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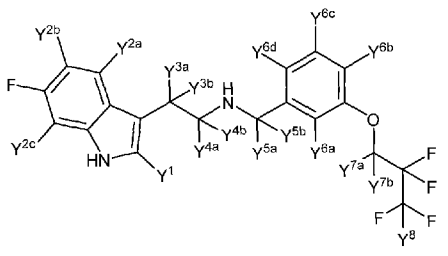
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(54) Title: DEUTERATED IDALOPIRDINE



(I)

(57) Abstract: This invention relates to indol-3-yl)ethyl]-3-(tetrafluoropropoxy)benzylamines of Formula (I), wherein each variable is defined herein, 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 an antagonist of the serotonin-6 (5-HT_6) receptor, such as Alzheimer's Disease.

DEUTERATED IDALOPIRDINE

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/361,316, filed on July 12, 2016. The entire teachings of the above application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

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

[0003] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving 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.

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

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

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

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

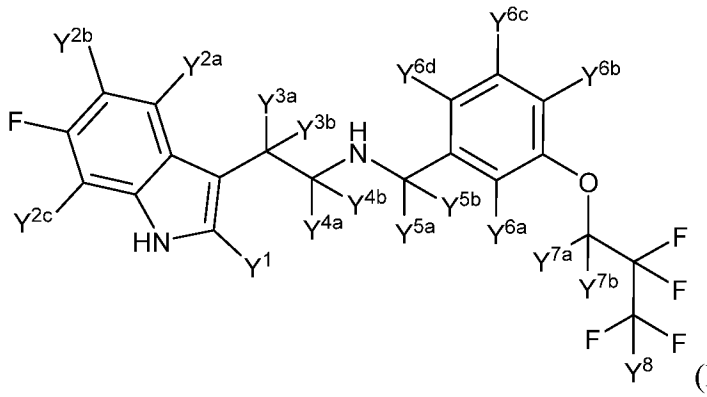
[0007] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol 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).

[0008] 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

[0009] This invention relates to deuterated forms of indol-3-yl)ethyl]-3-(tetrafluoropropoxy)benzylamines, and pharmaceutically acceptable salts thereof. In one aspect, the invention provides a compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, Y^{7b} and Y^8 is independently selected from hydrogen and deuterium, wherein at least one of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and Y^8 is deuterium.

[0010] This invention also provides compositions comprising a compound of this invention, including pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier. This invention also provides the use of such compounds and compositions in methods of treating diseases and

conditions that are beneficially treated by administering an antagonist of the serotonin-6 (5-HT_6) receptor. Some exemplary embodiments include a method of treating a disease or condition selected from mild Alzheimer's Disease (AD), moderate AD, severe AD, or mild to moderate AD, the method comprising the step of administering to a subject in need thereof a pharmaceutically acceptable composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Idalopirdine, also known as Lu-AE-58054, SGS-518, 59WCJ0YNWM and 2-(6-fluoro-1H-indol-3-yl)-N-(3-(2,2,3,3-tetrafluoropropoxy)benzyl)ethan-1-amine, is a potent and selective 5-HT_6 receptor antagonist. 5-HT_6 receptor subtype, the most recently identified member of the serotonin receptor superfamily, is expressed primarily in the regions of the brain involved in cognition, such as the cortex and the hippocampus. Antagonism of 5-HT_6 receptor modulates the activity of multiple neurotransmitter networks such as the cholinergic and glutamatergic neuronal systems, and blocking this receptor induces acetylcholine release, thereby restoring acetylcholine levels in deteriorated cholinergic systems. Cholinergic neuronal systems are important to memory formation and consolidation, and the loss of cholinergic neurons is one of the hallmarks of Alzheimer's disease (AD), a common form of dementia.

[0012] Idalopirdine has been evaluated in Phase III clinical trials for improving cognition in patients with mild to moderate AD, as adjunctive therapy to FDA approved donepezil, a reversible, specific acetylcholinesterase inhibitor. The same study includes a sub-study wherein certain patients also receive memantine.

[0013] Idalopirdine is generally well tolerated, and adverse events reported during phase II clinical trials included dizziness, aggression, diarrhea, headache, hypertension, vomiting and nausea. Additionally, increased values of liver enzymes (aspartate and alanine aminotransferases, γ-glutamyl transferase) are associated with the use of Idalopirdine.

[0014] Despite the potential beneficial activities of idalopirdine, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

Definitions

[0015] 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.

[0016] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[0017] 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.

[0018] 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 Idalopirdine 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.

[0019] 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. In some embodiments, when a position is designated specifically as "H" or "hydrogen", the position has at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% hydrogen. In some embodiments, when a position is designated specifically as "H" or "hydrogen", the position incorporates $\leq$20% deuterium, $\leq$10% deuterium, $\leq$5% deuterium, $\leq$4% deuterium, $\leq$3% deuterium, $\leq$2% deuterium, or $\leq$1% deuterium. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[0020] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[0021] 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).

[0022] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 52.5%.

[0023] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 60%.

[0024] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 67.5%.

[0025] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 75%.

[0026] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 82.5%.

[0027] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 90%.

[0028] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 95%.

[0029] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 97.5%.

[0030] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99%.

[0031] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99.5%.

[0032] 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.

[0033] 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.

[0034] The invention also provides salts of the compounds of the invention.

[0035] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to one embodiment, the compound is a pharmaceutically acceptable acid addition salt. In one embodiment the acid addition salt may be a deuterated acid addition salt.

[0036] 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.

[0037] 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, methanesu1fonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2- sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid. In one embodiment, the acids commonly employed to form pharmaceutically acceptable salts include the above-listed inorganic acids, wherein at least one hydrogen is replaced with deuterium.

[0038] The compounds of the present invention (e.g., compounds of Formula I), 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. "Stereoisomer" refers to both enantiomers and diastereomers. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[0039] 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.

[0040] 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).

