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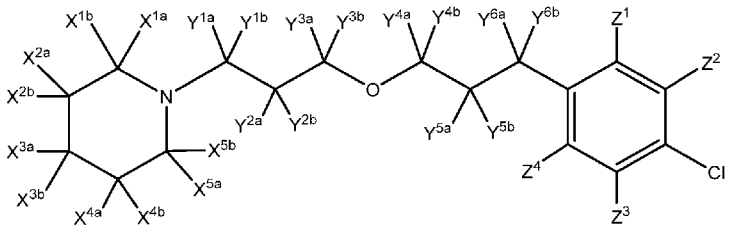

(I)

(57) Abstract: This invention also provides compound of Formula (I) including pharmaceutical compositions comprising a compound of Formula (I) 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 pitolisant. Some exemplary embodiments include a method of treating a disease or condition selected from narcolepsy, daytime sleepiness (particularly in subjects suffering from Parkinson's disease or obstructive sleep apnea syndrome), and cognitive defects in psychiatric conditions, the method comprising the step of administering to a subject in need thereof a pharmaceutically acceptable composition of the present invention.

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DEUTERATED PITOLISANT

CLAIM OF PRIORITY

[1] This application claims priority to U.S. Patent Application Serial No. 62/752,600, filed on 10/30/2018, the entire contents of which 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.

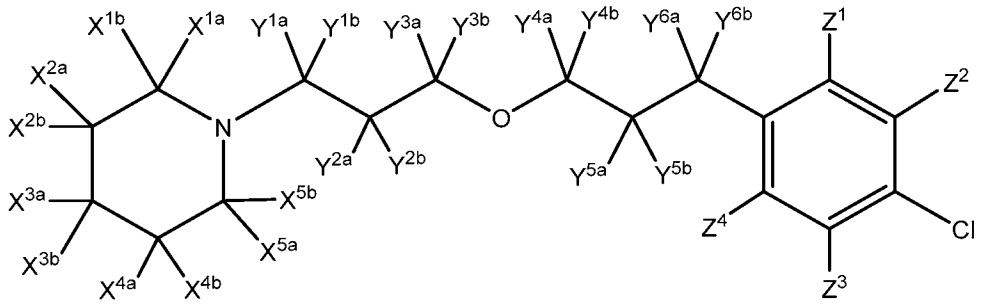
[6] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. 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).

SUMMARY OF THE INVENTION

[8] This invention relates to deuterated forms of pitolisant, 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 X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a} and X^{5b} is independently deuterium or hydrogen;

each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a} and Y^{6b} is independently deuterium or hydrogen;

each of Z^1, Z^2, Z^3, and Z^4 is independently deuterium or hydrogen; and

at least one of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Z^1, Z^2, Z^3, or Z^4 is deuterium.

[9] 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 pitolisant. Some exemplary embodiments include a method of treating a disease or condition selected from Alzheimer's disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo, motion sickness, allergic and inflammatory diseases, narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, daytime sleepiness associated with Parkinson's disease, schizophrenia, schizoaffective disorder, and Prader-Willi syndrome, the method comprising the step of administering to a subject in need

thereof a pharmaceutically acceptable composition of the present invention. Other exemplary embodiments include a method of treating an addiction disorder due to dependency on stimulants, depressants, opiates, cocaine, nicotine or alcohol, the method comprising the step of administering to a subject in need thereof a pharmaceutically acceptable composition of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[10] FIG. 1 is a graph showing the disappearance of test compound (Compound 115, 103, 125, 300, 301, 302, 303 or pitolisant), as a function of incubation time in the enzymatic assay employing CYP2D6 supersomes (25pmol/mL) and 0.1μM compound.

DETAILED DESCRIPTION OF THE INVENTION

[11] Pitolisant, also known as 1-[3-[3-(4-chlorophenyl)propoxy]propyl]piperidine hydrochloride, and Wakix®, is a histamine H3 receptor competitive antagonist and inverse agonist.

[12] Pitolisant is currently approved for the treatment of narcolepsy with or without cataplexy in certain European countries. Pitolisant is in human clinical trials in the United States for the treatment of narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, and daytime sleepiness associated with Parkinson's disease.

[13] The most common side effects with pitolisant are insomnia, headache, nausea, anxiety, irritability, dizziness, depression, tremor, sleep disorders, tiredness, vomiting, vertigo and dyspepsia.

[14] Despite the beneficial activities of pitolisant, there is a continuing need for new compounds to treat the aforementioned diseases and conditions, preferably with less side effects.

Definitions

[15] 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.

[16] "Disease" means any condition or disorder that damages or interferes with the

normal function of a cell, tissue, or organ.

[17] 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.

[18] 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 pitolisant 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.

[19] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. However, in certain embodiments where stated, when a position is designated specifically as "H" or "hydrogen", the position has at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% hydrogen. In some embodiments, when a position is designated specifically as "H" or "hydrogen", the position incorporates ≤20% deuterium, ≤10% deuterium, ≤5% deuterium, ≤4% deuterium, ≤3% deuterium, ≤2% deuterium, or ≤1% deuterium. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

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

[21] 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).

[22] In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 52.5%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 60%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 67.5%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 75%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 80%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 82.5%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 85%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 90%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 95%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 97%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 97.5%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 98%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99%. In some embodiments, in a compound of this invention, each designated deuterium atom has deuterium incorporation of at least 99.5%.

[23] The term "isotopologue" refers to a molecule in which the chemical structure differs from another molecule of this invention only in the isotopic composition thereof.

[24] 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 will contain molecules having deuterium at each of the positions

designated as deuterium in the chemical structure, and may also contain 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. In certain embodiments, the relative amount of such isotopologues *in toto* will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

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

[26] 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.

[27] 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. 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.

[28] In some embodiments, the compound of the invention is in the form of a hydrochloride salt.

[29] 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. 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.

[30] 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.

[31] 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).

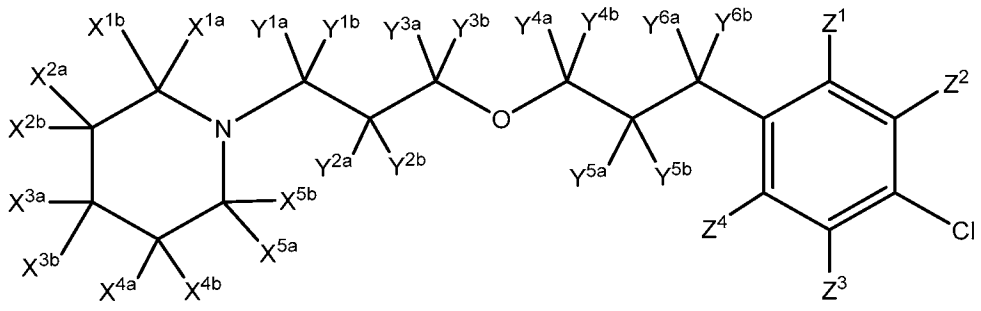
[32] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "*Sec*" or "*s*-" each refer to secondary. "*n*-" refers to normal. "*i*-" refers to iso. "US" refers to the United States of America.

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

[34] 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

[35] In certain embodiments, the present invention provides a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Z^1, Z^2, Z^3, and Z^4 is independently deuterium or hydrogen, and wherein at least one of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Z^1, Z^2, Z^3, or Z^4 is deuterium.

[36] In some embodiments, each X attached to the same carbon is the same, and each Y attached to the same carbon is the same.

[37] In some embodiments, X^{1a} and X^{1b} are the same, X^{2a} and X^{2b} are the same, X^{3a} and X^{3b} are the same, X^{4a} and X^{4b} are the same, and X^{5a} and X^{5b} are the same. In one

aspect of these embodiments, each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is the same. In another aspect of these embodiments, each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is the same. In still another aspect of these embodiments, each X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, and X^{4b} is the same. In one aspect of these embodiments, each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is hydrogen. In one aspect of these embodiments, each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is deuterium. In one aspect of these embodiments, each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is hydrogen. In one aspect of these embodiments, each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is deuterium. In one aspect of these embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is deuterium. In one aspect of these embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is hydrogen. In one aspect of these embodiments, each of X^{3a} and X^{3b} is deuterium. In one aspect of these embodiments, each of X^{2a} and X^{2b} is deuterium. In one aspect of these embodiments, each of X^{1a} and X^{1b} is deuterium.

[38] In some embodiments, Y^{1a} and Y^{1b} are the same, Y^{2a} and Y^{2b} are the same, and Y^{3a} and Y^{3b} are the same. In one aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same. In a more specific aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is hydrogen. In another more specific aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is deuterium. In one aspect of these embodiments, each of Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is deuterium. In one aspect of these embodiments, each of Y^{3a} and Y^{3b} is deuterium. In one aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{3a}, and Y^{3b} is deuterium. In one aspect of these embodiments, each of Y^{2a} and Y^{2b} is deuterium. In one aspect of these embodiments, each of Y^{1a}, Y^{1b}, Y^{2a}, and Y^{2b} is deuterium. In one aspect of these embodiments, each of Y^{1a} and Y^{1b} is deuterium.

[39] In some embodiments, Y^{4a} and Y^{4b} are the same, Y^{5a} and Y^{5b} are the same, and Y^{6a} and Y^{6b} are the same. In one aspect of these embodiments, each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is the same. In a more specific aspect of these embodiments, each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is hydrogen. In another more specific aspect of these embodiments, each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is deuterium. In one aspect of these embodiments, each of Y^{4a} and Y^{4b} is deuterium. In one aspect of these embodiments, each of Y^{5a} and Y^{5b} is deuterium. In one aspect of these embodiments, each of Y^{6a} and Y^{6b} is deuterium.

[40] In some embodiments, each of Y^{4a}, Y^{4b}, Y^{6a}, and Y^{6b} is the same, and Y^{5a} and Y^{5b} are the same. In one aspect of these embodiments, each of Y^{4a}, Y^{4b}, Y^{6a}, and Y^{6b} is hydrogen and each Y^{5a} and Y^{5b} is deuterium. In another aspect of these

embodiments, each of Y^{4a}, Y^{4b}, Y^{6a}, and Y^{6b} is deuterium, and each Y^{5a} and Y^{5b} is hydrogen.

[41] In some embodiments, each of Z^1, Z^2, Z^3, and Z^4 are the same. In one aspect of these embodiment each of Z^1, Z^2, Z^3, and Z^4 is hydrogen. In another aspect of these embodiment each of Z^1, Z^2, Z^3, and Z^4 is deuterium.

[42] In some embodiments, X^{1a} and X^{1b} are the same, X^{2a} and X^{2b} are the same, X^{3a} and X^{3b} are the same, X^{4a} and X^{4b} are the same, X^{5a} and X^{5b} are the same, 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, and Y^{6a} and Y^{6b} are the same. In one aspect of these embodiment, each of Z^1, Z^2, Z^3, and Z^4 is the same.

[43] In some embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is the same. In one aspect of these embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is hydrogen. In another aspect of these embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is deuterium.

