10} are each deuterium, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1g (below):

Table 1g: Exemplary Embodiments of Formula I

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
100g	CD_3	D	D	D	D	D	D	H	D
101g	CD_3	D	D	D	D	D	D	D	H
102g	CD_3	D	D	D	D	D	H	D	D
103g	CD_3	D	D	D	D	H	D	H	D
104g	CD_3	D	D	D	D	H	D	D	H
105g	CD_3	D	D	D	D	H	H	D	D
106g	CD_3	D	D	D	D	H	D	D	D
107g	CD_3	D	D	D	D	H	H	H	H

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
108g	CD_3	D	D	D	H	D	D	H	D
109g	CD_3	D	D	D	H	D	D	D	H
110g	CD_3	D	D	D	H	D	H	D	D
111g	CD_3	D	D	D	H	D	D	D	D
112g	CD_3	D	D	D	H	D	H	H	H
113g	CD_3	D	D	D	H	H	D	H	D
114g	CD_3	D	D	D	H	H	D	D	H
115g	CD_3	D	D	D	H	H	H	D	D
116g	CH_3	D	D	D	D	D	D	H	D
117g	CH_3	D	D	D	D	D	D	D	H
118g	CH_3	D	D	D	D	D	H	D	D
119g	CH_3	D	D	D	D	H	D	H	D
120g	CH_3	D	D	D	D	H	D	D	H
121g	CH_3	D	D	D	D	H	H	D	D
122g	CH_3	D	D	D	D	H	D	D	D
123g	CH_3	D	D	D	D	H	H	H	H
124g	CH_3	D	D	D	H	D	D	H	D
125g	CH_3	D	D	D	H	D	D	D	H
126g	CH_3	D	D	D	H	D	H	D	D
127g	CH_3	D	D	D	H	D	D	D	D
128g	CH_3	D	D	D	H	D	H	H	H
129g	CH_3	D	D	D	H	H	D	H	D
130g	CH_3	D	D	D	H	H	D	D	H
131g	CH_3	D	D	D	H	H	H	D	D
132g	CD_3	D	H	D	D	D	D	D	D
133g	CD_3	D	D	H	D	D	D	D	D
134g	CD_3	H	D	D	D	D	D	D	D
135g	CD_3	D	H	D	D	D	H	H	H
136g	CD_3	D	D	H	D	D	H	H	H

Cmpd	R	Y^{6a}/Y^{6b}	Y^{7a}/Y^{7b}	Y^{8a}/Y^{8b}	Y^{12a}/Y^{12b}	Y^{13a}/Y^{13b}	Y^{11a}	Y^{11a}	Y^{11a}
137g	CD_3	H	D	D	D	D	H	H	H
138g	CD_3	D	H	D	D	D	D	H	D
139g	CD_3	D	D	H	D	D	D	D	H
140g	CD_3	H	D	D	D	D	H	D	D
141g	CD_3	D	H	D	H	H	D	H	D
142g	CD_3	D	D	H	H	H	D	D	H
143g	CD_3	H	D	D	H	H	H	D	D
144g	CH_3	D	H	D	D	D	D	D	D
145g	CH_3	D	D	H	D	D	D	D	D
146g	CH_3	H	D	D	D	D	D	D	D
147g	CH_3	D	H	D	D	D	H	H	H
148g	CH_3	D	D	H	D	D	H	H	H
149g	CH_3	H	D	D	D	D	H	H	H
150g	CH_3	D	H	D	D	D	D	H	D
151g	CH_3	D	D	H	D	D	D	D	H
152g	CH_3	H	D	D	D	D	H	D	D
153g	CH_3	D	H	D	H	H	D	H	D
154g	CH_3	D	D	H	H	H	D	D	H
155g	CH_3	H	D	D	H	H	H	D	D

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

[83] In one embodiment, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the each deuterium; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; Y^{9} and Y^{10} are each deuterium; Y^{11a}, Y^{11b} and Y^{11c} are each hydrogen; Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each hydrogen; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1h (below):

Table 1h: Exemplary Embodiments of Formula I

Cmpd	R	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}
100h	CD_3	D	D	H
101h	CD_3	D	H	D
102h	CD_3	H	D	D
103h	CH_3	D	D	H
104h	CH_3	D	H	D
105h	CH_3	H	D	D

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

[84] In one embodiment, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the each hydrogen; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen; Y^{9} and Y^{10} are each hydrogen; Y^{11a}, Y^{11b} and Y^{11c} are each deuterium; Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each deuterium; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1i (below):

Table 1i: Exemplary Embodiments of Formula I

Cmpd	R	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}
100i	CD_3	D	D	H
101i	CD_3	D	H	D
102i	CD_3	H	D	D
103i	CH_3	D	D	H
104i	CH_3	D	H	D
105i	CH_3	H	D	D

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

[85] In one embodiment, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the each deuterium; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; Y^{9} and Y^{10} are each hydrogen; Y^{11a}, Y^{11b} and Y^{11c} are each hydrogen; Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each deuterium; Y^{3a} and Y^{3b} are the

same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1j (below):

Table 1j: Exemplary Embodiments of Formula I

Cmpd	R	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}
100j	CD_3	D	D	H
101j	CD_3	D	H	D
102j	CD_3	H	D	D
103j	CH_3	D	D	H
104j	CH_3	D	H	D
105j	CH_3	H	D	D

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

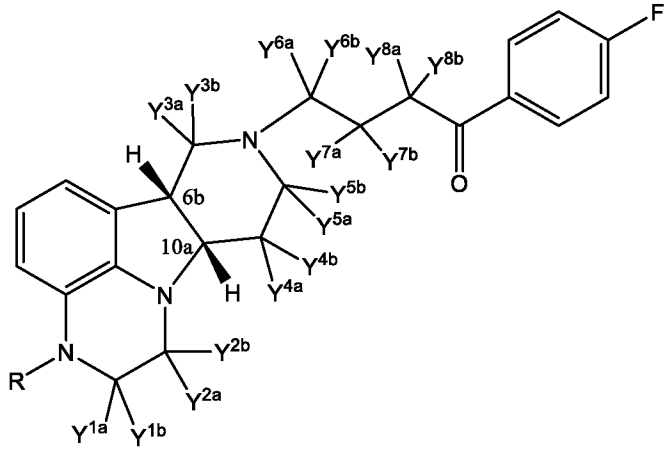
[86] In one embodiment, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the each deuterium; Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; Y^{9} and Y^{10} are each hydrogen; Y^{11a}, Y^{11b} and Y^{11c} are each deuterium; Y^{12a}, Y^{12b}, Y^{13a} and Y^{13b} are each hydrogen; Y^{3a} and Y^{3b} are the same; Y^{4a} and Y^{4b} are the same; Y^{5a} and Y^{5b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 1k (below):

Table 1k: Exemplary Embodiments of Formula I

Cmpd	R	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}
100k	CD_3	D	D	H
101k	CD_3	D	H	D
102k	CD_3	H	D	D
103k	CH_3	D	D	H
104k	CH_3	D	H	D
105k	CH_3	H	D	D

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

[87] In one embodiment, the compound of Formula I has the structure of Formula II:



(II)

, or a pharmaceutically acceptable salt thereof,

wherein R is CH_3, CH_2D, CHD_2 or CD_3;

and 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are independently selected from hydrogen and deuterium;

provided that at least one of R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} comprises deuterium.

[88] In some embodiments, R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} together comprise at least two deuterium atoms.

[89] In some embodiments, R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} together comprise at least four deuterium atoms.

[90] In some embodiments, R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} together comprise at least five deuterium atoms.

[91] In some embodiments, R is CH_3.

[92] In some embodiments, R is CD_3.

[93] In some embodiments, Y^{1a} and Y^{1b} are the same. In some aspects of these embodiments, Y^{1a} and Y^{1b} are each hydrogen. In other aspects of these embodiments, Y^{1a} and Y^{1b} are each deuterium.

[94] In some embodiments, Y^{2a} and Y^{2b} are the same. In some aspects of these embodiments, Y^{2a} and Y^{2b} are each hydrogen. In other aspects of these embodiments, Y^{2a} and Y^{2b} are each deuterium.

[95] In some embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the same. In some aspects of these embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each hydrogen. In other aspects of these embodiments, Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each deuterium.

[96] In some embodiments, Y^{1a} and Y^{1b} are each hydrogen; and Y^{2a} and Y^{2b} are each deuterium. In other embodiments, Y^{1a} and Y^{1b} are each deuterium; and Y^{2a} and Y^{2b} are each hydrogen.

[97] In some embodiments, Y^{3a} and Y^{3b} are the same. In some aspects of these embodiments, Y^{3a} and Y^{3b} are each hydrogen. In other aspects of these embodiments, Y^{3a} and Y^{3b} are each deuterium.

[98] In some embodiments, Y^{4a} and Y^{4b} are the same. In some aspects of these embodiments, Y^{4a} and Y^{4b} are each hydrogen. In other aspects of these embodiments, Y^{4a} and Y^{4b} are each deuterium.

[99] In some embodiments, Y^{5a} and Y^{5b} are the same. In some aspects of these embodiments, Y^{5a} and Y^{5b} are each hydrogen. In other aspects of these embodiments, Y^{5a} and Y^{5b} are each deuterium.

[100] In some embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are the same. In some aspects of these embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each hydrogen. In other aspects of these embodiments, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each deuterium.