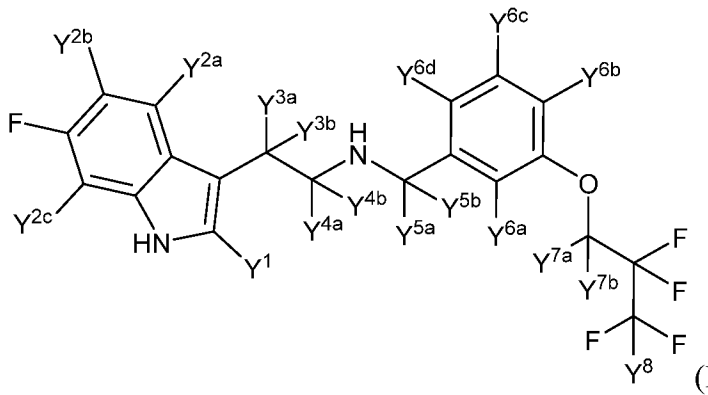
[0041] "D" and "d" both refer to deuterium. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[0042] "Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[0043] 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

[0044] The present invention provides a compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein: each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, Y^{7b} and Y^8 is independently selected from hydrogen and deuterium, wherein at least one of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and Y^8 is deuterium.

[0045] In some embodiments of Formula I, each of Y^{2a}, Y^{2b}, and Y^{2c} is the same; each of Y^{3a} and Y^{3b} is the same; each of Y^{4a} and Y^{4b} is the same; each of Y^{5a} and Y^{5b} is the same; each of Y^{6a}, Y^{6b}, Y^{6c} and Y^{6d} is the same; and each of Y^{7a} and Y^{7b} is the same.

[0046] In some embodiments of Formula I, each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is hydrogen. In one aspect of these embodiments, Y^8 is hydrogen. In one aspect of these embodiments, Y^8 is deuterium.

[0047] In some embodiments of Formula I, each of Y^1, Y^{2a}, Y^{2b} and Y^{2c} is hydrogen and each of Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is deuterium. In one aspect of these embodiments, Y^8 is hydrogen. In one aspect of these embodiments, Y^8 is deuterium.

[0048] In some embodiments of Formula I, each of Y^1, Y^{2a}, Y^{2b} and Y^{2c} is deuterium and each of Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is hydrogen. In one aspect of these embodiments, Y^8 is hydrogen. In one aspect of these embodiments, Y^8 is deuterium.

[0049] In some embodiments of Formula I, each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is deuterium. In one aspect of these embodiments, Y^8 is hydrogen. In one aspect of these embodiments, Y^8 is deuterium.

[0050] In some embodiments of Formula I, at least one pair of Y^{3a} and Y^{3b}, Y^{4a} and Y^{4b}, Y^{5a} and Y^{5b}, and Y^{7a} and Y^{7b} are deuterium. In some aspects of these embodiments, Y^{3a} and Y^{3b} are deuterium. In some aspects of these embodiments, Y^{4a} and Y^{4b} are deuterium. In some aspect of these embodiments. Y^{5a} and Y^{5b} are deuterium. In some aspect of these embodiments Y^{7a} and Y^{7b} are deuterium. In some more specific aspects of these embodiments, at least two pairs of Y^{3a} and Y^{3b}, Y^{4a} and Y^{4b}, and Y^{5a} and Y^{5b} are deuterium. In some even more specific aspects of these embodiments, each of Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b} is deuterium.

[0051] In some embodiments of Formula I, when each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, and Y^{7b} is deuterium, then Y^8 is hydrogen.

[0052] In one embodiment, each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is hydrogen and the compound is selected from any one of the compounds set forth in Table 1:

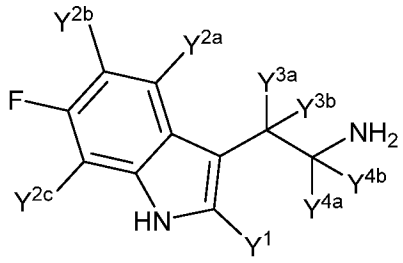
Table 1: Exemplary Embodiments of Formula I

Compound	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{7a}/Y^{7b}	Y^8
100	D	H	H	H	H
101	H	D	H	H	H
102	H	H	D	H	H
103	H	H	H	D	H
104	H	H	H	H	D
105	D	D	H	H	H
106	D	H	D	H	H
107	D	H	H	D	H

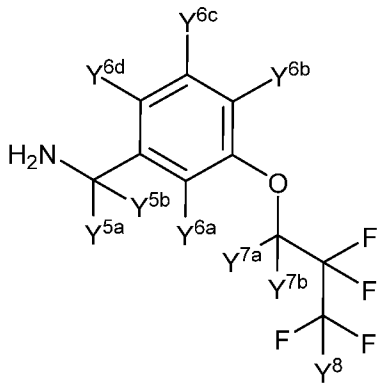
Compound	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{7a}/Y^{7b}	Y^8
108	D	H	H	H	D
109	H	D	D	H	H
110	H	D	H	D	H
111	H	D	H	H	D
112	H	H	D	D	H
113	H	H	D	H	D
114	H	H	H	D	D
115	D	D	D	H	H
116	D	D	H	D	H
117	D	D	H	H	D
118	D	H	D	D	H
119	D	H	D	H	D
120	D	H	H	D	D
121	H	D	D	D	H
122	H	D	D	H	D
123	H	D	H	D	D
124	H	H	D	D	D
125	D	D	D	D	H
126	D	D	D	H	D
127	D	D	H	D	D
128	D	H	D	D	D
129	H	D	D	D	D
130	D	D	D	D	D

or a pharmaceutically acceptable salt thereof.

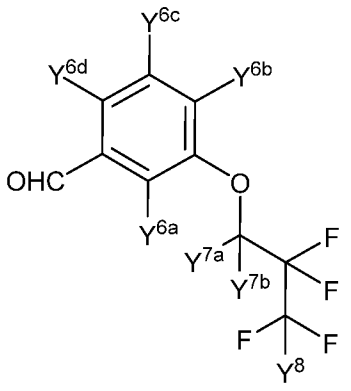
[0053] In one embodiment, the following intermediates are novel and fall within the scope of this invention:



(II),



(III), and



(IV), each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, Y^{7b} and Y^8 is

independently selected from hydrogen and deuterium, and wherein at least one of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and Y^8 present in each intermediate is deuterium.