[44] In some embodiments, each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is the same (represented by each X^1 and X^5 in Table 1), each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is the same (represented by each X^2 and X^4 in Table 1), each of X^{3a} and X^{3b} is the same (represented by each X^3 in Table 1), each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same (represented by each Y^1, Y^2, and Y^3 in Table 1), each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is the same (represented by each Y^4, Y^5, and Y^6 in Table 1), each of Z^1, Z^2, Z^3, and Z^4 is hydrogen and the compound is selected from any one of the compounds set forth in Table 1 (below):

Table 1: Exemplary Embodiments of Formula I

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
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

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
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, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

[45] In some embodiments, each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is the same (represented by each X^1 and X^5 in Table 2), each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is the same (represented by each X^2 and X^4 in Table 2), each of X^{3a} and X^{3b} is the same (represented by each X^3 in Table 2), each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same (represented by each Y^1, Y^2, and Y^3 in Table 2), each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is the same (represented by each Y^4, Y^5, and Y^6 in Table 2), each of Z^1, Z^2, Z^3, and Z^4 is deuterium and the compound is selected from any one of the compounds set forth in Table 2 (below):

Table 2: Exemplary Embodiments of Formula I

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
200	D	H	H	H	H
201	H	D	H	H	H
202	H	H	D	H	H
203	H	H	H	D	H
204	H	H	H	H	D
205	D	D	H	H	H
206	D	H	D	H	H
207	D	H	H	D	H
208	D	H	H	H	D
209	H	D	D	H	H
210	H	D	H	D	H
211	H	D	H	H	D
212	H	H	D	D	H
213	H	H	D	H	D
214	H	H	H	D	D
215	D	D	D	H	H
216	D	D	H	D	H
217	D	D	H	H	D
218	D	H	D	D	H
219	D	H	D	H	D
220	D	H	H	D	D
221	H	D	D	D	H
222	H	D	D	H	D
223	H	D	H	D	D
224	H	H	D	D	D
225	D	D	D	D	H
226	D	D	D	H	D
227	D	D	H	D	D
228	D	H	D	D	D
229	H	D	D	D	D

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
230	D	D	D	D	D
231	H	H	H	H	H

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

[46] In some embodiments, each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is the same (represented by each X^1, X^2, X^3, X^4, and X^5 in Table 3), each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same (represented by each Y^1, Y^2, and Y^3 in Table 3), each of Y^{4a}, Y^{4b}, Y^{6a}, and Y^{6b} is the same (represented by each Y^4, and Y^6 in Table 3), each of Y^{5a}, and Y^{5b} is the same (represented by each Y^5 in Table 3), each of Z^1, Z^2, Z^3, and Z^4 is hydrogen and the compound is selected from any one of the compounds set forth in Table 3 (below):

Table 3: Exemplary Embodiments of Formula I

Compound	Each X^1, X^2, X^3, X^4, and X^5	Each Y^1, Y^2, and Y^3	Each Y^4, and Y^6	Each Y^5
300	H	H	D	H
301	D	H	D	H
302	H	D	D	H
303	D	D	D	H
304	H	H	H	D
305	D	H	H	D
306	H	D	H	D
307	D	D	H	D

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

[47] In some embodiments of a compound of this invention, when X^{1a} and X^{1b} are deuterium, the level of deuterium incorporation at each X^{1a} and X^{1b} 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%.

[48] In some embodiments of a compound of this invention, when X^{2a} and X^{2b} are deuterium, the level of deuterium incorporation at each X^{2a} and X^{2b} 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%.

[49] In some embodiments of a compound of this invention, when X^{3a} and X^{3b} are deuterium, the level of deuterium incorporation at each of X^{3a} and X^{3b} 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%.

[50] In some embodiments of a compound of this invention, when X^{4a} and X^{4b} are deuterium, the level of deuterium incorporation at each of X^{4a} and X^{4b} 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%.

[51] In some embodiments of a compound of this invention, when X^{5a} and X^{5b} are deuterium, the level of deuterium incorporation at each of X^{5a} and X^{5b} 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%.

[52] In some embodiments of a compound of this invention, when Y^{1a} and Y^{1b} are deuterium, the level of deuterium incorporation at each of Y^{1a} and Y^{1b} 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%.

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

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

[55] In some embodiments of a compound of this invention, when Y^{4a} and Y^{4b} are deuterium, the level of deuterium incorporation at each of Y^{4a} and Y^{4b} 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%.

[56] In some embodiments of a compound of this invention, when Y^{5a} and Y^{5b} are deuterium, the level of deuterium incorporation at each of Y^{5a} and Y^{5b} 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%.

[57] In some embodiments of a compound of this invention, when Y^{6a} and Y^{6b} are deuterium, the level of deuterium incorporation at each of Y^{6a} and Y^{6b} 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%.

[58] In some embodiments of a compound of this invention, when any of Z^1, Z^2, Z^3, or Z^4 is deuterium, the level of deuterium incorporation at each Z^1, Z^2, Z^3, or Z^4 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%.

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

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

[61] In some embodiments of a compound of this invention, at least one of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Z^1, Z^2, Z^3, and Z^4 is hydrogen.

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

[63] 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 Patent No. 7,169,928 and CN103435575.

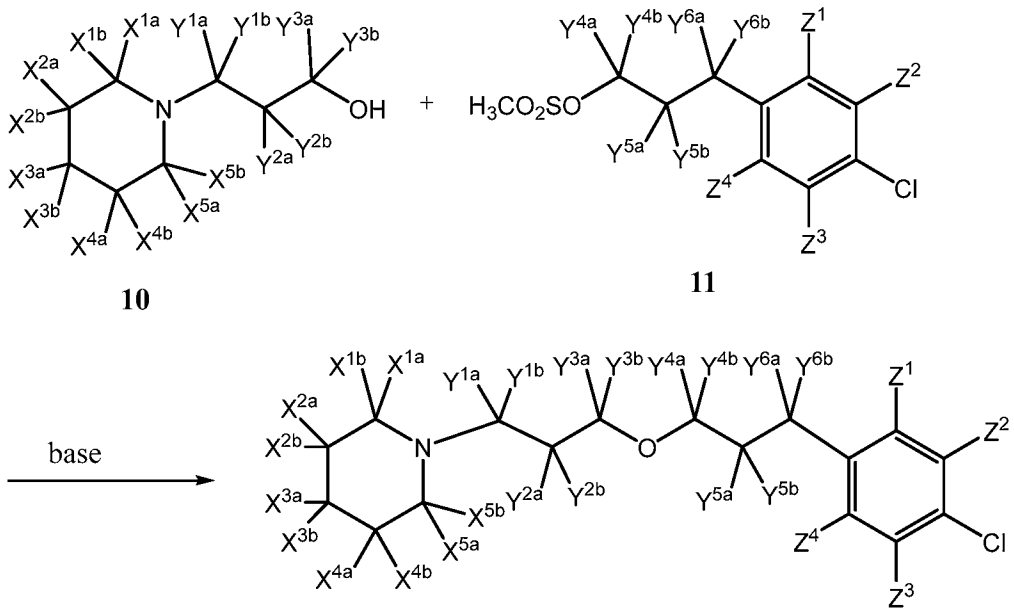
[64] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

[65] One skilled in the art will appreciate that the compounds of the invention may be prepared via methods analogous to those disclosed in the references herein, using appropriately deuterated reagents and intermediates, and by utilizing suitable chromatographic separations technologies such as chiral HPLC.

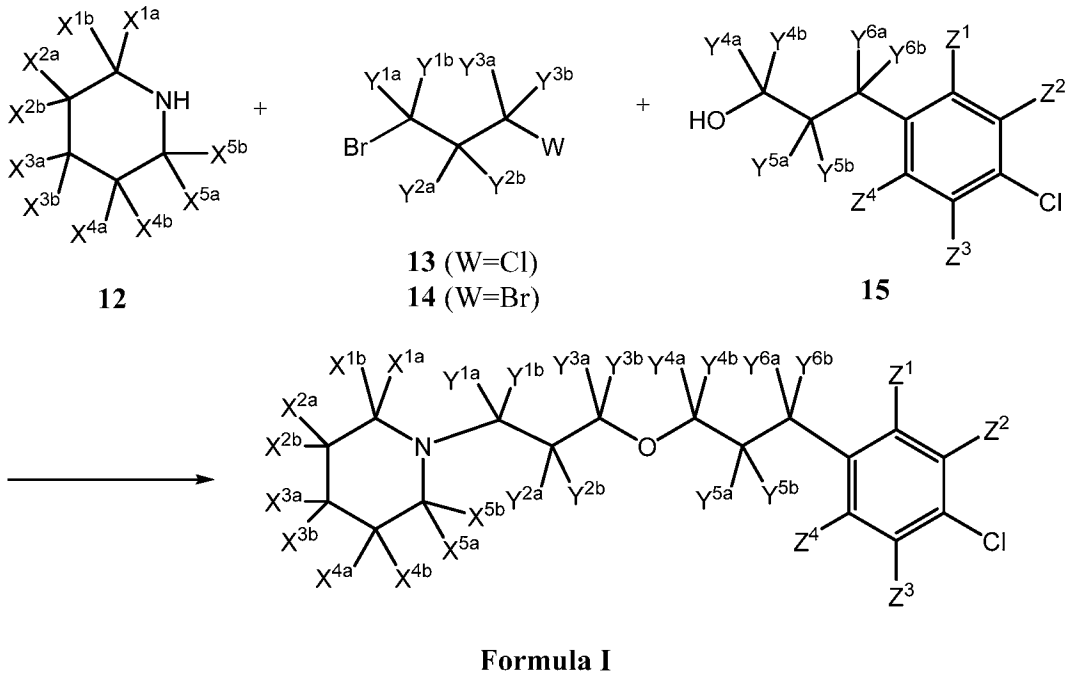
[66] In some embodiments, compounds of Formula I may be conveniently synthesized using methods and procedures analogous to those described in US Patent No. 7,169,928 and CN103435575, as depicted in Scheme 1a.

Scheme 1a



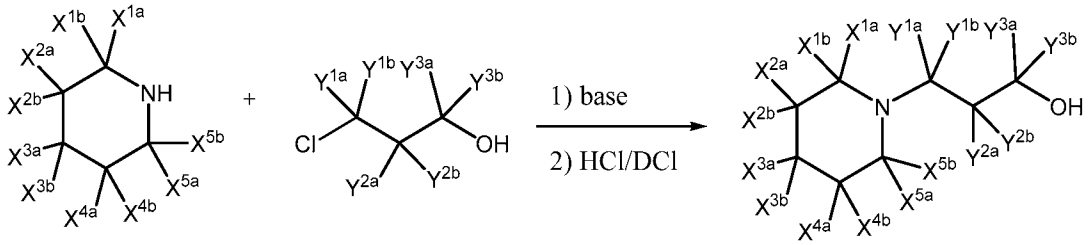
[67] In some embodiments, compounds of Formula I may be conveniently synthesized using methods and procedures analogous to those described in CN104447620, as depicted in Scheme 1b.

Scheme 1b



[68] Appropriately deuterated examples of compound **10** may be synthesized using methods and procedures analogous to those described by Lipani, L. et al., European Journal of Medicinal Chemistry, 86, 578-588; 2014 and in CN103435575, as depicted in Scheme 2.

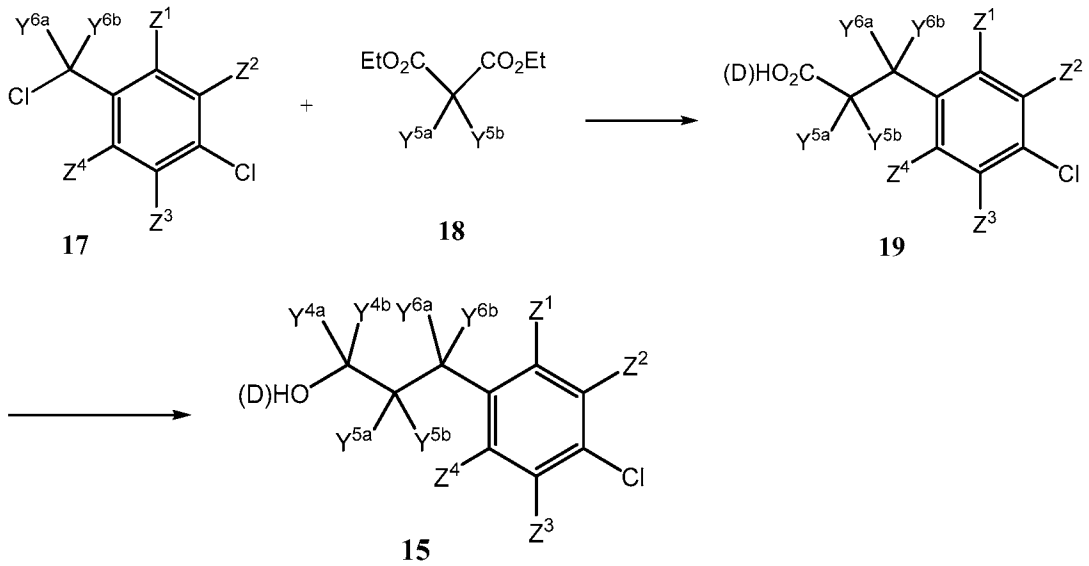
Scheme 2



12 **16** **10**

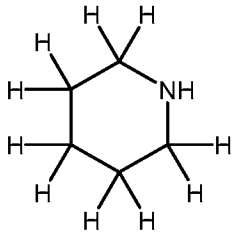
[69] Appropriately deuterated examples of compound **19** may be synthesized using methods and procedures analogous to those described by Martin, O.R. et al., Journal of Organic Chemistry, 53(14), 3287-3292, 1988. Further, appropriately deuterated examples of compound **15** may be synthesized from **19** using methods and procedures analogous to those described by in CN103435575, as depicted in Scheme 3.