[101] In some embodiments, Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each hydrogen; and Y^{4a} and Y^{4b} are each deuterium. In other embodiments, Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each deuterium; and Y^{4a} and Y^{4b} are each hydrogen.

[102] In some embodiments, Y^{6a} and Y^{6b} are the same. In some aspects of these embodiments, Y^{6a} and Y^{6b} are each hydrogen. In other aspects of these embodiments, Y^{6a} and Y^{6b} are each deuterium.

[103] In some embodiments, Y^{7a} and Y^{7b} are the same. In some aspects of these embodiments, Y^{7a} and Y^{7b} are each hydrogen. In other aspects of these embodiments, Y^{7a} and Y^{7b} are each deuterium.

[104] In some embodiments, Y^{8a} and Y^{8b} are the same. In some aspects of these embodiments, Y^{8a} and Y^{8b} are each hydrogen. In other aspects of these embodiments, Y^{8a} and Y^{8b} are each deuterium.

[105] In some embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are the same. In some aspects of these embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen. In other aspects of these embodiments, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium.

[106] In some embodiments, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{6a} and Y^{6b} are each deuterium. In other embodiments, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{6a} and Y^{6b} are each hydrogen.

[107] In some embodiments, Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{7a} and Y^{7b} are each deuterium. In other embodiments, Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{7a} and Y^{7b} are each hydrogen.

[108] In some embodiments, Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each hydrogen; and Y^{8a} and Y^{8b} are each deuterium. In other embodiments, Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each deuterium; and Y^{8a} and Y^{8b} are each hydrogen.

[109] In some embodiments, the configuration of the carbon atom at position 10a is *(S)* according to Cahn-Ingold-Prelog nomenclature. In some embodiments, the configuration of the carbon atom at 6b is *(R)* according to Cahn-Ingold-Prelog nomenclature. In some embodiments, the configuration of the carbon atom at position 10a is *(S)* according to Cahn-Ingold-Prelog nomenclature and the configuration of the carbon atom at position 6b is *(R)* according to Cahn-Ingold-Prelog nomenclature.

[110] In some embodiments, the compound of Formula II is not a compound in which R is CD_3, and 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^{7a}, Y^{7b}, Y^{8a}, and Y^{8b} are each deuterium

[111] In one embodiment, R is CD_3; 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^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 2a (below):

Table 2a: Exemplary Embodiments of Formula II

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
200a	D	D	D	D	D	D	D	D
201a	H	H	H	H	H	H	H	H
202a	D	D	H	H	H	D	D	D

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
203a	D	D	D	D	D	H	H	H
204a	H	H	D	D	D	D	D	D
205a	H	H	D	D	D	H	H	H
206a	D	D	H	H	H	H	H	H
207a	H	H	H	H	H	D	D	D
208a	D	D	D	D	H	D	D	D
209a	D	D	D	H	D	D	D	D
210a	D	D	H	D	D	D	D	D
211a	D	D	H	D	H	D	D	D
212a	D	D	D	D	D	D	D	H
213a	D	D	D	D	D	D	H	D
214a	D	D	D	D	D	H	D	D
215a	D	H	D	D	D	D	D	D
216a	H	D	D	D	D	D	D	D
217a	D	H	D	D	D	D	H	H
218a	H	D	D	D	D	H	D	D
219a	D	D	D	D	H	D	D	H
220a	D	D	D	H	D	D	H	D
221a	D	D	H	D	D	H	D	D
222a	D	D	H	D	H	D	H	H
223a	D	H	H	D	H	D	D	D
224a	H	D	D	H	D	D	D	D
225a	D	H	H	H	H	H	H	H
226a	H	D	H	H	H	H	H	H
227a	H	H	D	D	H	H	H	H
228a	H	H	D	H	D	H	H	H
229a	H	H	H	D	D	H	H	H
230a	H	H	H	D	H	H	H	H
231a	H	H	H	H	H	D	D	H

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
232a	H	H	H	H	H	D	H	D
233a	H	H	H	H	H	H	D	D
234a	H	H	H	H	H	D	H	H
235a	D	H	H	D	H	H	H	H
236a	H	D	D	H	D	H	H	H
237a	D	H	H	H	H	D	H	H
238a	H	D	H	H	H	H	D	D
239a	H	H	D	D	H	D	D	H
240a	H	H	D	H	D	D	H	D
241a	H	H	H	D	D	H	D	D
242a	H	H	H	D	H	D	H	H

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

[112] In one embodiment, R is CH_3; 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^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in Table 2b (below):

Table 2b: Exemplary Embodiments of Formula II

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
200b	D	D	D	D	D	D	D	D
201b	D	D	H	H	H	D	D	D
202b	D	D	D	D	D	H	H	H
203b	H	H	D	D	D	D	D	D
204b	H	H	D	D	D	H	H	H
205b	D	D	H	H	H	H	H	H
206b	H	H	H	H	H	D	D	D
207b	D	D	D	D	H	D	D	D

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
208b	D	D	D	H	D	D	D	D
209b	D	D	H	D	D	D	D	D
210b	D	D	H	D	H	D	D	D
211b	D	D	D	D	D	D	D	H
212b	D	D	D	D	D	D	H	D
213b	D	D	D	D	D	H	D	D
214b	D	H	D	D	D	D	D	D
215b	H	D	D	D	D	D	D	D
216b	D	H	D	D	D	D	H	H
217b	H	D	D	D	D	H	D	D
218b	D	D	D	D	H	D	D	H
219b	D	D	D	H	D	D	H	D
220b	D	D	H	D	D	H	D	D
221b	D	D	H	D	H	D	H	H
222b	D	H	H	D	H	D	D	D
223b	H	D	D	H	D	D	D	D
224b	D	H	H	H	H	H	H	H
225b	H	D	H	H	H	H	H	H
226b	H	H	D	D	H	H	H	H
227b	H	H	D	H	D	H	H	H
228b	H	H	H	D	D	H	H	H
229b	H	H	H	D	H	H	H	H
230b	H	H	H	H	H	D	D	H
231b	H	H	H	H	H	D	H	D
232b	H	H	H	H	H	H	D	D
233b	H	H	H	H	H	D	H	H
234b	D	H	H	D	H	H	H	H
235b	H	D	D	H	D	H	H	H
236b	D	H	H	H	H	D	H	H

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
237b	H	D	H	H	H	H	D	D
238b	H	H	D	D	H	D	D	H
239b	H	H	D	H	D	D	H	D
240b	H	H	H	D	D	H	D	D
241b	H	H	H	D	H	D	H	H

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

[113] In some embodiments, when Y^{1a} or Y^{1b} is deuterium, the level of deuterium incorporation at each Y^{1a} or 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%.

[114] In some embodiments of a compound of this invention, when Y^{2a} or Y^{2b} is deuterium, the level of deuterium incorporation at each Y^{2a} or 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%.

[115] In some embodiments of a compound of this invention, when Y^{3a} or Y^{3b} is deuterium, the level of deuterium incorporation at each Y^{3a} or 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%.

[116] In some embodiments, when Y^{4a} or Y^{4b} is deuterium, the level of deuterium incorporation at each Y^{4a} or 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%.

[117] In some embodiments, when Y^{5a} or Y^{5b} is deuterium, the level of deuterium incorporation at each Y^{5a} or 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%.

[118] In some embodiments, when Y^{6a} or Y^{6b} is deuterium, the level of deuterium incorporation at each Y^{6a} or 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%.

[119] In some embodiments, when Y^{7a} or Y^{7b} is deuterium, the level of deuterium incorporation at each Y^{7a} or Y^{7b} 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%.

[120] In some embodiments, when Y^{8a} or Y^{8b} is deuterium, the level of deuterium incorporation at each Y^{8a} or 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%.

[121] In some embodiments, when Y^{9} or Y^{10} is deuterium, the level of deuterium incorporation at each Y^{9} or Y^{10} 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%.

[122] In some embodiments, when Y^{11a}, Y^{11b}, or Y^{11c} is deuterium, the level of deuterium incorporation at each Y^{11a}, Y^{11b}, or Y^{11c} 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%.

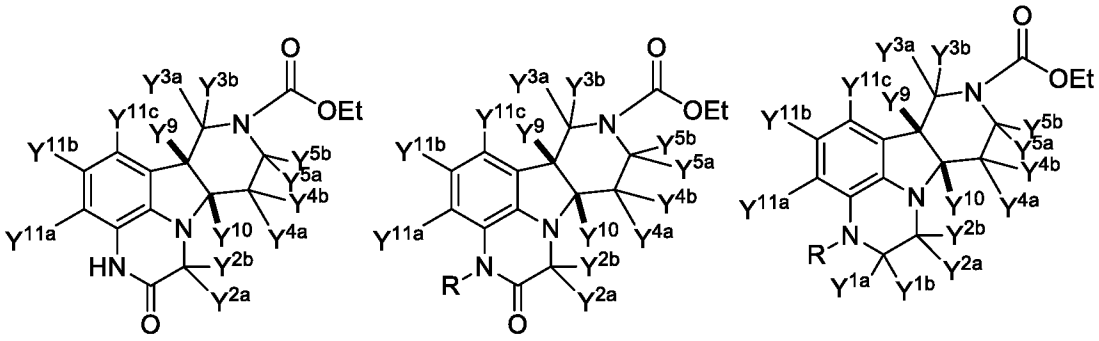
[123] In some embodiments, when Y^{12a} or Y^{12b} is deuterium, the level of deuterium incorporation at each Y^{12a} or Y^{12b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

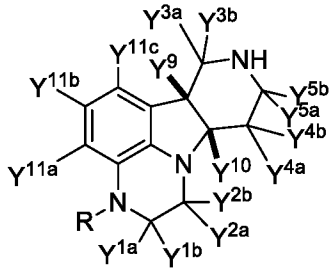
[124] In some embodiments, when Y^{13a} or Y^{13b} is deuterium, the level of deuterium incorporation at each Y^{13a} or Y^{13b} is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, is at least 97%, or at least 99%.