[0054] In some embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

[0055] In some embodiments, when any atom is designated as deuterium in any of the embodiments set forth above, the level of deuterium incorporation at that 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%.

[0056] In some embodiments of a compound of this invention, when Y^1 is deuterium, the level of deuterium incorporation at each Y^1 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%.

[0057] In some embodiments of a compound of this invention, when Y^{2a}, Y^{2b} or Y^{2c} is deuterium, the level of deuterium incorporation at each Y^{2a}, Y^{2b} or Y^{2c} designated as deuterium 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%.

[1] 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} designated as deuterium 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%.

[0058] In some embodiments of a compound of this invention, when Y^{4a} or Y^{4b} is deuterium, the level of deuterium incorporation at each Y^{4a} or Y^{4b} designated as deuterium is at least 52.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, or at least 99%.

[0059] In some embodiments of a compound of this invention, when Y^{5a} or Y^{5b} is deuterium, the level of deuterium incorporation at each Y^{5a} or Y^{5b} designated as deuterium 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%.

[0060] In some embodiments of a compound of this invention, when Y^{6a}, Y^{6b}, Y^{6c} or Y^{6d} is deuterium, the level of deuterium incorporation at each Y^{6a}, Y^{6b}, Y^{6c} or Y^{6d} designated as deuterium 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%.

[0061] In some embodiments of a compound of this invention, when Y^{7a} or Y^{7b} is deuterium, the level of deuterium incorporation at each Y^{7a} or Y^{7b} designated as deuterium 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%.

[0062] In some embodiments of a compound of this invention, when Y^{8} is deuterium, the level of deuterium incorporation at each Y^{8} 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%.

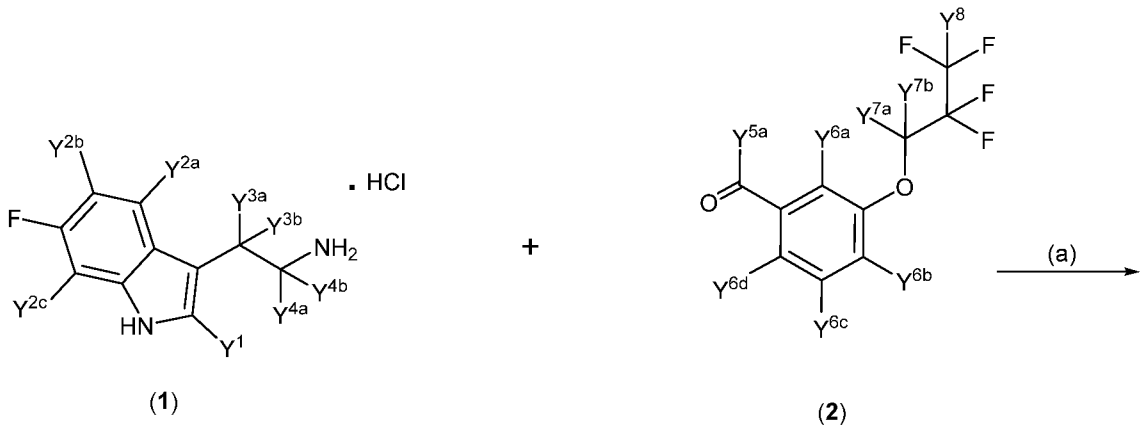
[0063] The synthesis of compounds of Formula I may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I and intermediates thereof are disclosed, for instance in US Patents 7,157,488, 8,044,090 and WO 2014/037532.

[0064] 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.

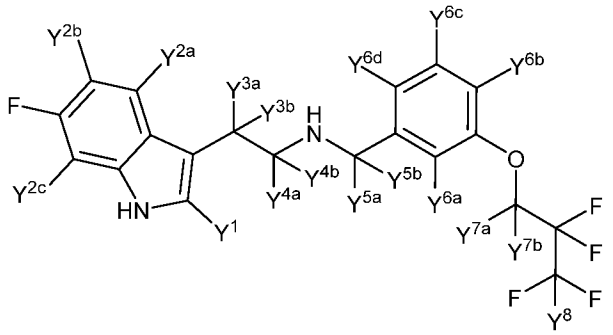
Exemplary Synthesis

[0065] A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1, below.

[0066] Scheme 1: General Synthesis of Compounds of Formula I



(1) (2)