Scheme 3

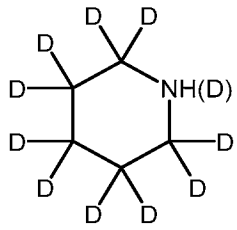


17 **18** **19** **15**

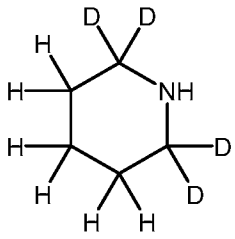
[70] Representative examples of compound **12** for use in preparing examples of compound **10** as in Scheme 2 are depicted below:



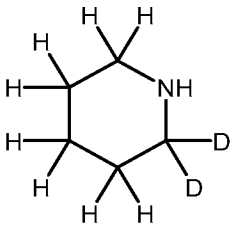
12a



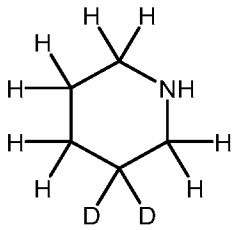
12b



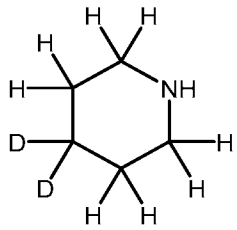
12c



12d

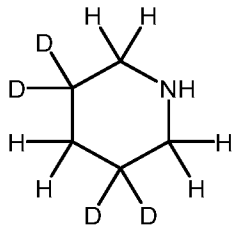


12e



12f

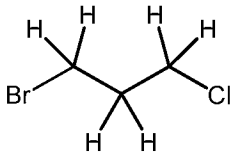
and



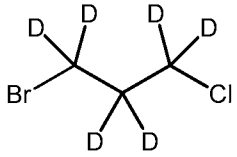
12e

Compounds **12a**, **12b** and **12c** are commercially available. Compound **12d** is reported in Xia, X-F., et al., RSC Advances, 2(2), 560-565, 2012 and in Djerassi, C., et al., JACS, 87(4), 817-826, 1965. Compound **12e** is reported in Masumoto, H., et al., Drug Metabolism and Disposition, 19(4), 768-780, 1991 and in Djerassi, C., et al., JACS, 87(4), 817-826, 1965. Compound **12f** is reported in US20150080377 and in Lambert, J., et al., JACS, 89(23), 5921-5924, 1967. Compound **12g** is reported in Lambert, J., et al., JACS, 88(3), 620-622, 1966 and in Lambert, J., et al., JACS, 89(23), 5921-5924, 1967.

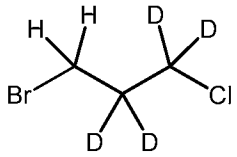
[71] Representative examples of compounds **13** and **14** for use in preparing compounds of Formula I as shown in Scheme 1b are depicted below:



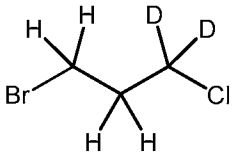
13a



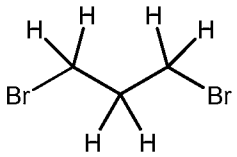
13b



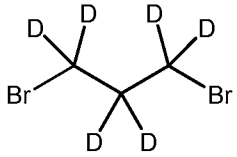
13c



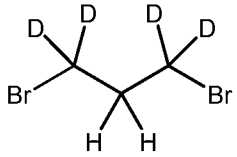
13d



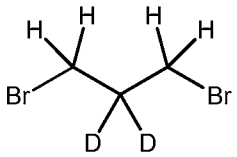
14a



14b



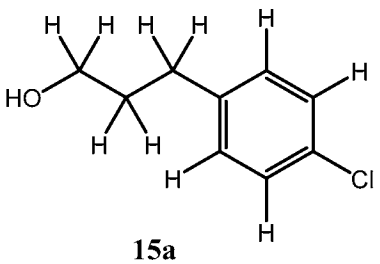
14c and



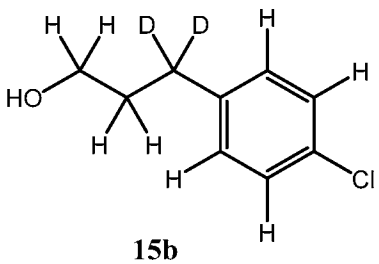
14d

Compounds **13a**, **13b**, **14a**, **14b** and **14c** are commercially available. Compound **13c** is reported in Borcic, S., et al., JACS, 84, 1615-1621, 1962, in US Patent Nos. 3022345 and 3023241. Compound **13d** is reported in Har, H., et al., JACS, 85(20), 3269-3273, 1963. And the preparation of compound **14d** is reported in Baldwin, J., et al., Journal of Labelled Compounds and Radiopharma., 42(1), 55-61, 1999.

[72] Representative examples of compound **15** for use in preparing compounds of Formula I as shown in Scheme 1b are depicted below:



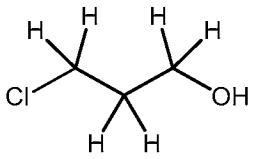
15a and



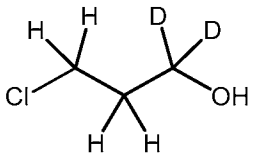
15b

Compound **15a** is commercially available. The preparation of compound **15b** is reported in Szostak, M., et al., Organic Letters, 16(19), 5052-5055, 2014. Additional deuterated examples of compound **15** may be prepared as in Scheme 3.

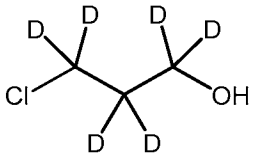
[73] Representative examples of compound **16** for use in preparing examples of compound **10** as in Scheme 2 are depicted below:



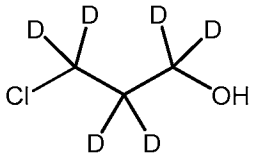
16a



16b



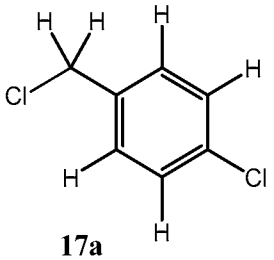
16c and



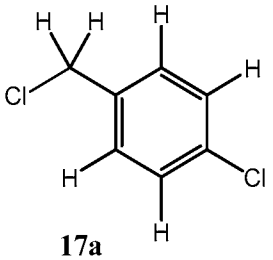
16d

Compound **16a** is commercially available. The preparation of compound **16b** is reported in Maercker, A., et al., Chem. Berichte, 120(10), 1695-1706, 1987. The preparation of compound **16c** is reported in US20090202540. Compound **16d** is reported in Borcic, S., et al., JACS, 84, 1615-1621, 1962, and in US Patent Nos. 3022345 and 3023241.

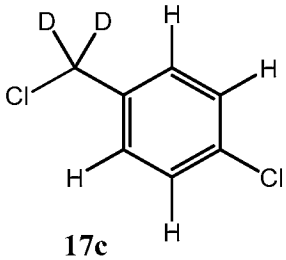
[74] Representative examples of compounds **17** and **18** for use in preparing examples of compound **19** as in Scheme 3 are depicted below:



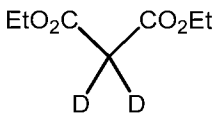
17a



17a



17c and



18b

[75] Compounds **17a**, **17b**, **18a** (protio diethyl malonate), and **18b** are commercially available. Compound **17c** is reported in Martin, O.R., et al., Journal of Organic Chemistry, 53(14), 3287-92, 1988.

[76] Use of appropriately deuterated reagents allows deuterium incorporation at the X, Y and Z positions of a compound of Formula I or any appropriate intermediate herein, e.g., about 90%, about 95%, about 97%, or about 99% deuterium incorporation at any X, Y or Z.

[77] 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.

[78] 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.

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

Compositions

[80] 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.

[81] 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.

[82] 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.

[83] 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.

[84] 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).

[85] 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.

[86] 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.

[87] 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.

[88] 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.

[89] 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.

[90] 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.

[91] 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.

[92] 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.

[93] 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.

[94] 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.

[95] 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.

[96] 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.

[97] 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.

[98] 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.

[99] 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.

[100] 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.

[101] In another embodiment, a composition of this invention further comprises one or more additional therapeutic agents. The additional 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 pitolisant. Such agents include those indicated as being useful in combination with pitolisant.

[102] Preferably, the additional therapeutic agent is an agent useful in the treatment of a disease or condition selected from Alzheimer's disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo, motion sickness, allergic and inflammatory diseases, narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, daytime sleepiness associated with Parkinson's disease, schizophrenia, schizoaffective disorder and Prader-Willi syndrome.

[103] 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).

[104] 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.

[105] 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.

[106] In one embodiment, an effective amount of a compound of Formula (I) can range from about 1.5 mg to about 20 mg, or from about 25 mg to about 80 mg, or from about 100 mg to about 200 mg, or from about 250 mg to about 1000 mg. For example, an effective amount of a compound of Formula (I) may be about 1.5 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, or about 100.0 mg. In a preferred embodiment, the effective amount of the compound of Formula (I) is administered once daily.

[107] In one embodiment, an effective amount of a compound of this invention can range from about 0.01 mg/kg to about 25 mg/kg of body weight per day, from about 0.1 to 10 mg/kg of body weight per day, or from about 0.1 mg/kg to 1 mg/kg of body weight per day.

[108] 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 pitolisant.

[109] For pharmaceutical compositions that comprise one or more additional therapeutic agents, an effective amount of the additional therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these

additional therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

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

Methods of Treatment

[111] In other embodiments, the invention provides a method of modulating the activity of histamine H3-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*.

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

[113] Such diseases are well known in the art and are disclosed in, but not limited to the following patents: US7138413, US7169928, US7910605, US8207197, and US83354430; and publications: Pullen, L. C. et al., J Pediatric Pharmacology and Therapeutics, 2019, 24(2):166–171. Such diseases include, but are not limited to, Alzheimer's disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo, motion sickness, allergic and inflammatory diseases, narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, daytime sleepiness associated with

Parkinson's disease, schizophrenia, schizoaffective disorder, and Prader-Willi syndrome.

[114] In certain embodiments, the method of this invention is used to treat a disease or condition selected from narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, daytime sleepiness associated with Parkinson's disease in a subject in need thereof.

[115] In another particular embodiment, the method of this invention is used to treat narcolepsy with or without cataplexy in a subject in need thereof.

[116] In certain embodiments, the invention provides a method of treating an addiction disorder, also referred to herein as substance dependency, dependency on an addictive substance, or drug addiction, in a subject in need of such treatment. In certain aspects, the addiction disorder is due to addiction to, or dependency on, an addictive substance or substances selected from stimulants including, but not limited to amphetamines; depressants including, but not limited to barbiturates; opiates; cocaine, nicotine and/or alcohol in a subject in need thereof.

[117] In another particular embodiment, the method of this invention is used to treat Prader-Willi syndrome in a subject in need thereof.