[125] In some embodiments, 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%.

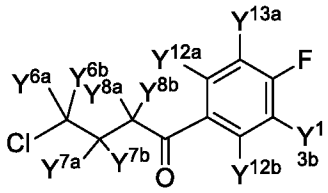
[126] In some embodiments, at least one of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} is hydrogen.

[127] In one embodiment, the following intermediates are novel and fall within the scope of this invention:

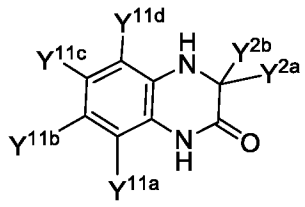




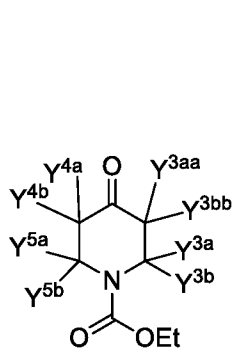
(5)



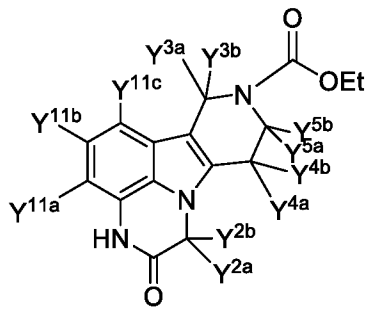
(6)



(8)



(11)



(12)

wherein R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are as described hereinabove; and Y^{11d}, Y^{3aa}, and Y^{3bb} are independently selected from hydrogen and deuterium.

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

[129] The synthesis of compounds of Formula I and/or Formula II may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I and/or Formula II and intermediates thereof are disclosed, for instance in PCT application No. PCT/US2008/003340 (published as WO2008112280); PCT application No. PCT/US2009/001608 (published as WO2009114181); PCT patent application No. PCT/US2000/016373 (published as WO2000/077010); U.S. Patent Application Publication No. 2006/0178362; U.S. Patent No. 6,552,017; U.S. Patent No. 7,183,282; and Journal of Medicinal Chemistry (2014), 57(6), 2670-2682.

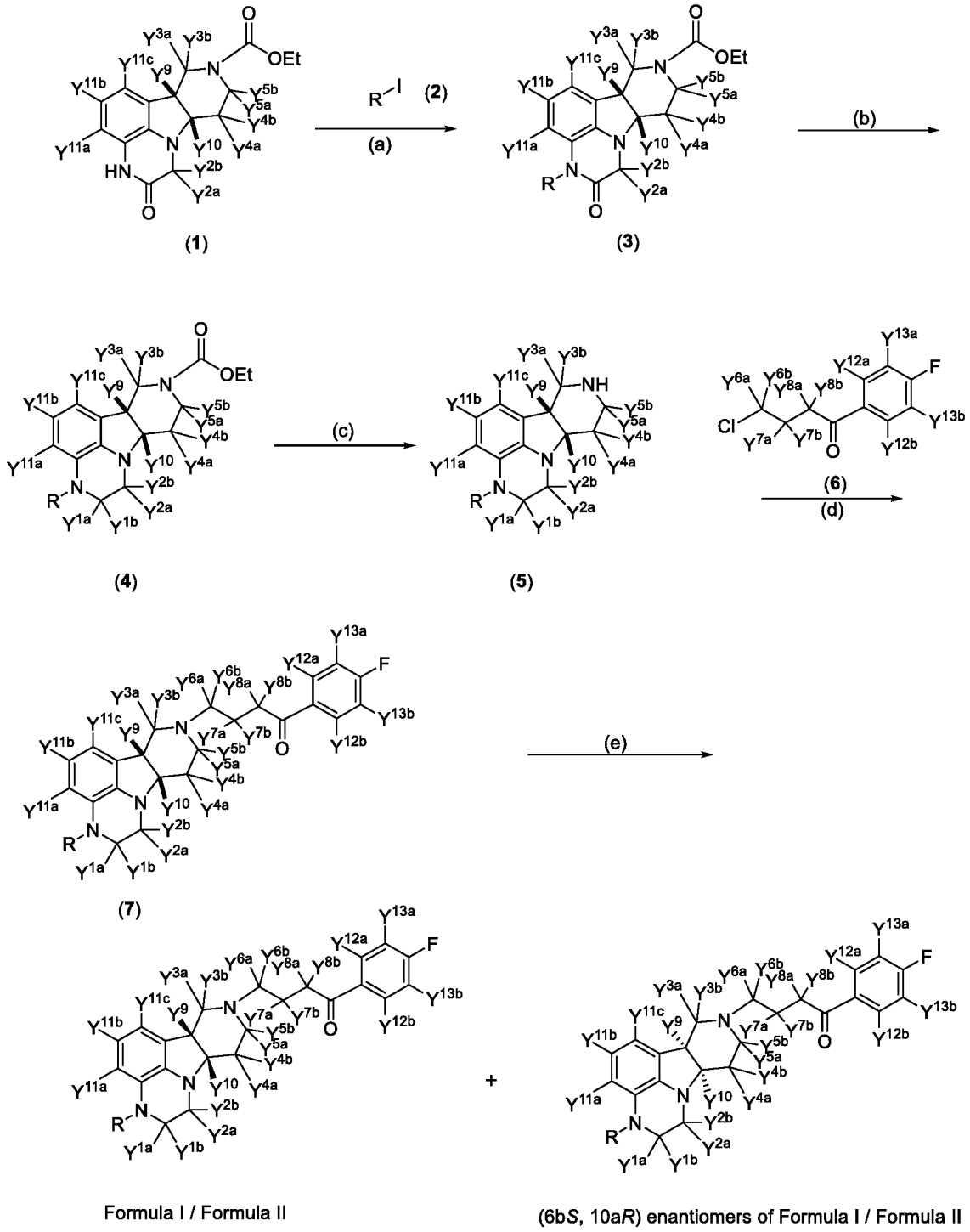
[130] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

[131] The synthesis of compounds of Formula I and/or Formula II may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis. Relevant procedures analogous to those of use for the preparation of compounds of Formula I and/or Formula II, and intermediates thereof are disclosed, for instance in PCT application No. PCT/US2008/003340 (published as WO2008112280); PCT application No. PCT/US2009/001608 (published as WO2009114181); PCT application No. PCT/US2000/016373 (published as WO2000077010); US Patent Application No. 20060178362; US patent No. 6,552,017; US patent No. 7,183,282; and Journal of Medicinal Chemistry (2014), 57(6), 2670-2682. 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.

[132] A convenient method for synthesizing compounds of Formula I and/or Formula II is depicted in Scheme 1 below:

[133] Scheme 1: General Synthesis of Compounds of Formula I and/or Formula II



wherein R, 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^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are as described hereinabove.

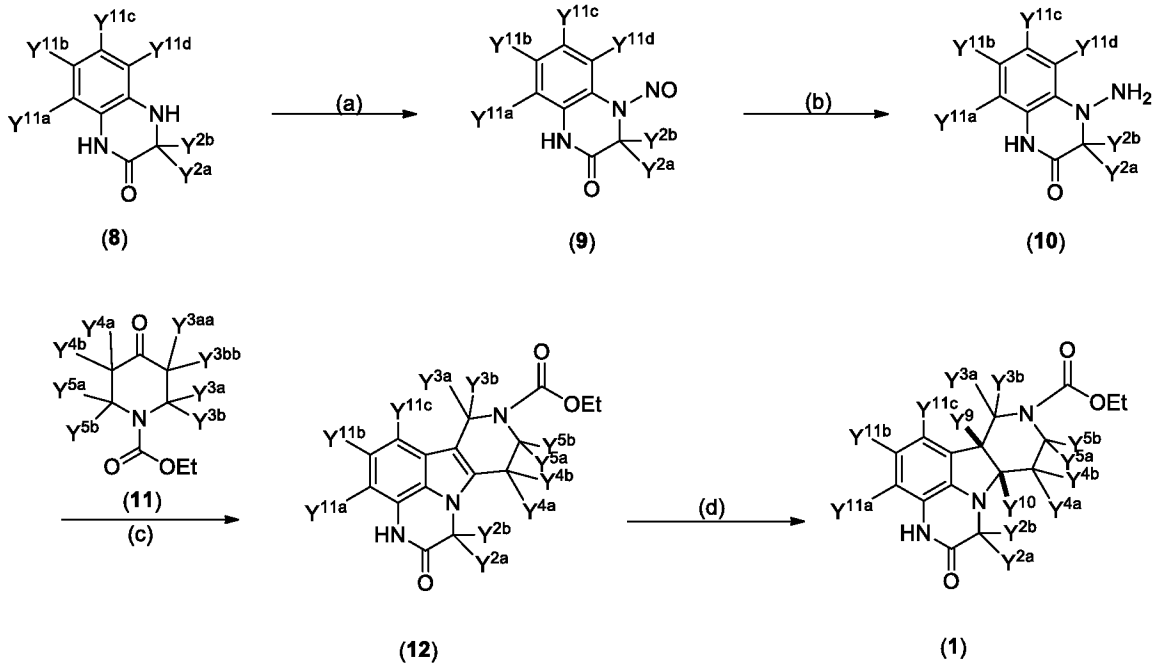
Reagents and conditions: (a) K_2CO_3 or NaH; (b) BD_3 in THF, reflux; (c) KOH; (d) Et_3N, KI; (e) chiral separation