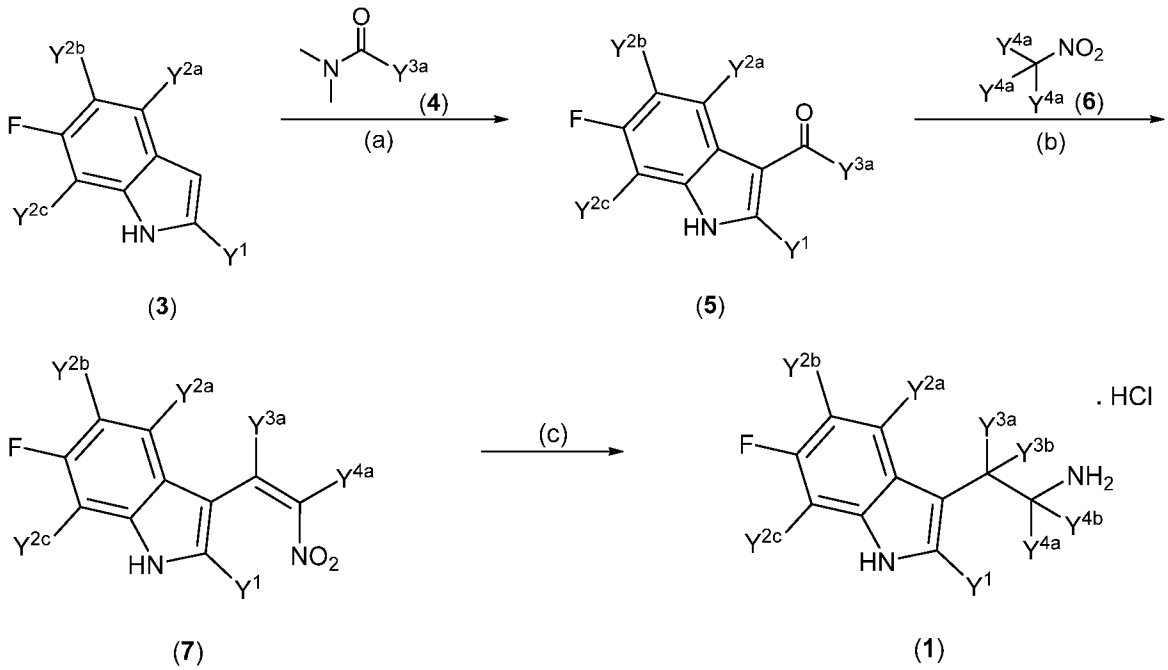
Formula I

Reagents and conditions: (a) NaOH, then $NaBD_4$ or $NaBH_4$

[0067] In a manner analogous to a procedure described in US 7, 158, 488 and US 8,044,090, appropriately deuterated tryptamine intermediate (**1**) is treated with sodium hydroxide to liberate the amino moiety. Subsequent treatment with appropriately deuterated arylether aldehyde intermediate (**2**) under reductive amination reaction conditions, using a reducing agent such as $NaBD_4$ or $NaBH_4$ produces appropriately deuterated compounds of Formula I.

[0068] Appropriately deuterated intermediate (**1**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 2.

[0069] Scheme 2: Preparation of Intermediate (**1**)



Reagents and conditions: (a) $POCl_3$; (b) NH_4OAc; (c) $LiAlH_4$ or $LiAlD_4$, NaOH, then HCl.

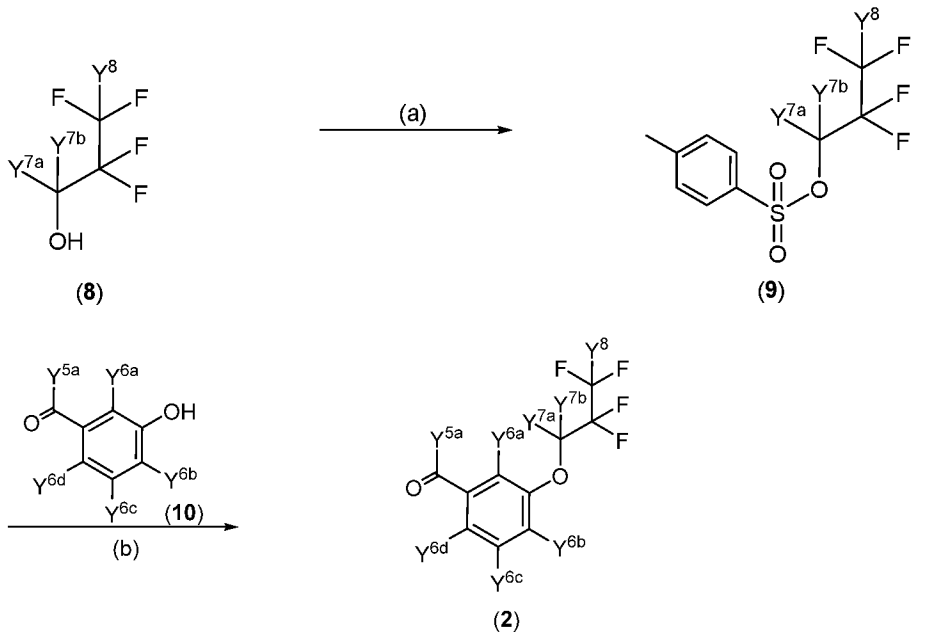
[0070] By analogy to a procedure described in US, 7, 157,488 or by Zhu, P. et al., ChemCatChem, 7(4), 595-600; 2015, Vilsmeier–Haack formylation of appropriately deuterated indole intermediate (**3**) using appropriately deuterated DMF intermediate (**4**) in the presence of phosphorus oxychloride, furnishes appropriately deuterated aldehyde intermediate (**5**). Subsequent Henry reaction of aldehyde in (**5**) with appropriately deuterated nitromethane intermediate (**6**) in the presence of NH_4OAc affords appropriately deuterated nitroolefine intermediate (**7**). Finally, reduction of the alkene and nitro moieties in (**7**) using a reducing agent such as $LiAlH_4$ or $LiAlD_4$ produces appropriately deuterated tryptamine intermediate (**1**), which is isolated as the hydrochloride salt by treating with HCl.

[0071] Commercially available intermediate (**4a**) may be selected from N,N-dimethylformamide-d_1 (99 atom %D), N,N-dimethylformamide-d_7 (99.5 atom % D). Nitromethane-d_3 (99 atom %D), intermediate (**6a**) is commercially available.

[0072] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b} positions of a compound of Formula I or any appropriate intermediate herein, e.g., 90, 95, 97, or 99% deuterium incorporation at any Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, and /or Y^{4b}.

[0073] Appropriately deuterated intermediate (**2**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 3.