[118] In one embodiment, the invention provides a method of treating dependency on an addictive substance wherein the addictive substance is a stimulant such as d-amphetamine, l-amphetamine, dl-amphetamine, methamphetamine, benzphetamine, phentermine, diethylpropion, phenmetrazine, phendimetrazine, chlorphentermine, clortermine, mazindol, phenylpropanolamine, cocaine, methylphenidate, nicotine, cathinone (khat plant) or any combination of these stimulants; a depressant such as meprobamate, chlordiazepoxide diazepam, oxazepam, lorazepam, flurazepam, prazepam, chlorazepate, alprazolam, triazolam, temazepam, halazepam, quadazepam, midazolam, estazolam, ethanol, pentobarbital, phenobarbital, secobarbital, amobarbital or any combination of these depressants; an opiate such as morphine, codeine, heroin, levorphanol, meperidine, methadone, propoxyphene, acetylmethadol (LAAM), pentazocine, butorphanol, nalbuphine, buprenorphine, dezoeine, fentanyl, or any combination of these opiates; or any combination of the foregoing addictive substances.

[119] In certain embodiments, the invention provides a method of treating dependency on an addictive substance wherein the addictive substance is an opiate selected from morphine, codeine, heroin, levorphanol, meperidine, methadone,

propoxyphene, acetylmethadol (LAAM), pentazocine, butorphanol, nalbuphine, buprenorphine, dezoeine and fentanyl, or any combination of these opiates in a subject in need thereof.

[120] In certain embodiments, the addictive substance is a stimulant selected from d-amphetamine, l-amphetamine, dl-amphetamine, methamphetamine, benzphetamine, phentermine, diethylpropion, phenmetrazine, phendimetrazine, chlorphentermine, clortermine, mazindol, phenylpropanolamine, cocaine, methylphenidate, nicotine and cathinone (khat plant) or any combination of these stimulants.

[121] In certain embodiments, the invention provides a method of treating dependency on an addictive substance wherein the addictive substance is a depressant selected from meprobamate, chlordiazepoxide diazepam, oxazepam, lorazepam, flurazepam, prazepam, chlorazepate, alprazolam, triazolam, temazepam, halazepam, quadazepam, midazolam, estazolam, ethanol, pentobarbital, phenobarbital, secobarbital and amobarbital, or any combination of these depressants.

[122] In certain embodiments, the addictive substance is nicotine.

[123] In certain embodiments, the addictive substance is alcohol.

[124] In another embodiment, the invention provides a method of preventing a substance dependency relapse in a subject in need of such treatment.

[125] In certain of the above embodiments the subject in need of such treatment is a human, such as a patient in need of such treatment.

[126] 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).

[127] 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 pitolisant. 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.

[128] The term "co-administered" as used herein means that the additional therapeutic agent may be administered together with a compound of this invention as

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

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

[130] 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.

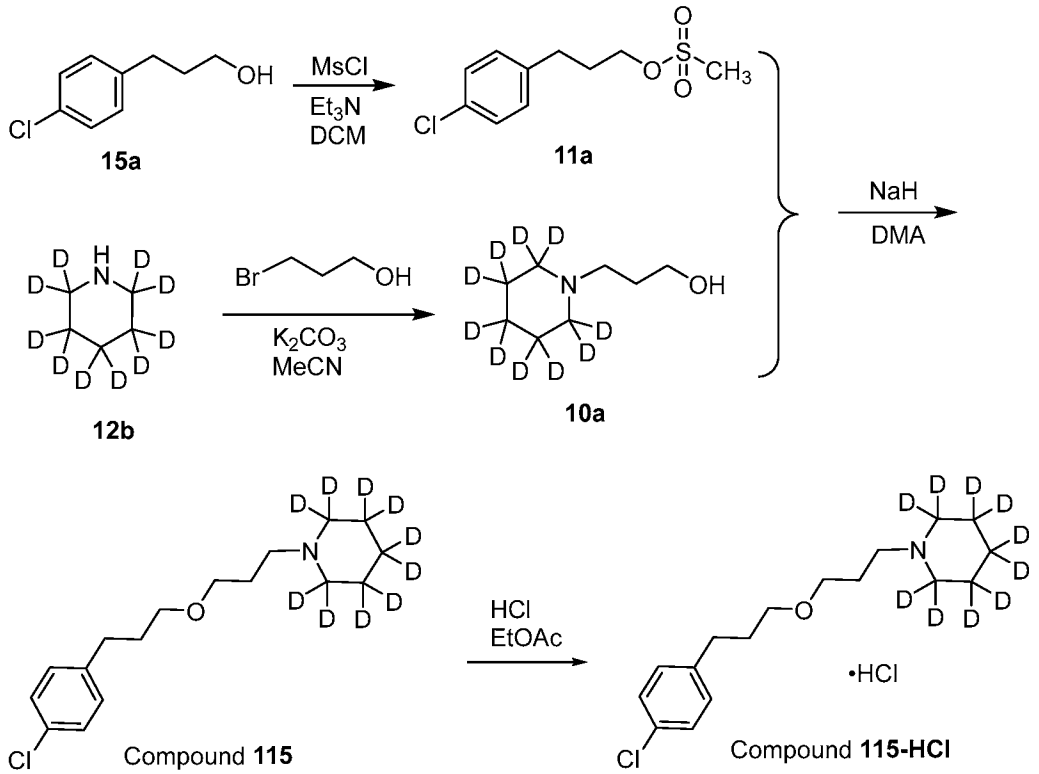
[131] In yet another aspect, the invention provides the use of a compound of Formula I alone or together with one or more of the above-described additional therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment in a subject of 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.

Examples

Example 1. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **115**)

Scheme 4. Preparation of 1-(3-(3-(4-Chlorophenyl)propoxy)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **115-HCl**)



[132] Step 1. 3-(4-Chlorophenyl)propyl methanesulfonate (**11a**). To a solution of **15a** (0.280 g, 1.64 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (0.15 mL, 1.93 mmol), followed by triethylamine (0.30 mL, 2.17 mmol). The reaction mixture was stirred at rt for 2 h then diluted with dichloromethane (5 mL), washed with water (2 mL), 1M hydrochloric acid (aq.) (4 mL) and saturated brine (4 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give **11a** (0.352 g, 86% yield) as a light yellow oil.

[133] Step 2. 3-(Piperidin-1-yl-2,2,3,3,4,4,5,5,6,6-d_{10})propan-1-ol (**10a**). To a mixture of piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (**12b**) (0.45 g, 4.8 mmol, Cambridge Isotope Laboratories, 98 atom% D) and potassium carbonate (0.82 g, 5.9 mmol) in

acetonitrile (2 mL) was added a solution of 3-bromopropan-1-ol (0.61 g, 4.4 mmol) in acetonitrile (3 mL). The reaction mixture was heated at 50 °C for 2 h then stirred at rt overnight. The reaction mixture was diluted with ethyl acetate (20 mL) and the solids were filtered. The filtrate was concentrated under reduced pressure to give **10a** (0.64 g, 95% yield) as a colorless oil, which was used without purification.

[134] Step 3. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **115**). To a solution of **10a** (0.37 g, 1.16 mmol) in *N,N*-dimethylacetamide (DMA) (4 mL) was added 60% sodium hydride in mineral oil (0.17 g, 4.3 mmol), and the reaction mixture was heated at 50 °C for 1 h. The reaction mixture was cooled to rt, then a solution of **11a** (0.72 g, 2.89 mmol, 1.2 equiv) in DMA (4 mL) was added. The reaction mixture was stirred at rt for 4 h, diluted with water (20 mL) and saturated brine (20 mL), then extracted with toluene (3 x 20 mL). The combined organic layers were washed with saturated brine (10 mL). The toluene solution was extracted with 1M hydrochloric acid (aq.) (3 x 30 mL). The acidic extract was washed with ethyl acetate (10 mL) then made basic with 15% aqueous sodium hydroxide (17 mL). The basic solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with saturated brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane, absorbed onto Celite (6 g) then purified by chromatography (Büchi automated system, Teledyne Isco 80 g basic alumina column, 0-3% methanol in dichloromethane) to give Compound **115** (0.58 g, 79% yield) as a colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 µm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 98.7%.

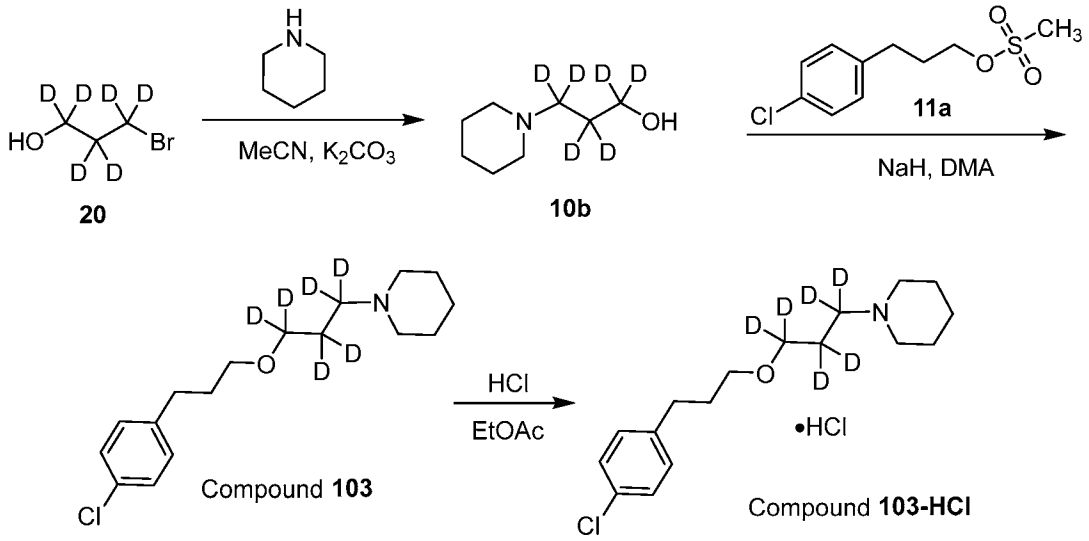
[135] Step 4. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **115-HCl**). To a solution of Compound **115** (0.58 g, 1.89 mmol) in ethyl acetate (6 mL) was added 1M hydrogen chloride in ethyl acetate (4 mL, 4 mmol). The solution was concentrated under reduced pressure then dried in a vacuum oven at 40 °C for 2 days to give Compound **115-HCl** (0.51 g, 79%) as a white solid.

[136] **^{1}H NMR** (D_2O, 400 MHz): δ 1.85-1.98 (m, 4H), 2.67 (t, J = 7.5, 2H), 3.01-3.11 (m, 2H), 3.51 (td, J = 6.1, 15.4, 4H), 7.22-7.28 (m, 2H), 7.33-7.38 (m, 2H). **LCMS** (method: SorbTech C_{18} AQ column, 2.1 x 50 mm; 0.3 µm 5-95%

acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.3 min; 98.2% purity; (EI-MS): *m/z*=306.2 ($[M+H]^+$).

Example 2. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine (Compound **103**)

Scheme 5. Preparation of 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine hydrochloride (Compound **103**)



[137] Step 1. 3-(Piperidin-1-yl)propan-1,1,2,2,3,3-d_6-1-ol (**10b**). To a mixture of piperidine (0.30 g, 3.5 mmol) and potassium carbonate (0.59 g, 4.2 mmol) in acetonitrile (1 mL) was added a solution of **20** (0.46 g, 3.2 mmol, CDN Isotopes, 99.9 atom% D) in acetonitrile (4 mL). The reaction mixture was heated at 50 °C for 2 h then stirred at rt for 90 min. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure to give an oil with residual solids. A solution of the oil in ethyl acetate (10 mL) was filtered a second time, then concentrated under reduced pressure to give **10b** (0.46 g, 96% yield) as a colorless oil which was used without further purification.