[134] In a manner analogous to a procedure described in US6552017, and by Li, P. et al., Journal of Medicinal Chemistry (2014), 57(6), 2670-2682, appropriately deuterated *cis*-indoline intermediate (**1**) is treated with appropriately deuterated alkyl halide intermediate (**2**), in the presence of a base such as potassium carbonate or sodium hydride to produce appropriately deuterated alkylated *cis*-indoline intermediate (**3**) which is reduced with an appropriately deuterated reducing agent such as Borane-d_3, to produce appropriately deuterated ethyl ester protected *cis*-indoline intermediate (**4**). Intermediate (**4**) is then treated with a base such as potassium hydroxide to remove the ethoxycarbonyl protection, furnishing appropriately deuterated free amino *cis*-indoline intermediate (**5**), which is alkylated with appropriately deuterated butyrophenone intermediate (**6**) under basic conditions to produce appropriately deuterated racemic butyrophenonyl *cis*-indoline intermediate (**7**). Finally, intermediate (**7**) is resolved (e.g., by chiral HPLC separation) to produce appropriately deuterated compounds of Formula I and/or Formula II (wherein the configuration of the carbon atom to which Y^{10} is attached is *(S)* and the configuration of the carbon atom to which Y^9 is attached is *(R)* according to Cahn-Ingold-Prelog nomenclature), as well as enantiomers of compounds of Formula I and/or Formula II (wherein the configuration of the carbon atom to which Y^{10} is attached is *(R)* and the configuration of the carbon atom to which Y^9 is attached is *(S)* according to Cahn-Ingold-Prelog nomenclature).

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

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

[137] Scheme 2: Preparation of Intermediate (**1**)



wherein Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{9}, Y^{10}, Y^{11a}, Y^{11b}, Y^{11c} are as described hereinabove; and Y^{11d}, Y^{3aa}, and Y^{3bb} are independently selected from hydrogen and deuterium.

Reagents and conditions: (a) $NaNO_2$, HOAc; (b) Zn, HOAc; (c) HOAc, HCl; (d) $NaBD_3CN$, d-TFA, NH_4OH, NaOH or $NaBH_3CN$, TFA, NH_4OH, NaOH.

[138] In a manner analogous to a procedure described in US6552017, and Li, P. et al., Journal of Medicinal Chemistry (2014), 57(6), 2670-2682, appropriately deuterated quinoxaline intermediate (**8**) is treated with sodium nitrite and acetic acid to furnish appropriately deuterated nitroso-quinoxaline intermediate (**9**), which is reduced with zinc in acetic acid to produce appropriately deuterated aryl hydrazine intermediate (**10**). Under acidic conditions at elevated temperature, Fischer indole cyclization of intermediate (**10**), and suitably protected and appropriately deuterated piperidone intermediate (**11**) produces appropriately deuterated tetracyclic indole intermediate (**12**). Finally, *cis*-reduction of intermediate (**12**) using $NaBD_3CN$ or $NaBH_3CN$ in d-TFA or TFA under ambient reaction conditions, produces appropriately deuterated *cis*-indoline intermediate (**1**).

[139] Appropriately deuterated intermediate (**2**), for use in the preparation of

compounds of Formula I and/or Formula II according to Scheme 1 are commercially available, and are exemplified below.

[140] Intermediate (2)



(2)

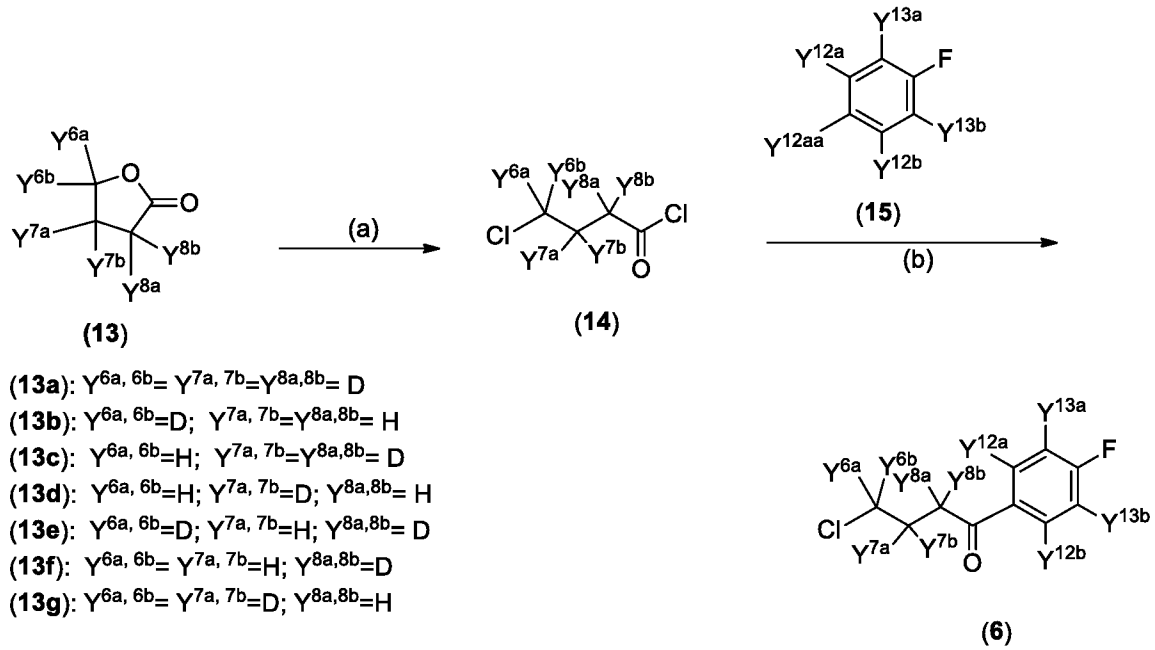
(2a): R= CD_3
(2b): R= CHD_2
(2c): R= CH_2D

[141] The following are commercially available deuterated alky iodide intermediates (**2**): Iodomethane-d_3 (99.5 atom %D) (**2a**), Iodomethane-d_2 (98 atom %D) (**2b**), Iodomethane-d (98 atom %D) (**2c**).

[142] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% (e.g., up to 98% or 99.5 %) deuterium incorporation at the position R in Formula I and Formula II.

[143] Appropriately deuterated intermediate (**6**), for use in the preparation of compounds of Formula I and/or Formula II according to Scheme 1 may be prepared from corresponding deuterated reagents exemplified in Scheme 3.

[144] Scheme 3: Preparation of Intermediate (6)



(13a): $Y^{6a, 6b}$= $Y^{7a, 7b}$=$Y^{8a,8b}$= D
(13b): $Y^{6a, 6b}$=D; $Y^{7a, 7b}$=$Y^{8a,8b}$= H
(13c): $Y^{6a, 6b}$=H; $Y^{7a, 7b}$=$Y^{8a,8b}$= D
(13d): $Y^{6a, 6b}$=H; $Y^{7a, 7b}$=D; $Y^{8a,8b}$= H
(13e): $Y^{6a, 6b}$=D; $Y^{7a, 7b}$=H; $Y^{8a,8b}$= D
(13f): $Y^{6a, 6b}$= $Y^{7a, 7b}$=H; $Y^{8a,8b}$=D
(13g): $Y^{6a, 6b}$= $Y^{7a, 7b}$=D; $Y^{8a,8b}$=H

(6)

wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a}, Y^{8b}, Y^{12a}, Y^{12b}, Y^{13a}, and Y^{13b} are as described

hereinabove; and Y^{12aa} is hydrogen or deuterium.

Reagents and conditions: (a) $SOCl_2$, $ZnCl_2$; (b) $AlCl_3$

[145] In a manner analogous to a procedure described in CN1654461, ring-opening of appropriately deuterated γ-butyrolactone intermediate (**13**) with $SOCl_2$ in the presence of $ZnCl_2$ produces appropriately deuterated chlorobutyric chloride intermediate (**14**) which is subsequently submitted to Friedel-Crafts acylation using appropriately deuterated aryl fluoride intermediate (**15**) in the presence of $AlCl_3$ to furnish appropriately deuterated aryl chloro-butanone intermediate (**6**).

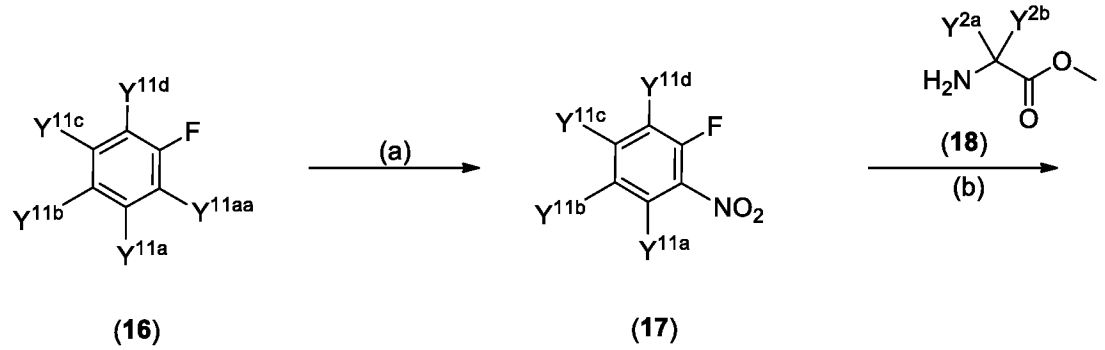
[146] The following intermediates (**13**) are commercially available: γ-Butyrolactone-d_6 (98 atom %D) (**13a**), γ-Butyrolactone-5,5,-d_2 (99 atom %D) (**13b**). Appropriately deuterated intermediates (**13c**), (**13d**), (**13e**), and (**13f**) are prepared in accordance with a method described in WO 2014031840. Intermediate (**13g**) is prepared according to a procedure described in US 20110257111.