[0074] Scheme 3: Preparation of Intermediate (**2**)



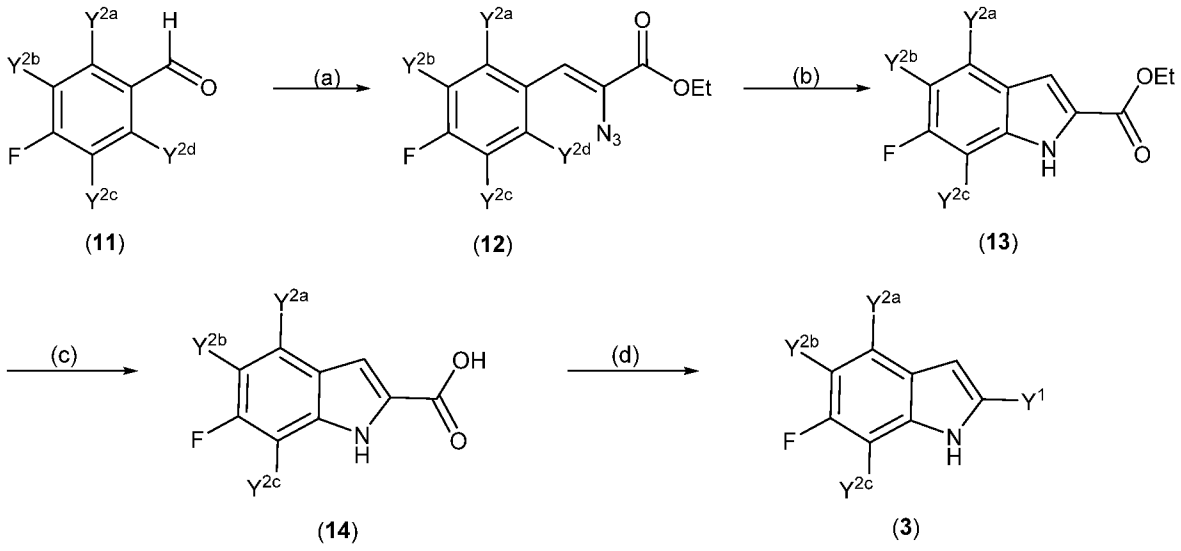
Reagents and conditions: (a) p-toluenesulfonyl chloride, C_5H_5N; (b) K_2CO_3

[0075] In a manner analogous to a procedure described in US 8,044,090, appropriately deuterated fluoro-propanol intermediate (**8**) is treated with tosyl chloride in the presence of a base such as pyridine to furnish appropriately deuterated tosylate intermediate (**9**). Subsequent alkylation of appropriately deuterated hydroxylaryl aldehyde intermediate (**10**) with (**9**), in the presence of a base such as potassium carbonate produces appropriately deuterated arylether aldehyde intermediate (**2**).

[0076] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^{5a}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b}, Y^8 positions of a compound of Formula I or any appropriate intermediate herein, e.g., 90, 95, 97, or 99% deuterium incorporation at any Y^{5a}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and /or Y^8.

[0077] Appropriately deuterated intermediate (**3**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 4.

[0078] Scheme 4: Preparation of Intermediate (**3**)



(11) (12) (13) (14) (3)

Reagents and conditions: (a) ethyl 2-azidoacetate, NaOEt; (b) Xylene, reflux; (c) NaOH; (d) Cu, Quinoline, HCl, pH 4 or Cu, Quinoline-d_7, DCl, pH 4

[0079] By analogy to a procedure described by Zhang, F. et al., European Journal of Medicinal Chemistry, 46(7), 3149-3157; 2011, appropriately deuterated aryl aldehyde (**11**) is treated with ethyl azidoacetate under Knoevenagel conditions using a base such as sodium ethoxide to furnish appropriately deuterated azido arylacrylate

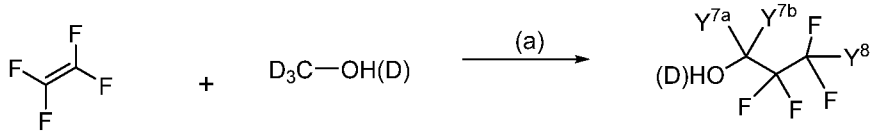
intermediate (**12**). Subsequent cyclization using the Hemetsberger–Knittel procedure by heating at reflux in a high boiling solvent such as xylene affords appropriately deuterated indole carboxylate intermediate (**13**). Base hydrolysis of ester in (**13**) using sodium hydroxide furnishes appropriately deuterated indole carboxylic acid (**14**). Finally, decarboxylation using copper powder and quinoline or copper powder and quinoline-d_7 produces appropriately deuterated indole intermediate (**3**).

[0080] 4-Fluorobenzaldehyde-2,3,5,6-d_4 (98 atom %D) intermediate (**11a**) is commercially available.

[0081] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^1, Y^{2a}, Y^{2b}, Y^{2c} positions of a compound of Formula I or any appropriate intermediate herein, e.g., 90, 95, 97, or 99% deuterium incorporation at any Y^1, Y^{2a}, Y^{2b} and/or Y^{2c}.

[0082] Appropriately deuterated intermediate (**8**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 5.

[0083] Scheme 5: Preparation of Intermediate (**8**)



(**15**) (**16**) (**8**)

Reagents and conditions: (a) Di-*tert*-butylperoxide, $CaCO_3$, $NaOCH_3$

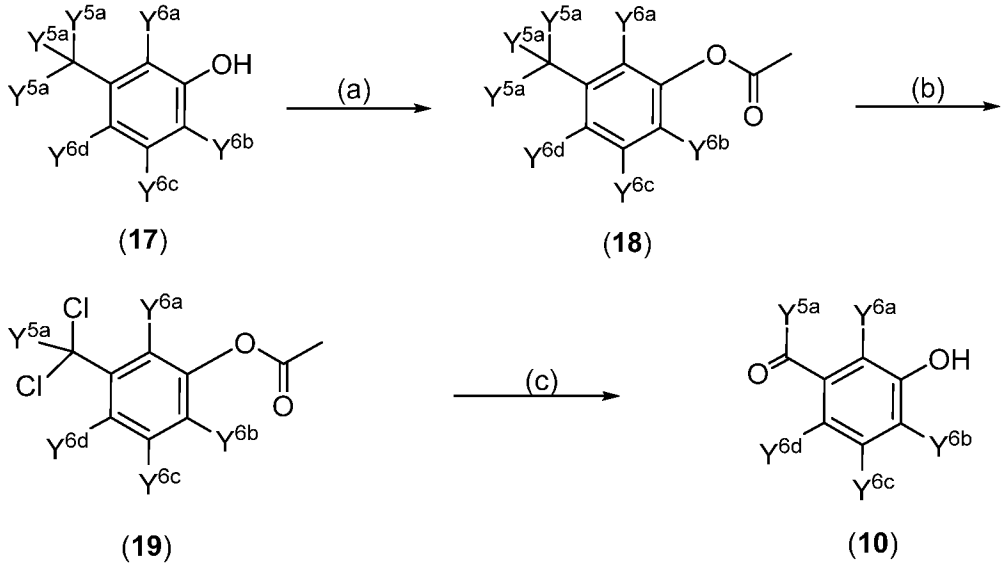
[0084] In a manner analogous to a procedure described in WO 2002018307, appropriately deuterated alcohol intermediate (**16**) together with calcium carbonate in the presence of a radical initiator such as di-*t*-butylperoxide were charged with tetrafluoroethylene intermediate (**15**) at elevated temperature. Alkali distillation using a base such as sodium methoxide produces appropriately deuterated tetrafluoropropanol intermediate (**8**).