[138] Step 2. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine hydrochloride (Compound **103**). To a solution of **10b** (0.23 g, 1.5 mmol) in DMA (4 mL) was added 60% sodium hydride in mineral oil (0.11 g, 2.7 mmol), and the reaction mixture was heated at 50 °C for 1 h. The reaction mixture was cooled to rt then solid **11a** (0.45 g, 1.8 mmol) was added, followed by additional DMA (2 mL). The reaction mixture was stirred at rt for 3 h, diluted with water (30 mL) then extracted with toluene (3x 25 mL). The combined organic layers were washed with

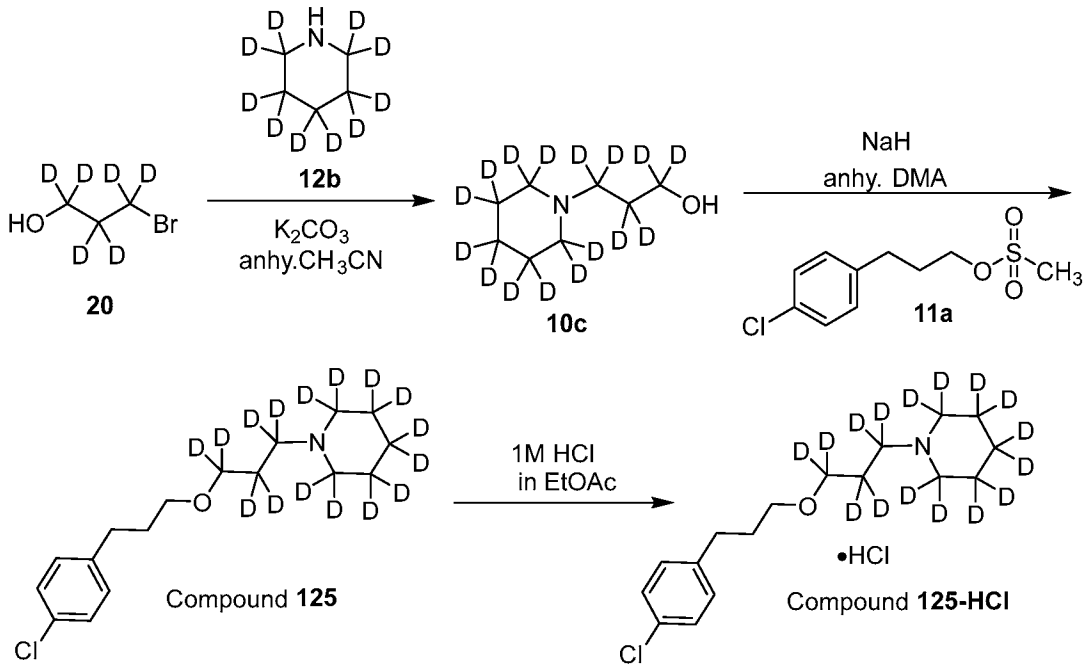
water (10 mL). The toluene layer was extracted with 1M aqueous hydrochloric acid (3 x 15 mL). The combined acidic layers were washed with toluene (10 mL), made basic with 24% aqueous sodium hydroxide (10 mL) and extracted with toluene (3x 20 mL). The combined organic layers were washed with saturated brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane, absorbed onto Celite, and purified by chromatography (Büchi automated system, RediSep 48 g basic alumina column, 0-20% ethyl acetate/hexanes) to give Compound **103** (154 mg, 61% yield) as a colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 μm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 97.5%.

[139] Step 3. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine hydrochloride (Compound **103-HCl**). A solution of Compound **103** (144 mg, 0.48 mmol) in ethyl acetate (2 mL) was treated with 1M hydrogen chloride solution in ethyl acetate (0.95 mL, 0.96 mmol). After stirring at rt for 2 h, the reaction mixture was concentrated under reduced pressure and dried in a vacuum oven at 40 °C for 16 h to give Compound **103-HCl** (155 mg, 96% yield, 99% HPLC purity) as an off-white solid.

[140] **^{1}H NMR** (D_2O, 400 MHz): δ 1.41-1.53 (m, 1H); 1.63-1.75 (m, 2H); 1.81 (td, J = 3.4, 13.2 Hz, 1H); 1.85-1.93 (m, 3H); 1.96 (br s, 1H); 2.68 (t, J = 7.4 Hz, 2H); 2.87 (dt, J = 2.9, 12.6 Hz, 2H); 3.49 (t, J = 6.4 Hz, 4H); 7.24-7.27 (m, 2H); 7.34-7.38 (m, 2H). **LCMS** (method: SorbTech C18 AQ column, 2.1 x 50 mm; 0.3 μm; 5 – 95% acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.3 min; 99.1% purity; (EI-MS): m/z = 302.2 ($[M+H]^+$).

Example 3. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **125**)

Scheme 6. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **125**)



[141] Step 1. 3-(Piperidin-1-yl-d_{10})propan-1,1,2,2,3,3-d_6-1-ol (**10c**). A solution of **20** (0.50 g, 3.45 mmol, CDN Isotope, 99.4 atom% D) in acetonitrile (2 mL) was added to a mixture of **12b** (0.36 g, 3.79 mmol, Cambridge Isotope, 98 atom% D) and potassium carbonate (0.62 g, 4.48 mmol) in acetonitrile (1 mL). The reaction mixture was heated at 50 °C for 2 h, then cooled to rt. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered, rinsing solids with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure at 22 °C to give **10c** (0.43 g, 78% yield) as a light-yellow oil which was used without purification.

[142] Step 2. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **125**). A solution of **10c** (0.2 g,1.26 mmol) in DMA (2.5 mL) was treated with 60% sodium hydride in mineral oil (0.1 g, 2.13 mmol) at rt. The mixture was heated at 50 °C, for 1 h then cooled to rt. A solution of **11a** (0.38 g, 1.51 mmol) in anhydrous DMA (2.5 mL) was added and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with a 1:1 mixture of water and saturated brine (40 mL) and extracted with toluene (3 x 10 mL). The combined organic layers were washed with saturated brine (6 mL) and extracted with 1N aqueous hydrochloric acid (3 x 15 mL). The combined aqueous layers were washed with ethyl acetate (6 mL). The aqueous layer was made basic with 15% aqueous

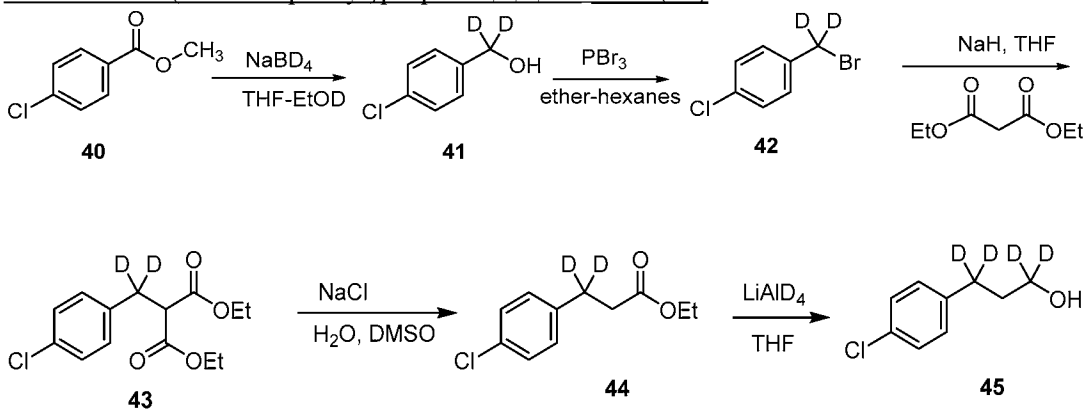
sodium hydroxide (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with saturated brine (6 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was absorbed onto Celite® (6 g) and purified by chromatography (Büchi automated system, RediSep 80 g basic alumina column, 20-100% ethyl acetate/hexanes) to give Compound **125** (135 mg, 35% yield, 99% HPLC purity) as a clear oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 µm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 98.7%.

[143] Step 3. 1-(3-(3-(4-Chlorophenyl)propoxy)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **125-HCl**). A solution of Compound **125** (135 mg, 0.44 mmol) in ethyl acetate (2 mL) was treated with 1M hydrogen chloride solution in ethyl acetate (0.90 mL, 0.91 mmol). After stirring at rt for 2 h, the reaction mixture was concentrated under reduced pressure and dried in a vacuum oven at 35 °C for 4 h to give Compound **125-HCl** (147 mg, 97% yield) as an off-white solid.

[144] **^{1}H NMR** (D_2O, 400 MHz): δ 1.85 – 1.93 (m, 2H); 2.68 (t, J = 7.4 Hz, 2H); 3.50 (t, J = 6.4 Hz, 2H); 7.24 – 7.27 (m, 2H); 7.34 – 7.39 (m, 2H). **LCMS** (method: SorbTech C18 AQ column, 2.1 x 50 mm; 0.3µm; 5 – 95% acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.4 min; 97.5% purity; (EI-MS): m/z = 312.2 ($[M+H]^+$).

Example 4. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d4)propyl)piperidine (Compound **300**)

Scheme 7. 3-(4-Chlorophenyl)propan-1,1,3,3-d_4-1-ol (**45**)



[145] Step 1. 4-Chlorophenyl)methan-d_2-ol (**41**). A solution of methyl 4-chlorobenzoate (**40**) in ethanol-d (100 mL, 99 atom% D, Sigma Aldrich) and

anhydrous THF (100 mL) was cooled to 3 °C. Sodium borodeuteride (4.9 g, 117.2 mmol, 98 atom% D, Sigma Aldrich) was added, and the reaction mixture was warmed gradually to rt, then stirred for 26 h. The reaction mixture was poured into deuterium oxide (300 mL, 99 atom% D, Cambridge Isotopes) and extracted with diethyl ether (3x 300 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a white solid. The residue was purified by chromatography (Büchi automated system, SorbTech 120 g silica column, 0-100% ethyl acetate/hexanes) to give **41** (7.3 g, 87% yield) as a white solid.

[146] Step 2. 1-(Bromomethyl-d_2)-4-chlorobenzene (**42**). A mixture of **41** (4.8 g, 33.6 mmol), diethyl ether (52 mL) and hexanes (5 mL) was cooled to -30 °C (external temperature) with stirring under nitrogen. A solution of phosphorus tribromide (4.6 g, 1.6 mL, 17.0 mmol) in hexanes (3 mL) was added dropwise over 5 min. The reaction mixture was stirred for 30 min, warmed gradually to rt over 5 h then poured carefully onto a saturated aqueous sodium bicarbonate solution (100 mL). The mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give **42** (6.8 g, 98% yield) as a white solid which was used without purification.

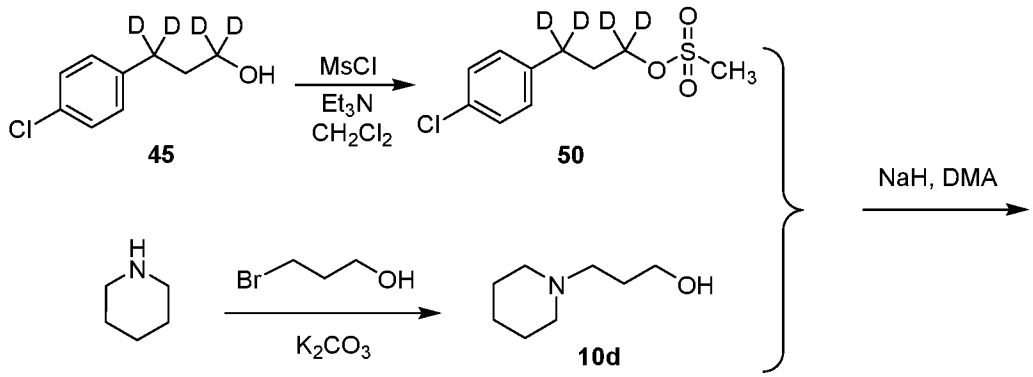
[147] Step 3. Diethyl 2-((4-chlorophenyl)methyl-d_2)malonate (**43**). Diethyl malonate (8.2 g, 42.4 mmol) was added over 10 min with stirring to a suspension of 60% sodium hydride in mineral oil (1.7 g, 42.4 mmol) in anhydrous THF (56 mL) at 0-5 °C (internal temperature) under nitrogen. The reaction mixture was warmed gradually to rt over 1 h. A solution of **42** (8.5 g, 41.9 mmol,1.0 equiv) in anhydrous THF (56 mL) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was poured onto water (180 mL) and extracted with diethyl ether (3 x 180 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. This oil was dissolved in dichloromethane (100 mL), absorbed onto silica gel (70 g), and purified by chromatography (Interchim automated system, SorbTech 120 g silica column, 0-20% ethyl acetate/hexanes) to give crude **43** (5.6 g, 47% yield, 70% NMR purity) as a clear colorless oil.