[147] Synthetic chemists of ordinary skills will appreciate that preparation of additional partially and appropriately deuterated analogs may be readily achieved using relevant and analogous methods known in the art that successfully accomplishes the synthesis of intermediates (**13**) and (**14**) for use in preparation of intermediate (**6**).

[148] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% (e.g., up to 98% or 99%) deuterium incorporation at some or all of Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} Y^{8b}, Y^{12a}, Y^{12b}, Y^{13a}, and/or Y^{13b} in Formula I and Formula II.

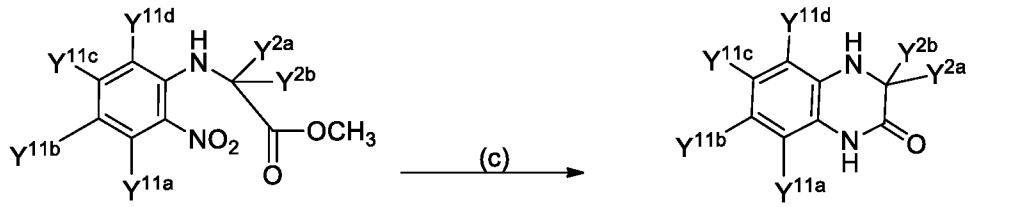
[149] Appropriately deuterated intermediate (**8**), for use in the preparation of compounds of Formula I and/or Formula II according to Scheme 1 may be prepared from corresponding deuterated reagents exemplified in Scheme 4.

[150] Scheme 4: Preparation of Intermediate (**8**)



(**16**) (**17**)

(**16a**):Y^{11aa}= Y^{11b}=Y^{11d}= D;Y^{11a}=Y^{11c}=H
(**16b**):Y^{11aa}= Y^{11b}=Y^{11d}= H;Y^{11a}=Y^{11c}=D
(**16c**):Y^{11aa}= Y^{11b}=Y^{11d}= Y^{11a}=Y^{11c}=D
(**16d**):Y^{11aa}= Y^{11b}=Y^{11d}= Y^{11a}=Y^{11c}=H



(**19**) (**8**)

(**8a**): Y^{11b}=Y^{11d}= D;Y^{11a}=Y^{11c}=H
(**8b**): Y^{11b}=Y^{11d}= H;Y^{11a}=Y^{11c}=D
(**8c**): Y^{11b}=Y^{11d}= Y^{11a}=Y^{11c}=D
(**8d**): Y^{11b}=Y^{11d}= Y^{11a}=Y^{11c}=H

wherein Y^{2a}, Y^{2b}, Y^{11a}, Y^{11b}, Y^{11c} are as described hereinabove; and Y^{11d} and Y^{11aa} are selected from hydrogen and deuterium.

Reagents and conditions: (a) N_2O_5, Bismuth triflate; (b) $EtN(Pr\text{-}i)_2$, KF,18-Crown-6; (c) H_2, Pd.

[151] In manner analogous to a procedure described by Qian, H. et al., Letters in Organic Chemistry, 11(7), 509-512; 2014, bismuth triflate catalyzed nitration of appropriately deuterated aryl fluoride intermediate (**16**) affords appropriately deuterated fluoro-nitro aryl intermediate (**17**). Subsequent treatment of intermediate (**17**) with appropriately deuterated glycinate such as methyl ester intermediate (**18**) furnishes appropriately deuterated nitrophenyl ester intermediate (**19**), which upon reduction, and

ring closure produces appropriately deuterated quinoxalinone intermediate (**8**) by analogy to a procedure described in WO 2003078398.

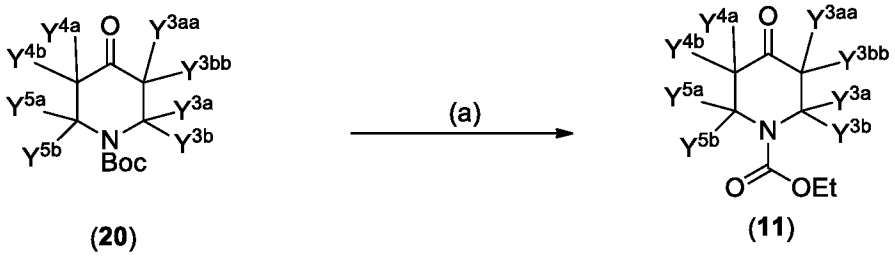
[152] Appropriately deuterated intermediate (**16a**) and (**16b**) are prepared in accordance with a procedure described by Matimba, H. et al., Journal of the American Society for Mass Spectrometry (1993), 4(1), 73-81, and fluorobenzene-d_5 (98 atom % D) (**16c**) is commercially available. Intermediate (**16d**) is commercially available.

[153] [Intermediates (**16b**) and (**16c**) are equivalent to intermediates (**15b**) and (**15a**) respectively (*vide infra*)].

[154] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% (e.g., up to 98%) deuterium incorporation at some or all of Y^{2a}, Y^{2b}, Y^{11a}, Y^{11b}, and/or Y^{11c} in Formula I and at Y^{2a} and/or Y^{2b} in Formula II.

[155] Appropriately deuterated intermediate (**11**), for use in the preparation of compounds of Formula I and/or Formula II according to Scheme 1 may be prepared from corresponding deuterated reagents exemplified in Scheme 5.

[156] Scheme 5: Preparation of Intermediate (**11**)



(**20**) (**11**)

(**20a**): $Y^{3a,3b}$=$Y^{3aa,3bb}$=$Y^{4a,4b}$=$Y^{5a,}Y^{5b}$=D
(**20b**): $Y^{3a,3b}$=D; $Y^{3aa,3bb}$=$Y^{4a,4b}$=H; $Y^{5a,}Y^{5b}$=D
(**20c**): $Y^{3a,3b}$=H; $Y^{3aa,3bb}$=$Y^{4a,4b}$=D; $Y^{5a,}Y^{5b}$=H

wherein Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b} are as described hereinabove; and Y^{3aa} and Y^{3bb} are selected from hydrogen and deuterium.

Reagents and conditions: (a) 1) HCl or TFA, 2) Ethyl chloroformate, Et_3N.

[157] Using a procedure known to anyone skilled in the art, or by analogy to a procedure described in WO2008137436, appropriately deuterated Boc-protected

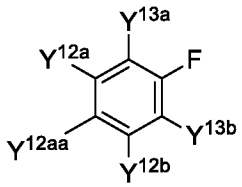
intermediate (**20**) is treated with acid such as HCl or TFA to remove the protecting group. In a manner analogous to a procedure described in WO 2009/037001, subsequent treatment with ethyl chloroformate in the presence of a base such as Et_3N produces appropriately deuterated intermediate (**11**).

[158] The following deuterated intermediates (**20**) are commercially available: N-Boc-4-Piperidone-2,2,3,3,5,5,6,6-d_8 (98 atom % D) (**20a**), [2,6-$^2H_4$]-*N*-Boc-4-Piperidinone (98 atom % D) (**20b**), N-Boc-4-Piperidone-3,3,5,5-d_4 (98 atom % D) (**20c**). Alternatively, appropriately deuterated (**20a**), (**20b**), and (**20c**) may be prepared as described in WO 2010/108103.

[159] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% (e.g., 98%) deuterium incorporation at some or all of Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and/or Y^{5b} in Formula I and/or Formula II.

[160] Appropriately deuterated intermediate (**15**) exemplified below, for use in the preparation of compounds of Formula I and/or Formula II according to Scheme 1 may be prepared from corresponding deuterated reagents.

[161] Intermediate (**15**)



(**15**)

(**15a**): $Y^{12aa}= Y^{12a}=Y^{12b}=Y^{13a}=Y^{13b}= D$
(**15b**): $Y^{12aa}=H$; $Y^{12a}=Y^{12b}=D$; $Y^{13a}=Y^{13b}= H$
(**15c**): $Y^{12aa}=Y^{12a}=Y^{12b}=H$; $Y^{13a}=Y^{13b}= D$
(**15d**): $Y^{12aa}=Y^{12a}=Y^{12b}=Y^{13a}=Y^{13b}= H$

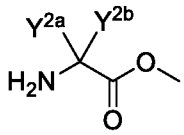
[162] The following deuterated intermediates (**15**) are prepared in accordance with published procedures: intermediate (**15b**) is prepared according to a procedure described by Matimba, H. et al., Journal of the American Society for Mass Spectrometry (1993), 4(1), 73-81, and intermediate (**15c**) is prepared as described by Yao, J. et al., Journal of the American Chemical Society (1994), 116(25), 11229-33. Fluorobenzene-d_5 (98 atom %D) (**15a**) is commercially available. Intermediate (**15d**) is commercially available.