[0085] Intermediate (**16a**) is commercially available, and may be selected from methanol-d_4 (99.8 atom %D) or methyl-d_3 alcohol (99.8 atom %D).

[0086] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^{7a}, Y^{7b}, Y^8 positions of a compound of Formula I or any appropriate intermediate herein, e.g., 90, 95, 97, or 99% deuterium incorporation at any Y^{7a}, Y^{7b} and /or Y^8.

[0087] Appropriately deuterated intermediate (**10**), for use in the preparation of compounds of Formula I according to Scheme 1, may be prepared from corresponding deuterated reagents exemplified in Scheme 6.

[0088] Scheme 6: Preparation of Intermediate (**10**)



Reagents and conditions: (a) Ac_2O, heat; (b) Cl_2, HMTA, AIBN; (c) $CaCO_3$, H_2O or $CaCO_3$, D_2O

[0089] In a manner analogous to a procedure described in CN103333062, hydoxy moiety in appropriately deuterated cresol intermediate (**17**) is acetylated using acetic anhydride at elevated temperature to furnish appropriately deuterated acetate intermediate (**18**). Subsequent chlorination of methyl moiety in (**18**) using chlorine gas, in the presence of AIBN and hexamethylentetramine affords appropriately deuterated (dichloromethyl)aryl acetate (**19**). Finally, hydrolysis of the dichloromethyl and acetate moieties in (**19**) using a base such as calcium carbonate produces appropriately deuterated hydroxylaryl aldehyde intermediate (**10**).

[0090] Certain deuterated intermediate (**17**) are commercially available: *m*-Cresol-d_7 (98 atom %D) (**17a**); *m*-Cresol-d_3 (methyl-d_3) (98 atom %D) (**17b**); *m*-Cresol-2,4,6-d_3 (>90 atom %D) (**17c**).

[0091] Use of appropriately deuterated reagents allows deuterium incorporation at the Y^{5a}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d} positions of a compound of Formula I or any appropriate intermediate herein, e.g., 90, 95, 97, or 99% deuterium incorporation at any Y^{5a}, Y^{6a}, Y^{6b} and /or Y^{6c}.

[0092] 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.

[0093] 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.

[0094] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

[0095] The invention also provides pharmaceutical compositions comprising an effective amount of a compound of Formula I (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.

[0096] Pharmaceutically acceptable carriers, adjuvants, excipients and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates (e.g., phosphate-buffered saline, etc.), glycine, sorbic acid, potassium sorbate, partial glyceride

mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0097] 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.

[0098] 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.

[0099] 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).

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] In another embodiment, a composition of this invention further comprises one or more additional therapeutic agents. The additional therapeutic agent(s) may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as Idalopirdine. Such agents include those indicated as being useful in combination with Idalopirdine, including but not limited to, those described in US Patents 7,157,488, 8,044,090 and WO 2014/037532.

[00114] Preferably, each additional therapeutic agent is an agent useful in the treatment of a disease or condition selected from Alzheimer's type dementia, Alzheimer's disease, dementia caused by vascular diseases, dementia associated with Parkinson's disease, Lewy Body dementia, AIDS dementia, mild cognitive impairments, age-associated memory impairments, cognitive impairments and/or dementia associated with neurologic and/or psychiatric conditions, including epilepsy, brain tumors, brain lesions, multiple sclerosis, Down's syndrome, Rett's syndrome, progressive supranuclear palsy, frontal lobe syndrome, and schizophrenia and related psychiatric disorders; cognitive impairments caused by traumatic brain injury, post coronary artery by-pass graft surgery, electroconvulsive shock therapy, and chemotherapy, delirium, Tourette's syndrome, myasthenia gravis, attention deficit hyperactivity disorder, autism, dyslexia, mania, depression, apathy, and myopathy associated with or caused by diabetes, sleep apnea, dysfunctions of Huntington's disease, pyschosis, anxiety (particularly including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), idiopathic and drug induced Parkinson's disease, convulsions, migraine (including migraine headache), substance withdrawal (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), sleep disorders (including narcolepsy), conduct disorder, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, amylotrophic lateral sclerosis.

[00115] In certain embodiments, each additional therapeutic agent is selected from one or more of donepezil, memantine, rivastigmine, galantamine, or any acetylcholinesterase inhibitor indicated for treating or modifying AD. In one specific aspect of these embodiments, the second therapeutic agent is donepezil. In another

specific aspect of these embodiments, the second therapeutic agent is a combination of donepezil and memantine.

[00116] In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described additional therapeutic agents, wherein the compound and additional therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[00117] 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.

[00118] 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.

[00119] In one embodiment, an effective amount of a compound of this invention can range from about 1 mg per dose to about 300 mg per dose, from about 2 mg per dose to about 120 mg per dose, from about 10 mg per dose to about 60 mg per dose, from about 30-60 mg per dose, or from about 10 mg per dose to 30 mg per dose. In some embodiments, the dose is administered once daily, twice daily, or three times daily. In some aspects of these embodiments, the dose is administered once daily.