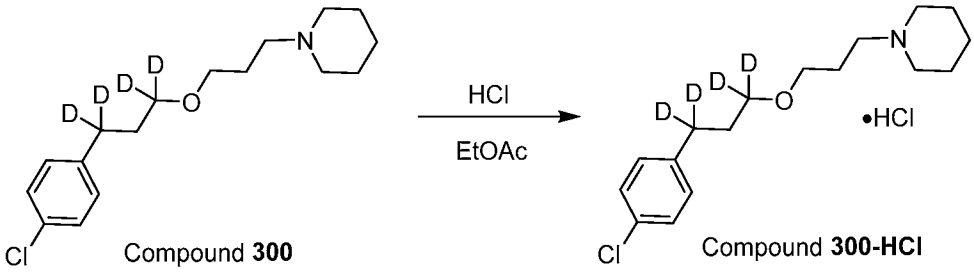
[148] Step 4. Ethyl 3-(4-chlorophenyl)propanoate-3,3-d_2 (**44**). A mixture of **43** (5.6 g, 19.7 mmol), sodium chloride (2.3 g, 39. 4 mmol), water (0.7 mL, 39.4 mmol) and dimethyl sulfoxide (30 mL) was heated to 180 °C under nitrogen for 3.5 h. The reaction mixture was cooled to rt, poured onto water (100 mL) and extracted with

diethyl ether (4 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The oil was purified by chromatography (Interchim system, SorbTech 80 g silica column, 0-20% ethyl acetate/hexanes) to give **44** (3.2 g, 75% yield) as a clear colorless oil.

[149] Step 5. 3-(4-Chlorophenyl)propan-1,1,3,3-d_4-1-ol (**45**). To a solution of **44** (3.2 g, 14.7 mmol) in anhydrous THF (60 mL) which was cooled to -75 °C under a nitrogen was added lithium aluminum deuteride (1.2 g, 29.4 mmol, 98 atom% D, BOC Sciences). The reaction mixture was stirred at -75 °C for 1.25 h, then warmed to rt over 2.5 h. The reaction mixture was cooled to 0-5 °C. Deuterium oxide (1.2 mL, 99.9 atom% D, Cambridge Isotopes) was added dropwise over 3 min, followed by a 20% solution of sodium deuteroxide in deuterium oxide (1.2 mL, 99 atom% D, Cambridge Isotopes) over 3 min, then deuterium oxide (3.6 mL, 99 atom% D, Cambridge Isotopes). After 15 min, the reaction mixture was filtered through Celite®, the filter pad was washed with THF (40 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in MTBE (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. This oil was dissolved in dichloromethane (50 mL), absorbed onto silica gel (20 g), and purified by chromatography (Interchim system, SorbTech 80 g silica column, 0-30% ethyl acetate/hexanes) to give **45** (1.9 g, 74% yield) as a clear colorless oil.

[150] Scheme 8. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d4)propyl)piperidine (Compound **300**).





Compound **300** Compound **300-HCl**

[151] Step 6. 3-(4-Chlorophenyl)propyl-1,1,3,3-d_4 methanesulfonate (**50**). To a solution of **45** (1.0 g, 5.7 mmol) in dichloromethane, cooled to 0 to 5 °C, methanesulfonyl chloride (0.5 mL, 6.8 mmol) and triethylamine (1.1 mL, 7.6 mmol) were added sequentially. The reaction mixture was stirred at 0 to 5 °C for 30 min, then warmed gradually to rt over 1.5 h. Water (10 mL) was added to the reaction mixture with stirring and the layers were separated. The organic layer was washed with a 1N aqueous hydrochloric acid (8 mL), then with saturated brine (10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give **50** (1.6 g, 110 % yield) as a pale yellow solid which was used without purification.

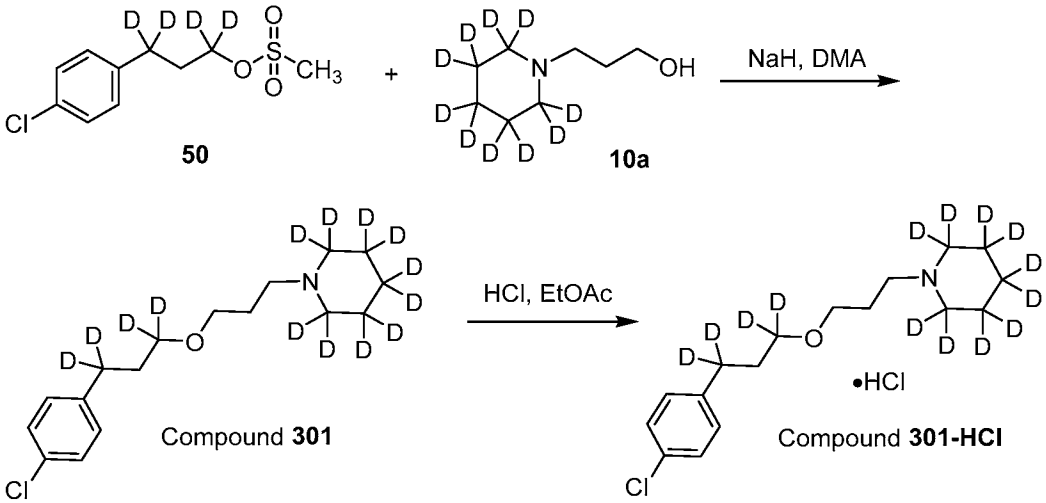
[152] Step 7. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)piperidine (Compound **300**). To a solution of **10d** (0.3 g, 2.3 mmol) in DMA (4 mL) was added 60% sodium hydride in mineral oil (0.16 g, 3.9 mmol). The reaction mixture was stirred for 5 min at rt then at 50 °C for 1 h. The reaction mixture was cooled to rt and a solution of **50** (0.7 g, 2.8 mmol, 1.2 equiv) in DMA (4 mL) was added. The reaction mixture was stirred for 18 h then poured onto a 1:1 mixture of water and saturated brine (40 mL). The mixture was extracted with toluene (3 x 35 mL). The combined organic layers were extracted with 1N aqueous hydrochloric acid (3 x 35 mL). The combined aqueous layers were adjusted to pH 12 with concentrated aqueous sodium hydroxide solution. The mixture was cooled to rt and extracted with diethyl ether (3 x 35 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The oil was absorbed onto Celite (5 g) and purified by chromatography (Interchim system, Teledyne basic alumina 80 g column, 0-25% ethyl acetate/hexanes) to give Compound **300** (228 mg, 33% yield) as a clear colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 μm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 99.5%.

[153] Step 8. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)piperidine hydrochloride (Compound **300-HCl**). To a solution of Compound **300** (228 mg, 0.8 mmol, 1.0 equiv) in ethyl acetate (2 mL) was added 1N hydrogen chloride in ethyl acetate (2.0 mL, 2.0 mmol, 2.5 equiv) with stirring. The mixture was concentrated under reduced pressure at rt. The product was dried in a vacuum oven at 40 °C for 48 h to give Compound **300-HCl** (200 mg, 78% yield) as a white solid.

[154] **^{1}H NMR** (D_2O, 400 MHz): δ 1.41-1.53 (m, 1H), 1.63-1.75 (m, 2H), 1.81 (td, J = 3.5, 13.2, 1H), 1.86 (s, 2H), 1.90-1.98 (m, 4H), 2.88 (dt, J = 2.8, 12.6, 2H), 3.04-3.09 (m, 2H), 3.49 (br s, 1H), 3.51-3.56 (m, 3H), 7.23-7.27 (m, 2H), 7.33-7.38 (m, 2H). **LCMS** (method: SorbTech C_{18} AQ column, 2.1 x 50 mm, 3 μm; 5 – 95% acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.4 min; 99.5% purity; (EI-MS): *m/z*=300.2 ($[M+H]^+$).

Example 5. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **301**)

Scheme 9. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **301**)



[155] Step 1. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **301**). To a solution of **10a** (0.4 g, 2.4 mmol) in DMA (4 mL) at rt was added 60% sodium hydride in mineral oil (0.16 g, 4.0 mmol). The reaction mixture was stirred at rt for 5 min then at 50 °C for 1 h. The reaction mixture was cooled to rt then a solution of **50** (0.7 g, 2.8 mmol) in DMA (4 mL) added. The reaction mixture was stirred for 17 h then poured onto a 1:1 mixture of

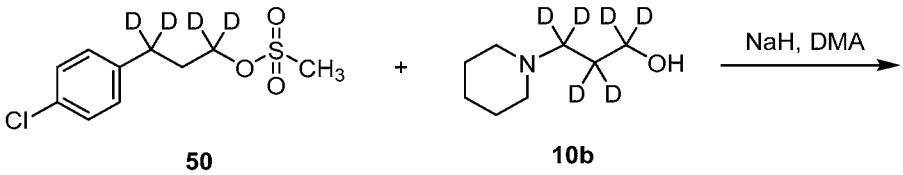
water and saturated brine (40 mL). The mixture was extracted with toluene (3 x 35 mL). The combined organic layers were extracted with 1N aqueous hydrochloric acid (3 x 35 mL). The combined aqueous layers were adjusted to pH 12 with concentrated aqueous sodium hydroxide solution. The mixture was cooled to room temperature and extracted with diethyl ether (3 x 35 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The oil was absorbed on Celite (5 g) and purified by chromatography (Interchim system, Teledyne basic alumina 80 g column, 0-25% ethyl acetate/hexanes) to give Compound **301** (315 mg, 43% yield) as a clear colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 μm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 99.6%.

[156] Step 2. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl)-piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **301-HCl**). To a solution of Compound **301** (315 mg, 1.0 mmol) in ethyl acetate (3 mL) was added a 1N hydrogen chloride solution in ethyl acetate (2.1 mL, 2.1 mmol, 2.5 equiv) with stirring. The mixture was concentrated under reduced pressure at rt. The product was dried in a vacuum oven at 40 °C for 48 h to give Compound **301-HCl** (279 mg, 81% yield) as a white solid.

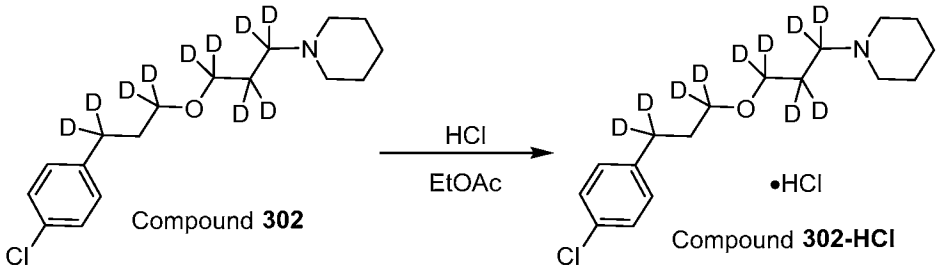
[157] **^{1}H NMR** (D_2O, 400 MHz): δ 1.86 (s, 2H), 1.90-1.97 (m, 2H), 3.03-3.08 (m, 2H), 3.53 (t, J = 6.0, 2H), 7.23-7.27 (m, 2H), 7.35 (d, J = 7.4, 2H). **LCMS** (method: SorbTech C_{18} AQ column, 2.1 x 50 mm; 5 – 95% acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.4 min; 99.8% purity; (EI-MS): m/z=310.2 ($[M+H]^+$).