[163] [Intermediates (**15b**) and (**15a**) are equivalent to intermediates (**16b**) and (**16c**) respectively (*vide supra*)].

[164] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% (e.g., up to 98%) deuterium incorporation at some or all of Y^{12a}, Y^{12b}, Y^{13a}, and/or Y^{13b} in Formula I.

[165] Appropriately deuterated intermediate (**18**) exemplified below, for use in the preparation of compounds of Formula I and/or Formula II according to Scheme 1 may be prepared from corresponding deuterated reagents.

[166] Intermediate (**18**)



(18)

(18a): $Y^{2a}=Y^{2b}=D$

[167] Appropriately deuterated glycine ester intermediate (**18a**) is prepared according to a procedure described by Springer, J. et al., Journal of Labelled Compounds and Radiopharmaceuticals, 50(2), 115-122; 2007.

[168] Using such commercially available reagents and deuterated reagents that can be readily prepared by known methods, compounds of Formula I and/or Formula II can be prepared with greater than 90% or greater than 95% deuterium incorporation at Y^{2a} and/or Y^{2b} in Formula I and Formula II.

[169] 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.

[170] 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.

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

Compositions

[172] The invention also provides pharmaceutical compositions comprising an effective amount of a compound of Formula I and/or Formula II (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.

[173] Pharmaceutically acceptable carriers, adjuvants 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, 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.

[174] 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.

[175] 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™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[176] 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).

[177] 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.

[178] 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.

[179] 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.

[180] 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.

[181] 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.

[182] 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.

[183] 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.

[184] 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 JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[185] 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 topically 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.

[186] 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.

[187] 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 Patents 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 in 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.

[188] 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.

[189] 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.

[190] 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.

[191] 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.

[192] 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.

[193] In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent 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 ITI-007. Such agents include those indicated as being useful in combination with ITI-007, including but not limited to, those described in PCT application No. PCT/US2008/009357 (published as WO2009/017836).

[194] Preferably, the second therapeutic agent is selected from selective serotonin re-uptake inhibitor (SSRI) (e.g. citalopram (Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox, Cital); dapoxetine (Priligy); escitalopram (Lexapro, Cipralex, Seroplex, Esertia); fluoxetine (Depex, Prozac, Fontex, Seromex, Seronil, Sarafem, Lactose, Motivest, Flutop, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS), Prodep (IND)); fluvoxamine (Luvox, Fevarin, Faverin, Dumyrox, Favoxil, Movox); indalpine (Upstene); paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine, Deparoc); sertraline (Zoloft, Lustral, Serlain, Asentra); vilazodone (Viibryd); or zimelidine (Zelmid, Normud)), therapeutic agents useful for the prophylaxis or treatment of dementia, particularly Alzheimer's disease: cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor), such as Tacrine, rivastigmine (Exelon), donepezil (Aricept), and galantamine (Razadyne, formerly called Reminyl)), or an N-Methyl D-Asparate (NMDA) receptor antagonist, such as memantine, combination of agents useful for the prophylaxis or treatment of Alzheimer's disease (donepezil and memantine), anti-depressant, anti-psychotic, other hypnotic agents, agents use to treat Parkinson's disease or mood disorders, compounds that modulate GABA activity (e.g. enhances the activity and facilitates GABA transmission) (e.g. doxepin, alprazolam, bromazepam, clobazam, clonazepam, clorazepate, diazepam, flunitrazepam,

fiurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazapam, triazolam, indiplon, zopiclone, eszopiclone, zaleplon, Zolpidem, gabaxadol, vigabatrin, tiagabine, EVT 201 (Evotec Pharmaceuticals) and estazolam), a GABA-B agonist, a 5-HT modulator (e.g. a 5-HT_{2A} agonist, a 5-HT_{2A} antagonist (e.g. ketanserin, risperidone, eplivanserin, volinanserin (Sanofi-Aventis, France), pruvanserin, MDL 100907 (SanofiAventis, France), HY 10275 (Eli Lilly), APD 125 (Arena Pharmaceuticals, San Diego, CA), or AVE8488 (Sanofi-Aventis, France)), a 5-HT_{2A} inverse agonist, etc.), a melatonin agonist (e.g. melatonin, ramelteon (ROZEREM®, Takeda Pharmaceuticals, Japan), VEC-162 (Vanda Pharmaceuticals, Rockville, MD), PD-6735 (Phase II Discovery) or agomelatine), an ion channel modulator (e.g. blocker) (e.g. lamotrigine, gabapentin and pregabalin), a serotonin-2 antagonist/reuptake inhibitor (SARI) (e.g. Org 50081 (Organon -Netherlands), ritanserin, nefazodone, serzone or trazodone), an orexin receptor antagonist (e.g. orexin, a 1,3-biarylurea, SB-334867-a (GlaxoSmithKline, UK), GW649868 (GlaxoSmithKline) and a benzamide derivative), an H3 agonist or antagonist, a noradrenergic agonist or antagonist, a galanin agonist, a CRH antagonist, human growth hormone, a growth hormone agonist, estrogen, an estrogen agonist, a neurokinin-1 drug (e.g. Casopitant), an anti-depressant (e.g. amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitaloprame, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenlzine sulfate, protiptyline, sertraline, tranylcypromine, trazodone, trimipramine, and velafaxine), and an antipsychotic agent (e.g. chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine molidone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, clozapine, aripiparazole, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone), an atypical antipsychotic agent (e.g. clozapine, aripiparazole, olanzapine, quetiapine, risperidone, ziprasidone, or paliperidone), $5HT_{1A}$ agonist (e.g. repinotan, sarizotan, eptapirone, buspirone or MN-305), anti-Parkinson's agent (e.g. L-dopa, co-careldopa, duodopa, stalova, Symmetrel, benzotropine, biperiden, bromocryiptine, entacapone, pergolide, pramipexole, procyclidine, ropinirole, selegiline or tolcapone), levodopa and levodopa adjuncts (carbidopa, COMT inhibitors, MAO-B inhibitors), dopamine agonists, anticholinergics (e.g. levodopa), atypical stimulant (e.g.

modafinil, adrafinil, or armodafinil), antidepressant (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants), antihistamine agents (e.g. latrepirdine).

[195] 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 second therapeutic agents, wherein the compound and second 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).

[196] 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.

[197] 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.

[198] In one embodiment, an effective amount of a compound of this invention can be 20 mg per dose. In one embodiment, an effective amount of a compound of this invention can be 30 mg per dose. In one embodiment, an effective amount of a compound of this invention can be 40 mg per dose. In one embodiment, an effective amount of a compound of this invention can be 60 mg per dose. In one embodiment, an effective amount of a compound of this invention can range from about 20 mg to about 60 mg per dose. In one embodiment, an effective amount of a compound of this invention can range from about 4 mg to about 120 mg per dose. In one embodiment, an effective amount of a compound of this invention can range from about 2 mg to about 300 mg per dose. In one embodiment, an effective amount of a compound of this invention can range from about

0.2 mg to about 600 mg per dose. In one embodiment, the dose is administered twice daily. In one embodiment, the dose is administered once daily.

[199] 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 ITI-007.

[200] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second 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 second 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.

[201] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

[202] In another embodiment, the invention provides a method of modulating the activity of serotonin, glutamate, and dopamine receptors in a cell (in vivo or in vitro), comprising contacting a cell with one or more compounds of Formula I herein, or a pharmaceutically acceptable salt thereof.

[203] In one embodiment, the invention provides a method of modulating the activity of

a 5-hydroxytryptamine (5-HT) receptor. The method comprises contacting a 5-hydroxytryptamine (5-HT) receptor in a cell, in vivo or in vitro, such that activity of the 5-hydroxytryptamine (5-HT) receptor is modulated (e.g., increased or decreased). In an aspect of this embodiment, the invention provides a method of modulating the activity of 5-HT_{2A} receptor. In a particular aspect of this embodiment, the invention provides a method of antagonizing the activity of 5-HT_{2A} receptor.

[204] In one embodiment, the invention provides a method of modulating the activity of a serotonin transporter (SERT). The method comprises contacting a serotonin transporter in a cell, in vivo or in vitro, such that activity of the serotonin transporter is modulated (e.g., increased or decreased). In an aspect of this embodiment, the invention provides a method of inhibiting a serotonin transporter.

[205] In one embodiment, the invention provides a method of modulating the activity of a dopamine (e.g. D_2) receptor. The method comprises contacting a dopamine receptor in a cell, in vivo or in vitro, such that activity of the dopamine receptor is modulated (e.g., increased or decreased). In an aspect of this embodiment, the invention provides a method of antagonizing a postsynaptic D2 receptor. In an aspect of this embodiment, the invention provides a method of partially agonizing a presynaptic striatal D2 receptor.

[206] In one embodiment, the invention provides a method of modulating the activity of GluN2B-type N-methyl-D-aspartate (NMDA) receptor. The method comprises contacting a GluN2B-type N-methyl-D-aspartate receptor in a cell, in vivo or in vitro, such that activity of the GluN2B-type N-methyl-D-aspartate receptor is modulated (e.g., increased or decreased). In an aspect of this embodiment, the invention provides a method of indirectly modulating glutamatergic neurotransmission by increasing phosphorylation of a GluN2B-type N-methyl-D-aspartate (NMDA) receptor.