[00120] 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 Idalopirdine.

[00121] For pharmaceutical compositions that comprise one or more additional therapeutic agents, an effective amount of each additional therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these additional therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[00122] It is expected that some of the additional therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the additional therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the additional 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

[00123] In another embodiment, the invention provides a method of modulating the activity of 5-HT_6 receptor in a cell, comprising contacting a cell with one or more compounds of Formula I herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the cell is contacted *in vitro*. In some embodiments, the cell is contacted *in vivo*. In some embodiments, the cell is contacted *ex vivo*.

[00124] According to another embodiment, the invention provides a method of treating a disease that is beneficially treated by idalopirdine 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. In certain embodiments the subject is a human. Such diseases are well known in the art and are disclosed in, but not limited to the following patents and published applications: US 7,157,488; US 8,044,090 and WO 2014/037532.

[00125] Such diseases include, but are not limited to Alzheimer's type dementia, Alzheimer's disease, dementia caused by vascular diseases, dementia associated with Parkinson's disease, Lewy Body dementia, AIDS dementia, mild cognitive impairments, age-associated memory impairments, cognitive impairments and/or dementia associated with neurologic and/or psychiatric conditions, including epilepsy, brain tumors, brain lesions, multiple sclerosis, Down's syndrome, Rett's syndrome, progressive supranuclear palsy, frontal lobe syndrome, and schizophrenia and related psychiatric disorders; cognitive impairments caused by traumatic brain injury, post coronary artery by-pass graft surgery, electroconvulsive shock therapy, and chemotherapy, delirium, Tourette's syndrome, myasthenia gravis, attention deficit hyperactivity disorder, autism, dyslexia, mania, depression, apathy, and myopathy associated with or caused by diabetes, sleep apnea, dysfunctions of Huntington's disease, psychosis, anxiety (particularly including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), idiopathic and drug induced Parkinson's disease, convulsions, migraine (including migraine headache), substance withdrawal (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), sleep disorders (including narcolepsy), conduct disorder, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, amylotrophic lateral sclerosis. In another particular embodiment, the method of this invention is used to treat a disease or condition selected from mild, moderate, and/or severe Alzheimer's Disease, dementia with Lewy bodies, and mild to moderate dementia associated with Parkinson's disease in a subject in need thereof.

[00126] In yet another one particular embodiment, the method of this invention is used to treat a disease or condition selected from mild Alzheimer's disease, moderate Alzheimer's disease, severe Alzheimer's disease, or mild to moderate Alzheimer's disease.

[00127] 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).

[00128] 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

additional therapeutic agents. The choice of additional therapeutic agent may be made from any additional therapeutic agent known to be useful for co-administration with idalopirdine. The choice of additional therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of additional 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 an additional therapeutic agent.

[00129] In a more specific embodiment, the combination therapies of this invention include co-administering a compound of Formula I and donezepil to a subject in need thereof for treatment of mild AD, moderate AD, severe AD, or mild to moderate AD.

[00130] In another more specific embodiment, the combination therapies of this invention include co-administering a compound of Formula I, donezepil and memantine to a subject in need thereof for treatment of mild AD, moderate AD, severe AD, or mild to moderate AD.

[00131] The term "co-administered" as used herein means that the additional therapeutic agents may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an additional therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the additional therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and an additional therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other additional therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[00132] Effective amounts of these additional therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well

within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[00133] In one embodiment of the invention, where an additional therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the additional therapeutic agent is not administered. In another embodiment, the effective amount of the additional therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[00134] 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 additional therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I for use in the treatment in a subject of a disease, disorder or symptom thereof delineated herein.

Example X. Evaluation of Metabolic Stability

[00135] ***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.

[00136] ***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.

[00137] ***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]

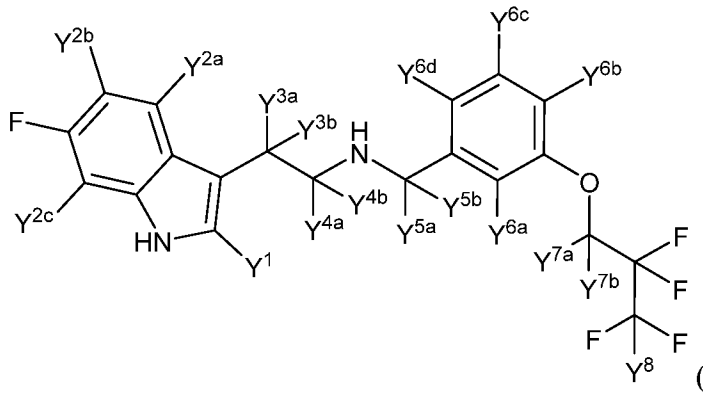
[00138] Data analysis is performed using Microsoft Excel Software.

[00139] The relevant teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

[00140] 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.

What is claimed is:

1. A compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, Y^{7b} and Y^8 is independently selected from hydrogen and deuterium; and

at least one of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and Y^8 is deuterium.

2. The compound or salt of claim 1, wherein:

each of Y^{2a}, Y^{2b}, and Y^{2c} is the same;

each of Y^{3a} and Y^{3b} is the same;

each of Y^{4a} and Y^{4b} is the same;

each of Y^{5a} and Y^{5b} is the same;

each of Y^{6a}, Y^{6b}, Y^{6c} and Y^{6d} is the same; and

each of Y^{7a} and Y^{7b} is the same.

3. The compound or salt of claim 1 or 2, wherein each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} is hydrogen.

4. The compound or salt of any one of claims 1-3, wherein Y^8 is hydrogen.

5. The compound or salt of any one of claims 1-4, wherein each member of at least one pair selected from Y^{3a} and Y^{3b}, Y^{4a} and Y^{4b}, Y^{5a} and Y^{5b}, or Y^{7a} and Y^{7b} is deuterium.

6. The compound or salt of claim 5, wherein each member of at least two pairs

selected from Y^{3a} and Y^{3b}, Y^{4a} and Y^{4b}, and Y^{5a} and Y^{5b} is deuterium.