Example 6. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine (Compound **302**)

Scheme 10. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine hydrochloride(Compound **302**)



50 **10b**



Compound **302** Compound **302-HCl**

[158] Step 1. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine (Compound **302**). To a solution of **10b** (0.22 g, 1.5 mmol) in DMA (3 mL) was added 60% sodium hydride in mineral oil (0.1 g, 2.5 mmol) at rt. The reaction mixture was stirred at rt for 5 min, then warmed to 50 °C and stirred for 1 h. The reaction mixture was cooled to rt then a solution of **50** (0.44 g, 1.8 mmol, 1.2 equiv) in DMA (3 mL) was added. The reaction mixture was stirred for 24 h then poured onto a 1:1 mixture of water and saturated brine (30 mL). The mixture was extracted with toluene (3 x 30 mL). The combined organic layers were extracted with 1N aqueous hydrochloric acid solution (3 x 25 mL). The combined aqueous layers were made basic with concentrated aqueous sodium hydroxide solution. The mixture was cooled to rt and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The oil was absorbed onto Celite® (6 g) and purified by chromatography (Interchim system, Teledyne basic alumina 40 g column, 0-25% ethyl acetate/hexanes) to give Compound **302** (105 mg, 24% yield) as a clear colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30 m x 0.25mm, 0.25 μm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 99.0%.

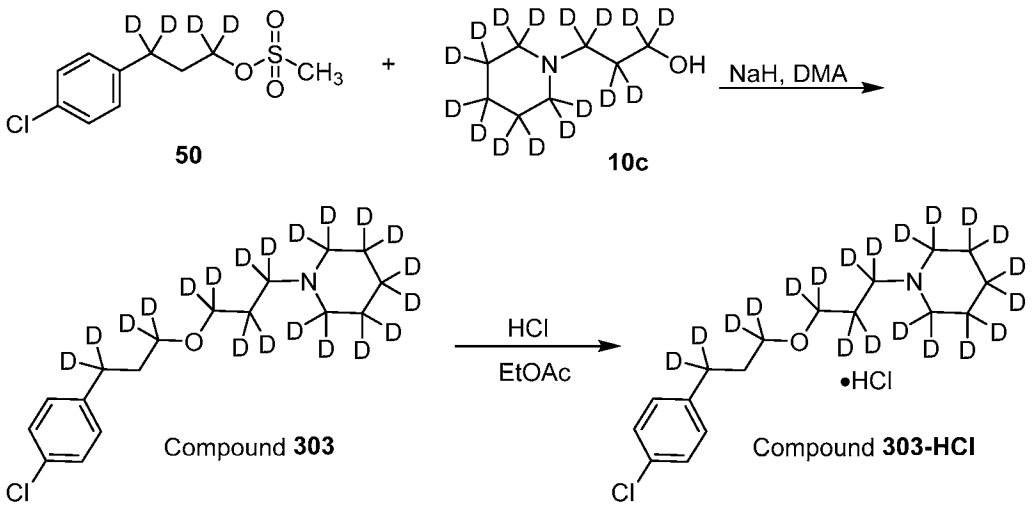
[159] Step 2. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine hydrochloride (Compound **302-HCl**). To a solution of Compound **302** (105 mg, 1.5 mmol) in ethyl acetate (4 mL) was added a 1N hydrogen chloride solution in ethyl acetate (3 mL, 3 mmol) with stirring. The reaction mixture was concentrated under reduced pressure and then dried in a vacuum oven at 40 °C for 48 h to give Compound **302-HCl** (74 mg, 66% yield) as a white solid.

[160] **^{1}H NMR** (D_2O, 400 MHz): δ 1.47 (quintet, J = 12.8, 1H), 1.63-1.75 (m, 2H), 1.81 (br d, J = 12.6, 1H), 1.86 (s, 2H), 1.94 (br d, J = 14.2, 2H), 2.87 (br t, J = 11.5, 2H), 3.49 (br d, J = 12.0, 2H), 7.23-7.27 (m, 2H), 7.33-7.38 (m, 2H). **LCMS** (method: SorbTech C_{18} AQ column, 2.1 x 50 mm; 5 – 95% acetonitrile/water with 0.1% formic

acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.6 min; 98.7% purity; (EI-MS): *m/z*=306.2 ($[M+H]^+$).

Example 7. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **303**)

Scheme 11. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **303-HCl**)



[161] Step 1. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} (Compound **303**). To a solution of **10c** (0.56 g, 3.5 mmol) in DMA (6 mL) was added 60% sodium hydride in mineral oil (0.24 g, 6.0 mmol) at rt, and the reaction mixture was stirred at rt for 5 min. The reaction mixture was then warmed to 50 °C and stirred for 1 h. The reaction mixture was cooled to rt then a solution of **50** (1.1 g, 4.2 mmol, 1.2 equiv) in DMA (6 mL) was added. The reaction mixture was stirred for 23 h then poured onto a 1:1 mixture of water and brine (80 mL). The mixture was extracted with toluene (3 x 50 mL). The combined organic layers were extracted with 1N aqueous hydrochloric acid (4 x 50 mL). The combined aqueous layers were made basic with concentrated sodium hydroxide solution. The mixture was cooled to rt and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The oil was absorbed onto Celite® (15 g) and purified by chromatography (Interchim system, Teledyne basic alumina 120 g column, 0-25% ethyl acetate/hexanes) to give Compound **303** (448 mg, 41% yield) as a clear colorless oil. **GC** (method: Phenomenex ZB-1MS column, 30

m x 0.25mm, 0.25 μm; start temp 50 °C, ramp 20 °C /min to 300 °C, hold for 5 min): retention time: 11.2 min; purity 99.6%.

[162] Step 2. 1-(3-(3-(4-Chlorophenyl)propoxy-1,1,3,3-d_4)propyl-1,1,2,2,3,3-d_6)piperidine-2,2,3,3,4,4,5,5,6,6-d_{10} hydrochloride (Compound **303-HCl**). To a solution of Compound **303** (448 mg, 1.5 mmol) in ethyl acetate (4 mL) was added a 1N hydrogen chloride solution in ethyl acetate (3 mL, 3 mmol) with stirring. The reaction mixture was concentrated under reduced pressure and dried in a vacuum oven at 40 °C for 48 h to give Compound **303-HCl** (427 mg, 84% yield) as a white solid.

[163] **^{1}H NMR** (D_2O, 400 MHz): δ1.84 (s, 2H), 7.22-7.25 (m, 2H), 7.32-7.37 (m, 2H). **LCMS** (method: SorbTech C_{18} AQ column, 2.1 x 50 mm; 5 – 95% acetonitrile/water with 0.1% formic acid in 14 min, with 4 min hold; wavelength: 210 nm): retention time: 5.4 min; 99.5% purity; (EI-MS): m/z=316.3 ($[M+H]^+$).

Example 8. Evaluation of Metabolic Stability of Compounds of the Invention in Human Liver Microsomes

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

[165] ***Determination of Metabolic Stability:*** 10.0 mM stock solutions of test compounds were prepared in DMSO. The 10.0 mM stock solutions were diluted to 12.5 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes were diluted to 2.5 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5 μM test compound was added to the microsomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 2.0 mg/mL human liver microsomes, 0.25 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 were incubated at 37 °C, and 50 μL aliquots were removed at 0, 10, 20, 30, 45 and 60 minutes and added to shallow-well 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4 °C for 20 minutes after which 100 μL of water was added to

the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were 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 was followed for pitolisant, the non-deuterated counterpart of the compound of Formula I, and the positive control, 7-ethoxycoumarin (1 μM). Testing was done in triplicate.

[166] Of the above-tested compounds, only the positive control, 7-ethoxycoumarin, was consumed to any appreciable amount. None of the deuterated test compounds, nor pitolisant showed any appreciable disappearance of parent under the above test conditions. As the results of the HLM study were inconclusive, further studies were conducted in CYP2D6 supersomes.

Example 9. Evaluation of Metabolic Stability of Compounds of the Invention in CYP2D6 Supersomes

[167] ***Materials:*** CYP 2D6 Supersomes (1000 pmol/mL) were obtained from Corning Gentest (Woburn, MA). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich.

Determination of Metabolic Stability: 10 mM stock solutions of test compounds were prepared in DMSO. The 10 mM stock solutions were diluted to 5.0μM in acetonitrile (ACN). The supersomes were diluted in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted supersomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 5.0 μM test compound was added to the microsomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 25 pmol/mL of CYP2D6 supersomes, 0.10 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 were incubated at 37°C, and 50 μL aliquots were removed at 0, 5, 10, 15, 20, and 30 minutes and added to shallow-well 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4 °C for 20 minutes after which 100 μL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate

and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Biosystems mass spectrometer.

[168] ***Data analysis:*** The *in vitro* $t_{1/2}$s for test compounds were 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]

[169] Data analysis was performed using Microsoft Excel Software.

[170] Figure 1 depicts graphically the results of this *in vitro* assay, showing the disappearance of test drug as a function of incubation time for each test compound at a concentration of 0.10 μM. Table 4, below, shows the numerical results for each compound tested at a concentration of 0.10 μM.

Table 4: Metabolic Stability of Compounds of the Invention versus Pitolisant in CYP2D6 Supersomes

Compound ID	AVE $t_{1/2}$ (min) [% Δ]*	AVE Clearance CLint (mL/min/kg) [Ratio (PCE/DCE)]
Pitolisant	9.7	1.6
115	4.7 **[-51.1%]**	3.0 **[1.9]**
300	7.6 **[-21.7%]**	1.9 **[1.2]**
301	5.0 **[-47.7%]**	2.9 **[1.8]**
103	6.7 **[-30.7%]**	2.2 **[1.4]**
125	4.5 **[-53.7%]**	3.2 **[2.0]**
303	7.4 **[-23.6%]**	2.1 **[1.3]**
302	4.3 **[-55.0%]**	3.3 **[2.1]**

PCE = protio chemical entity (pitolisant); DCE = deutero chemical entity (Compound 115, 103, 125, 300, 301, 302 or 303)

*% Δ = [(deuterated species)-(nondeuterated species)](100)/(nondeuterated species)

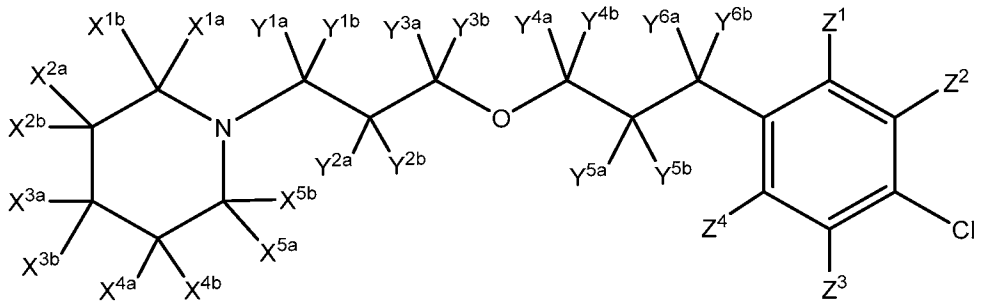
[171] Under the conditions outlined above for the CYP2D6 assay, all tested DCEs were consumed more rapidly than the PCE, pitolisant.

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

[173] 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.

We claim:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a} and X^{5b} is independently deuterium or hydrogen;

each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a} and Y^{6b} is independently deuterium or hydrogen; and

each of Z^1, Z^2, Z^3, and Z^4 is independently deuterium or hydrogen;

wherein at least one of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, Y^{3b}, Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, Y^{6b}, Z^1, Z^2, Z^3, or Z^4 is deuterium.