[207] According to another embodiment, the invention provides a method of treating a disease that is beneficially treated by ITI-007 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 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 patents and published applications: PCT application No. PCT/US2008/003340 (published as WO2008112280); PCT application No. PCT/US2009/001608 (published as

WO2009114181); PCT application No. PCT/US2000/016373 (published as WO2000077010); PCT application No. PCT/US2014/029914 (published asWO2014145192); PCT application No. PCT/US2013/036515 (published as WO2013155506); PCT application No. PCT/US2013/036512 (published as WO2013155504); Psychopharmacology (2015), 232(3), 605-621.

[208] Such diseases include, but are not limited to, addictive behavior (e.g. behavior associated with and/or caused by physical and/or psychological dependence on narcotics, opiates, analgesics, painkillers, amphetamines, cocaine, heroin, opium, marijuana, alcohol, smoking, nicotine, gambling or eating), affective disorders, aggressive and assaultive behavior, aggressive behavior, agitation, agitation in Alzheimer's disease, agitation in autism and/or related autistic disorders, agitation in dementia (e.g. agitation in Alzheimer's disease), Alzheimer's disease, amyotrophic lateral sclerosis, anger, anorexia, anxiety, assaultive behavior, attention deficit disorder, attention deficit hyperactivity disorder, behavioral disturbances in patients with dementia (e.g. agitation and irritability), behavioral or mood disorders (e.g. agitation/irritation), bipolar depression, bipolar disorder, brain/spinal cord trauma, bulemia, cancer, central nervous system disorders, cephalic pain, cognition associated with schizophrenia, conditions associated with cephalic pain, corticobasal degenerations, dementia, dementia with Lewy bodies, dementing illnesses (e.g. senile dementia, Alzheimer's disease, Pick' s disease, frontotemporal dementia, parasupranculear palsy, dementia with Lewy bodies, vascular dementia), depression (e.g. refractory depression, co-morbid depression, MDD), depression in a patient suffering from psychosis (e.g. schizophrenia), Down syndrome, dyskinesia, elderly depression, excessive sleepiness, fatigue in conditions such as Parkinson's disease, frontotemporal dementia, gastrointestinal disorders, gastrointestinal disorders (e.g. dysfunction of the gastrointestinal tract motility), Huntington's disease, impulse control disorder, impulse control disorder or intermittent explosive disorder in patients suffering from psychosis (e.g. schizophrenia), intermittent explosive disorder, irritation, major depressive disorder, migraine, mild cognition impairment, mood disorders associated with Parkinson's disease, mood disorders associated with psychosis (e.g. schizophrenia), multiple sclerosis, neurodegenerative diseases, obesity, obsessive-compulsive disorder, other psychiatric or neurological diseases, parasupranculear palsy,

Parkinson's disease, physical or emotional outbursts, Pick's disease, post-traumatic stress disorder, prion disease, psychosis, schizophrenia, senile dementia, sexual disorders, sleep disorder (e.g. maintenance insomnia, frequent awakenings, waking up feeling unrefreshed, insomnia, narcolepsy, sleep apnea), sleep disorders (particularly sleep disorders associated with schizophrenia), sleep disorders associated with Parkinson's disease, sleep disorders associated with psychosis (e.g. schizophrenia), sleep disorders in patients suffering from dementia (e.g. Alzheimer's disease), social phobias, traumatic conditions, vascular dementia, Wemicke-Korsakoffs syndrome..

[209] In some embodiments, the method of this invention is used to treat a disease or condition selected from schizophrenia, schizophrenia having an acute exacerbation of psychosis, acute exacerbation of psychosis, depression, bipolar disorder, agitation, insomnia, dementia, and Alzheimer's Disease, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound or a composition of the present invention.

[210] In one particular embodiment, the method of this invention is used to treat a disease or condition selected from schizophrenia, schizophrenia having an acute exacerbation of psychosis, acute exacerbation of psychosis, and Alzheimer's Disease in a subject in need thereof.

[211] 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).

[212] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject in need thereof one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with ITI-007. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

[213] The term “co-administered” as used herein means that the second 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 second 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 second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[214] Effective amounts of these second 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 second therapeutic agent's optimal effective-amount range.

[215] In one embodiment of the invention, where a second 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 second therapeutic agent is not administered. In another embodiment, the effective amount of the second 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.

[216] In yet another aspect, the invention provides the use of a compound of Formula I alone or together with one or more of the above-described second 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 for use in the treatment in a subject of a disease, disorder or symptom thereof delineated herein.

Example X. Evaluation of Metabolic Stability

[217] ***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.

[218] ***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.

[219] ***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]

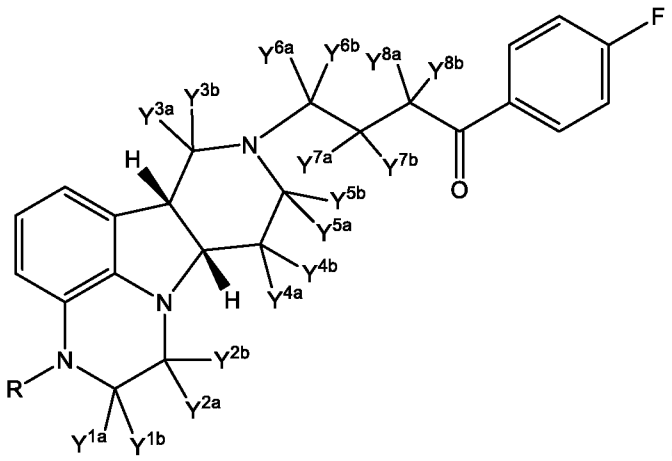
[220] Data analysis is performed using Microsoft Excel Software.

[221] 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

We claim:

1. A compound of Formula II:



(II)

, or a pharmaceutically acceptable salt thereof,

wherein R is CH_3, CH_2D, CHD_2 or CD_3;

and 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are independently selected from hydrogen and deuterium;

provided that at least one of R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} comprises deuterium.

2. The compound of claim 1, wherein R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} comprise at least two deuterium atoms.

3. The compound of claim 1, wherein R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} comprise at least four deuterium atoms.

4. The compound of claim 1, wherein R, 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^{7a}, Y^{7b}, Y^{8a} and Y^{8b} comprise at least five deuterium atoms.

5. The compound of claim 1, wherein R is CH_3.

6. The compound of claim 1, wherein R is CD_3.

7. The compound of claim 1, wherein Y^{1a} and Y^{1b} are the same.

8. The compound of claim 7, wherein Y^{1a} and Y^{1b} are each hydrogen.

9. The compound of claim 7, wherein Y^{1a} and Y^{1b} are each deuterium.

10. The compound of claim 1, wherein Y^{2a} and Y^{2b} are the same.

11. The compound of claim 10, wherein Y^{2a} and Y^{2b} are each hydrogen.

12. The compound of claim 10, wherein Y^{2a} and Y^{2b} are each deuterium.

13. The compound of claim 1, wherein Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are the same.

14. The compound of claim 13, wherein Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each hydrogen.

15. The compound of claim 13, wherein Y^{1a}, Y^{1b}, Y^{2a} and Y^{2b} are each deuterium.

16. The compound of claim 1, wherein Y^{1a} and Y^{1b} are each hydrogen; and Y^{2a} and Y^{2b} are each deuterium.

17. The compound of claim 1, wherein Y^{1a} and Y^{1b} are each deuterium; and Y^{2a} and Y^{2b} are each hydrogen.

18. The compound of claim 1, wherein Y^{3a} and Y^{3b} are the same.

19. The compound of claim 18, wherein Y^{3a} and Y^{3b} are each hydrogen.

20. The compound of claim 18, wherein Y^{3a} and Y^{3b} are each deuterium.

21. The compound of claim 1, wherein Y^{4a} and Y^{4b} are the same.

22. The compound of claim 21, wherein Y^{4a} and Y^{4b} are each hydrogen.

23. The compound of claim 21, wherein Y^{4a} and Y^{4b} are each deuterium.

24. The compound of claim 1, wherein Y^{5a} and Y^{5b} are the same.

25. The compound of claim 24, wherein Y^{5a} and Y^{5b} are each hydrogen.

26. The compound of claim 24, wherein Y^{5a} and Y^{5b} are each deuterium.

27. The compound of claim 1, wherein Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are the same.

28. The compound of claim 27, wherein Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each hydrogen.

29. The compound of claim 27, wherein Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a} and Y^{5b} are each deuterium.

30. The compound of claim 1, wherein Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each hydrogen; and Y^{4a} and Y^{4b} are each deuterium.

31. The compound of claim 1, wherein Y^{3a}, Y^{3b}, Y^{5a} and Y^{5b} are each deuterium; and Y^{4a} and Y^{4b} are each hydrogen.

32. The compound of claim 1, wherein Y^{6a} and Y^{6b} are the same.

33. The compound of claim 32, wherein Y^{6a} and Y^{6b} are each hydrogen

34. The compound of claim 32, wherein Y^{6a} and Y^{6b} are each deuterium.

35. The compound of claim 1, wherein Y^{7a} and Y^{7b} are the same.

36. The compound of claim 35, wherein Y^{7a} and Y^{7b} are each hydrogen.

37. The compound of claim 35, wherein Y^{7a} and Y^{7b} are each deuterium.

38. The compound of claim 1, wherein Y^{8a} and Y^{8b} are the same.

39. The compound of claim 38, wherein Y^{8a} and Y^{8b} are each hydrogen.

40. The compound of claim 38, wherein Y^{8a} and Y^{8b} are each deuterium.

41. The compound of claim 1, wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are the same.

42. The compound of claim 41, wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen.

43. The compound of claim 41, wherein Y^{6a}, Y^{6b}, Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium.

44. The compound of claim 1, wherein Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{6a} and Y^{6b} are each deuterium.