7. The compound or salt of claim 6, wherein each of Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, and Y^{5b} is deuterium.

8. The compound or salt of any one of claims 1-7, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

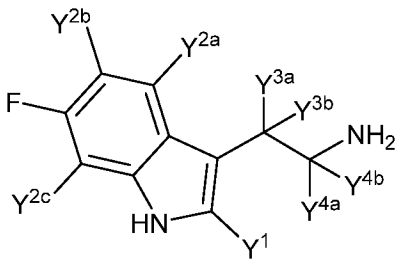
9. The compound of claim 1, wherein each of Y^{1}, Y^{2a}, Y^{2b}, Y^{2c}, Y^{6a}, Y^{6b}, Y^{6c}, and Y^{6d} are hydrogen, and the compound is selected from any one of the compounds set forth below:

Compound	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{7a}/Y^{7b}	Y^{8}
100	D	H	H	H	H
101	H	D	H	H	H
102	H	H	D	H	H
103	H	H	H	D	H
104	H	H	H	H	D
105	D	D	H	H	H
106	D	H	D	H	H
107	D	H	H	D	H
108	D	H	H	H	D
109	H	D	D	H	H
110	H	D	H	D	H
111	H	D	H	H	D
112	H	H	D	D	H
113	H	H	D	H	D
114	H	H	H	D	D
115	D	D	D	H	H
116	D	D	H	D	H
117	D	D	H	H	D
118	D	H	D	D	H
119	D	H	D	H	D
120	D	H	H	D	D
121	H	D	D	D	H
122	H	D	D	H	D
123	H	D	H	D	D
124	H	H	D	D	D
125	D	D	D	D	H
126	D	D	D	H	D
127	D	D	H	D	D
128	D	H	D	D	D

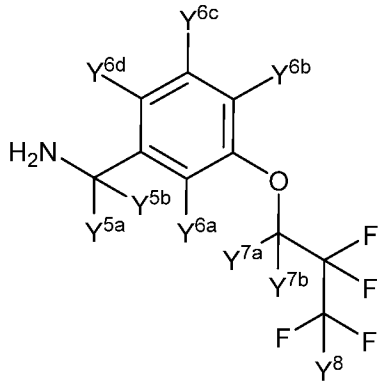
Compound	Y^{3a}/Y^{3b}	Y^{4a}/Y^{4b}	Y^{5a}/Y^{5b}	Y^{7a}/Y^{7b}	Y^8
129	H	D	D	D	D
130	D	D	D	D	D

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

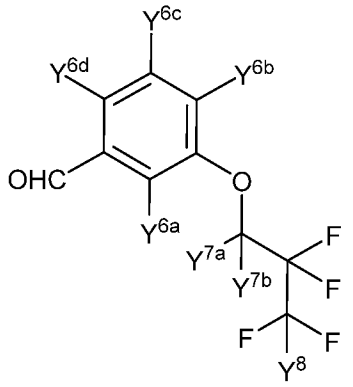
10. A compound selected from any one of:



(II),



(III), and



(IV), wherein each of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{6d}, Y^{7a}, Y^{7b} and Y^8 is independently selected from hydrogen and deuterium, and wherein at least one of Y^1, Y^{2a}, Y^{2b}, Y^{2c}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Y^{6c}, Y^{7a}, Y^{7b} and Y^8 present in each compound is deuterium.

11. The compound or salt of any one of claims 1-9, wherein any atom designated as deuterium has at least 90% deuterium incorporation at that atom.

12. The compound or salt of any one of claims 1-9, wherein any atom designated as deuterium has at least 95% deuterium incorporation at that atom.

13. The compound or salt of any one of claims 1-9, wherein any atom designated as deuterium has at least 99% deuterium incorporation at that atom.

14. The compound or salt of claim 10, wherein any atom designated as deuterium has at least 90% deuterium incorporation at that atom.

15. The compound or salt of claim 10, wherein any atom designated as deuterium has at least 95% deuterium incorporation at that atom.

16. The compound or salt of claim 10, wherein any atom designated as deuterium has at least 99% deuterium incorporation at that atom.

17. A pharmaceutically acceptable composition comprising a compound or salt of any one of claims 1-9 and 11-13; and a pharmaceutically acceptable carrier.

18. A method of treating a disease selected from mild Alzheimer's Disease (AD), moderate AD, severe AD, or mild to moderate AD comprising the step of administering to a subject in need thereof, a compound or salt of any one of claims 1-9 and 11-13, or a composition of claim 17.

19. The method of claim 18, additionally comprising the step of co-administering to the subject in need thereof donepezil.

20. The method of claim 18 or 19, additionally comprising the step of co-administering to the subject in need thereof memantine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/41709

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 209/14, A61K 31/4045 (2017.01)
CPC - C07B 2200/13, C07D 209/16, C07D 209/14

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	US 9,029,379 B2 (The University of Utah Research Foundation) 12 May 2015 (12.05.2015); col 11, ln 40-45, col 12, ln 30-32, col 13, ln 39-43	1-3, 9-10, 14-16
Y	WO 2010/068480 A1 (CONCERT PHARMACEUTICALS, INC.) 17 June 2010 (17.06.2010); para [5], [11], [17], [34], [44]	1-3, 9-10, 14-16
Y	US 7,157,488 B2 (Chen et al.) 02 January 2007 (02.01.2007); col 2, ln 65-67, col 9, ln 30-50, col 52, ln 30-50	10, 14-16
A	WO 2016/091997 A1 (H. LUNDBECK A/S) 16 June 2016 (16.06.2016); entire document	1-3, 9-10, 14-16
A	WO 2016/078587 A1 (CRYSTAL PHARMATECH CO., LTD) 26 May 2016 (26.05.2016); entire document	1-3, 9-10, 14-16

☐ 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
11 September 2017	28 SEP 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/41709

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

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

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

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

3. ☒ Claims Nos.: 4-8, 11-13, 17-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.