2. The compound of claim 1, wherein each of X^{1a} and X^{1b} is the same, each of X^{2a} and X^{2b} is the same, each of X^{3a} and X^{3b} is the same, each of X^{4a} and X^{4b} is the same, each of X^{5a} and X^{5b} is the same, each of Y^{1a} and Y^{1b} is the same, each of Y^{2a} and Y^{2b} 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, and each of Y^{6a} and Y^{6b} is the same.

3. The compound of claim 1 or 2, wherein each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is the same and each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is the same.

4. The compound of claim 3, wherein each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is deuterium and each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is hydrogen.

5. The compound of claim 3, wherein each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is hydrogen and each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is deuterium.

6. The compound of claim 3, wherein each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is deuterium and each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is deuterium.

7. The compound of claim 3, wherein each of X^{1a}, X^{1b}, X^{5a}, and X^{5b} is hydrogen and each of X^{2a}, X^{2b}, X^{4a}, and X^{4b} is hydrogen.

8. The compound of any of claims 1–7, wherein each of X^{3a} and X^{3b} is deuterium.

9. The compound of any of claims 1–7, wherein each of X^{3a} and X^{3b} is hydrogen.

10. The compound of any of claims 1-9, wherein each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is the same.

11. The compound of claim 10, wherein each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is deuterium.

12. The compound of claim 10, wherein each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is hydrogen.

13. The compound of any of claims 1-12, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same.

14. The compound of claim 13, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is deuterium.

15. The compound of claim 13, wherein each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is hydrogen.

16. The compound of any of claims 1-15, wherein each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is the same.

17. The compound of claim 16 wherein each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is deuterium.

18. The compound of claim 16, wherein each of Y^{4a}, Y^{4b}, Y^{5a}, Y^{5b}, Y^{6a}, and Y^{6b} is hydrogen.

19. The compound of any of claims 1-15, wherein each of Y^{4a}, Y^{4b}, Y^{6a}, and Y^{6b} is deuterium, and each Y^{5a} and Y^{5b} is hydrogen.

20. The compound of any of claims 1-18, wherein each of each of Z^1, Z^2, Z^3, and Z^4 are the same.

21. The compound of claim 19, wherein each of each of Z^1, Z^2, Z^3, and Z^4 is deuterium.

22. The compound of claim 19, wherein each of each of Z^1, Z^2, Z^3, and Z^4 is hydrogen.

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

24. The compound of claim 1, selected from any one of compounds in the following table, wherein each X^1 and X^5 is the same, each X^2 and X^4 is the same, each X^3 is the same, each Y^1,Y^2, and Y^3 is the same, each Y^4, Y^5, and Y^6 is the same, and each of Z^1, Z^2, Z^3, and Z^4 is hydrogen:

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
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

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
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, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

25. The compound of claim 1, selected from any one of compounds in the following table, wherein each X^1 and X^5 is the same, each X^2 and X^4 is the same, each X^3 is the same, each Y^1,Y^2, and Y^3 is the same, each Y^4, Y^5, and Y^6 is the same, and each of Z^1, Z^2, Z^3, and Z^4 is deuterium:

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
200	D	H	H	H	H
201	H	D	H	H	H
202	H	H	D	H	H
203	H	H	H	D	H
204	H	H	H	H	D
205	D	D	H	H	H
206	D	H	D	H	H
207	D	H	H	D	H

Compound	Each X^1 and X^5	Each X^2 and X^4	Each X^3	Each Y^1, Y^2, and Y^3	Each Y^4, Y^5, and Y^6
208	D	H	H	H	D
209	H	D	D	H	H
210	H	D	H	D	H
211	H	D	H	H	D
212	H	H	D	D	H
213	H	H	D	H	D
214	H	H	H	D	D
215	D	D	D	H	H
216	D	D	H	D	H
217	D	D	H	H	D
218	D	H	D	D	H
219	D	H	D	H	D
220	D	H	H	D	D
221	H	D	D	D	H
222	H	D	D	H	D
223	H	D	H	D	D
224	H	H	D	D	D
225	D	D	D	D	H
226	D	D	D	H	D
227	D	D	H	D	D
228	D	H	D	D	D
229	H	D	D	D	D
230	D	D	D	D	D
231	H	H	H	H	H

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

26. The compound of claim 1, selected from any one of compounds in the following table, wherein each of X^{1a}, X^{1b}, X^{2a}, X^{2b}, X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, and X^{5b} is the same (represented by each X^1, X^2, X^3, X^4, and X^5), each of Y^{1a}, Y^{1b}, Y^{2a}, Y^{2b}, Y^{3a}, and Y^{3b} is the same (represented by each Y^1, Y^2, and Y^3), each of Y^{4a}, Y^{4b}, Y^{6a}, and

Y^{6b} is the same (represented by each Y^4, and Y^6), each of Y^{5a}, and Y^{5b} is the same (represented by each Y^5), each of Z^1, Z^2, Z^3, and Z^4 is hydrogen:

Compound	Each X^1, X^2, X^3, X^4, and X^5	Each Y^1, Y^2, and Y^3	Each Y^4, and Y^6	Each Y^5
300	H	H	D	H
301	D	H	D	H
302	H	D	D	H
303	D	D	D	H
304	H	H	H	D
305	D	H	H	D
306	H	D	H	D
307	D	D	H	D

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

27. A pharmaceutical composition comprising a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. A method of inversely agonizing a histamine H3-receptor, or competitively antagonizing a histamine H3-receptor, in a cell, comprising contacting the cell with a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 26.

29. A method of treating a disease or condition beneficially treated by administering a histamine H3-receptor antagonist/inverse agonist to a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 26.

30. The method of claim 28, wherein the disease or condition is selected from Alzheimer's disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo, motion sickness, allergic and inflammatory diseases, narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime

sleepiness associated with obstructive sleep apnea, daytime sleepiness associated with Parkinson's disease, schizophrenia, schizoaffective disorder and Prader-Willi syndrome.

31. The method of claim 29, wherein the disease or condition is selected from narcolepsy with or without cataplexy, excessive daytime sleepiness, daytime sleepiness associated with obstructive sleep apnea, and daytime sleepiness associated with Parkinson's disease.

32. The method of claim 28, wherein the disease or condition is an addiction disorder due to dependency on stimulants, depressants, opiates, cocaine, nicotine or alcohol in a subject in need thereof.

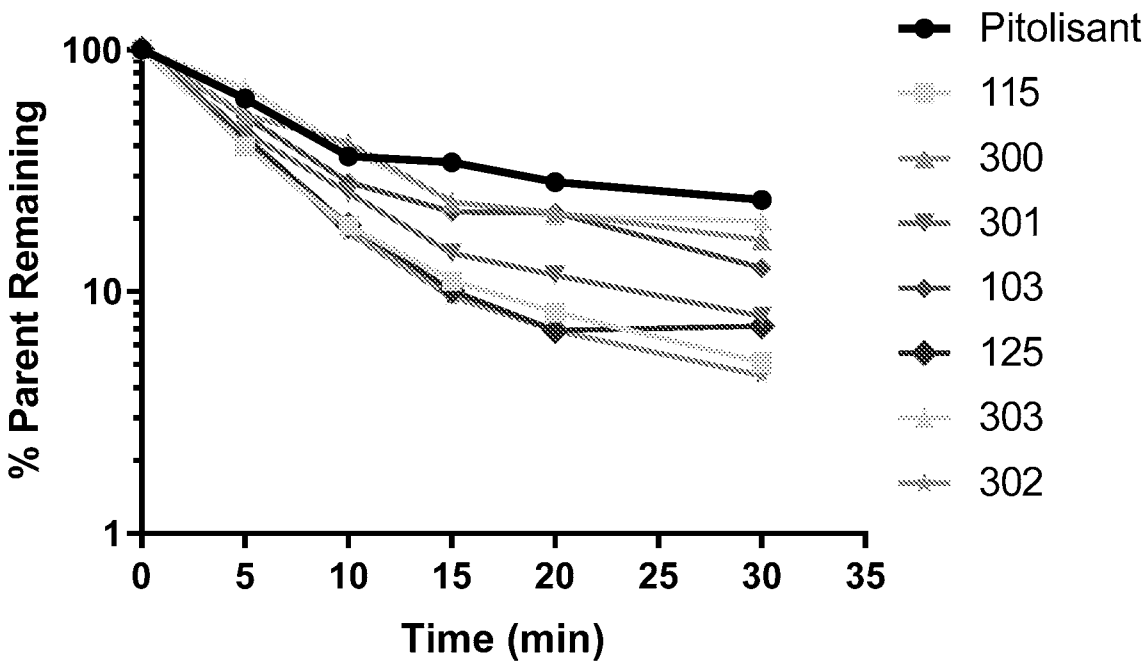

100
10
1
% Parent Remaining
0
5
10
15
20
25
30
35
Time (min)
Pitolisant
115
300
301
103
125
303
302

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/58909

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/137; A61K 31/4402 (2020.01)

CPC - A61K 31/137; A61K 31/4402; A61K 31/4422; A61K 31/522

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 8,207,197 B2 (Raga et al.) 26 June 2012 (26.06.2012); col 1, ln 40-45, col 11, ln 10-17	1-3, 6, 25
Y	US 2010/0240653 A1 (Santora et al.) 23 September 2010 (23.09.2010); abstract, para [0124], [0354]-[0355]	1-3, 6, 25
A	US 7,138,413 B1 (Schwartz et al.) 21 November 2006 (21.11.2006); entire document	1-3, 6, 25
A	WO 2018/172432 A1 (BIOPROJET PHARMA) 27 September 2018 (27.09.2018); entire document.	1-3, 6, 25
A	US 2008/0182876 A1 (Bertrand et al.) 31 July 2008 (31.07.2008); entire document	1-3, 6, 25

☐ 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
"D" document cited by the applicant in the international application
"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
03 February 2020	18 FEB 2020
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 Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/58909

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.: 8-23 and 27-32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6 and 25

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US 19/58909

--continued from Box No. III--

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

Group I+: Claims 1-7 and 24-26, directed to a compound of claim 1, formula I. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of formula listed wherein X1a, X1b, X2a, X2b, X3a, X3b, X4a, X4b, X5a and X5b is deuterium; Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a and Y6b is deuterium; Z1, Z2, Z3, and Z4 is deuterium. It is believed that claims 1-3, 6 and 25 reads on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1 wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of formula I wherein X1a, X1b, X2a, X2b, X3a, X3b, X4a, X4b, X5a and X5b is deuterium; Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a and Y6b is deuterium; Z1, Z2, Z3, and Z4 is hydrogen (i.e., claims 1-3, 6 and 24).

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

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 8,207,197 B2 to *Raga et al. (hereinafter Raga) in view of US 2010/0240653 A1 to Santora et al. (hereinafter Santora). Raga discloses the compound of* formula I wherein X1a, X1b, X2a, X2b, X3a, X3b, X4a, X4b, X5a and X5b is hydrogen; Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a and Y6b is hydrogen; Z1, Z2, Z3, and Z4 is hydrogen (col 1, ln 40-45) which is a histamine H3 receptor agonist (col 11, ln 10-17), but does not disclose wherein at least one of X1a, X1b, X2a, X2b, X3a, X3b, X4a, X4b, X5a, X5b, Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Z1, Z2, Z3, or Z4 is deuterium. However, Santora discloses compounds which are histamine H3 receptor agonists (abstract) are radiolabeled (para [0354]) wherein hydrogen atoms can be replaced with deuterium (para [0124]) at any/all positions (para [0354]). It would have been obvious to one with skill in the art to prepare the histamine H3 receptor agonist compound disclosed by Raga, wherein at least one hydrogen atom is radiolabeled as deuterium, as disclosed by Santora, at various positions (X1a, X1b, X2a, X2b, X3a, X3b, X4a, X4b, X5a, X5b, Y1a, Y1b, Y2a, Y2b, Y3a, Y3b, Y4a, Y4b, Y5a, Y5b, Y6a, Y6b, Z1, Z2, Z3, or Z4 is deuterium) by routine experimentation.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claims 8-23 and 27-32 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).