45. The compound of claim 1, wherein Y^{7a}, Y^{7b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{6a} and Y^{6b} are each hydrogen.

46. The compound of claim 1, wherein Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each hydrogen; and Y^{7a} and Y^{7b} are each deuterium.

47. The compound of claim 1, wherein Y^{6a}, Y^{6b}, Y^{8a} and Y^{8b} are each deuterium; and Y^{7a} and Y^{7b} are each hydrogen.

48. The compound of claim 1, wherein Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each hydrogen; and Y^{8a} and Y^{8b} are each deuterium.

49. The compound of claim 1, wherein Y^{6a}, Y^{6b}, Y^{7a} and Y^{7b} are each deuterium; and Y^{8a} and Y^{8b} are each hydrogen.

50. The compound of claim 1, wherein R is CD_3; 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^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in table (below):

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
200a	D	D	D	D	D	D	D	D
201a	H	H	H	H	H	H	H	H
202a	D	D	H	H	H	D	D	D
203a	D	D	D	D	D	H	H	H
204a	H	H	D	D	D	D	D	D
205a	H	H	D	D	D	H	H	H

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
206a	D	D	H	H	H	H	H	H
207a	H	H	H	H	H	D	D	D
208a	D	D	D	D	H	D	D	D
209a	D	D	D	H	D	D	D	D
210a	D	D	H	D	D	D	D	D
211a	D	D	H	D	H	D	D	D
212a	D	D	D	D	D	D	D	H
213a	D	D	D	D	D	D	H	D
214a	D	D	D	D	D	H	D	D
215a	D	H	D	D	D	D	D	D
216a	H	D	D	D	D	D	D	D
217a	D	H	D	D	D	D	H	H
218a	H	D	D	D	D	H	D	D
219a	D	D	D	D	H	D	D	H
220a	D	D	D	H	D	D	H	D
221a	D	D	H	D	D	H	D	D
222a	D	D	H	D	H	D	H	H
223a	D	H	H	D	H	D	D	D
224a	H	D	D	H	D	D	D	D
225a	D	H	H	H	H	H	H	H
226a	H	D	H	H	H	H	H	H
227a	H	H	D	D	H	H	H	H
228a	H	H	D	H	D	H	H	H
229a	H	H	H	D	D	H	H	H
230a	H	H	H	D	H	H	H	H
231a	H	H	H	H	H	D	D	H
232a	H	H	H	H	H	D	H	D
233a	H	H	H	H	H	H	D	D
234a	H	H	H	H	H	D	H	H

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
235a	D	H	H	D	H	H	H	H
236a	H	D	D	H	D	H	H	H
237a	D	H	H	H	H	D	H	H
238a	H	D	H	H	H	H	D	D
239a	H	H	D	D	H	D	D	H
240a	H	H	D	H	D	D	H	D
241a	H	H	H	D	D	H	D	D
242a	H	H	H	D	H	D	H	H

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

51. The compound of claim 1, wherein R is CH_3; 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^{7a} and Y^{7b} are the same; Y^{8a} and Y^{8b} are the same, and the compound is selected from any one of the compounds (Cmpd) set forth in table (below):

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
200b	D	D	D	D	D	D	D	D
201b	D	D	H	H	H	D	D	D
202b	D	D	D	D	D	H	H	H
203b	H	H	D	D	D	D	D	D
204b	H	H	D	D	D	H	H	H
205b	D	D	H	H	H	H	H	H
206b	H	H	H	H	H	D	D	D
207b	D	D	D	D	H	D	D	D
208b	D	D	D	H	D	D	D	D
209b	D	D	H	D	D	D	D	D
210b	D	D	H	D	H	D	D	D
211b	D	D	D	D	D	D	D	H

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
212b	D	D	D	D	D	D	H	D
213b	D	D	D	D	D	H	D	D
214b	D	H	D	D	D	D	D	D
215b	H	D	D	D	D	D	D	D
216b	D	H	D	D	D	D	H	H
217b	H	D	D	D	D	H	D	D
218b	D	D	D	D	H	D	D	H
219b	D	D	D	H	D	D	H	D
220b	D	D	H	D	D	H	D	D
221b	D	D	H	D	H	D	H	H
222b	D	H	H	D	H	D	D	D
223b	H	D	D	H	D	D	D	D
224b	D	H	H	H	H	H	H	H
225b	H	D	H	H	H	H	H	H
226b	H	H	D	D	H	H	H	H
227b	H	H	D	H	D	H	H	H
228b	H	H	H	D	D	H	H	H
229b	H	H	H	D	H	H	H	H
230b	H	H	H	H	H	D	D	H
231b	H	H	H	H	H	D	H	D
232b	H	H	H	H	H	H	D	D
233b	H	H	H	H	H	D	H	H
234b	D	H	H	D	H	H	H	H
235b	H	D	D	H	D	H	H	H
236b	D	H	H	H	H	D	H	H
237b	H	D	H	H	H	H	D	D
238b	H	H	D	D	H	D	D	H
239b	H	H	D	H	D	D	H	D
240b	H	H	H	D	D	H	D	D

Cmpd	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^{7a}/Y^{7b}	Y^{8a}/Y^{8b}
241b	H	H	H	D	H	D	H	H

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

52. The compound of any of the claims 1-51, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

53. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

54. A method of modulating activity of a 5-hydroxytryptamine (5-HT) receptor in a cell, comprising contacting the cell with the compound of claim 1 or the composition of claim 53.

55. The method of claim 54, comprising antagonizing the activity of the 5-HT_{2A} receptor.

56. A method of modulating activity of a serotonin transporter (SERT) in a cell, comprising contacting the cell with the compound of claim 1 or the composition of claim 53.

57. A method of modulating activity of a dopamine (D2) receptor in a cell, comprising contacting the cell with the compound of claim 1 or the composition of claim 53.

58. The method of claim 57, wherein the method of modulating a dopamine (D2) receptor comprises antagonizing a postsynaptic dopamine (D2) receptor.

59. The method of claim 57, comprising agonizing a presynaptic striatal dopamine (D2) receptor.

60. A method of modulating activity of a GluN2B-type N-methyl-D-aspartate (NMDA) receptor in a cell, comprising contacting the cell with the compound of claim 1 or the composition of claim 53.

61. The method of claim 60, comprising indirectly modulating glutamatergic neurotransmission by increasing phosphorylation of the GluN2B-type N-methyl-D-aspartate (NMDA) receptor.

62. A method of treating a disease or condition selected from schizophrenia, schizophrenia having an acute exacerbation of psychosis, acute exacerbation of psychosis, depression, bipolar disorder, agitation, insomnia, dementia, and Alzheimer's Disease, comprising the step of administering to a subject in need thereof a therapeutically effective amount of the compound of claim 1 or the composition of claim 53.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/69455

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/437; A61P 25/18; C07D 241/36 (2016.01)
CPC - A61K 31/4985; C07D 471/14, 471/16

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
See Search History document

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.
Y	SNYDER, GL et al., Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission, Psychopharmacology 232, pages 605-621, 2015 [published online 15 August 2014]; abstract; page 606, column 1, paragraph 2; page 611, figure 1	1-51, 52/1-51, 53, 54/1, 54/53, 55/54/1, 55/54/53, 56/1, 56/53, 57/1, 57/53, 58/57/1, 58/57/53, 59/57/1, 59/57/53, 60/1, 60/53, 61/60/1, 61/60/53, 62/1, 62/53
Y	US 2008/0255194 A1 (HARBESON, SL) 16 October 2008; paragraphs [0003], [0011], [0031], [0033], [0076], [0110]-[0111], [0114]	1-51, 52/1-51, 53, 54/1, 54/53, 55/54/1, 55/54/53, 56/1, 56/53, 57/1, 57/53, 58/57/1, 58/57/53, 59/57/1, 59/57/53, 60/1, 60/53, 61/60/1, 61/60/53, 62/1, 62/53
Y	WO 2015/154030 A1 (INTRA-CELLULAR THERAPIES, INC.) 08 October 2015; paragraphs [0001], [0013], [0033], [0035], [0043]	6, 9, 15, 17, 50, 52/6, 52/9, 52/15, 52/17, 52/50
Y	US 2014/0080816 A1 (ABBVIE INC., et al.) 20 March 2014; paragraphs [0067], [0069], [0075], [0082], [0095], [0098]; claim 58	12, 15-16, 52/12, 52/15-16
Y	US 2011/0152308 A1 (SHI, L) 23 June 2011; paragraphs [0010]-[0012], [0026], [0135]	20, 23, 26, 29-31, 52/20, 52/23, 52/26, 52/29-31

☒ 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
16 February 2017 (16.02.2017)	09 MAR 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0018348 A1 (JAVITT, DC) 16 January 2014; paragraphs [0051]-[0053]	54/1, 54/53, 55/54/1, 55/54/53
Y	US 2014/0050783 A1 (INTRA-CELLULAR THERAPIES INC.) 20 February 2014; paragraphs [0008], [0013], [0016], [0039], [0086], [0091]	56/1, 56/53
Y	WO 2015/085004 A1 (INTRA-CELLULAR THERAPIES INC.) 11 June 2015; paragraphs [0006], [0008], [0018], [0046], [0076]	57/1, 57/53, 58/57/1, 58/57/53, 59/57/1, 59/57/53, 60/1, 60/53, 61/60/1, 61/60/53