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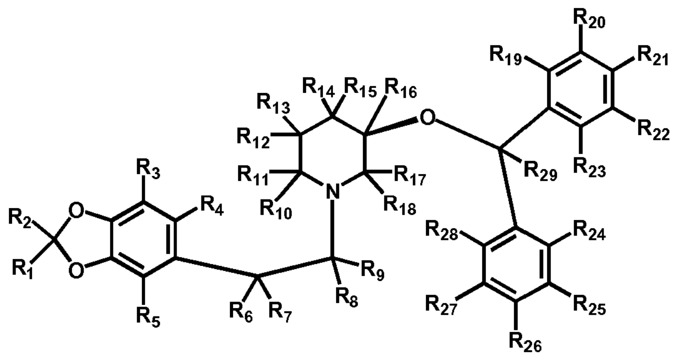
(54) Title: DEUTERATED ZAMIFENACIN DERIVATIVES




(I)

**(57) Abstract:** Disclosed herein are substituted piperidine-based muscarinic receptor modulators of Formula (I), process of preparation thereof, pharmaceutical compositions thereof, and methods of use thereof. At least one of the R groups is a deuterium atom.

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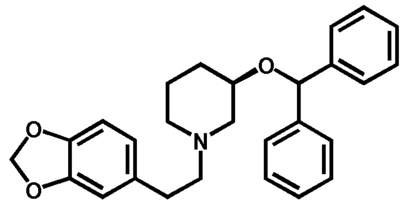
# DEUTERATED ZAMIFENACIN DERIVATIVES

[0001] This application claims the benefit of priority of United States provisional application No. 60/938,820, filed May 18, 2007, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

## FIELD

[0002] The present invention is directed to substituted piperidines, pharmaceutically acceptable salts and prodrugs thereof, the chemical synthesis thereof, and medical use of such compounds for the treatment and/or management of irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, any disorder associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by modulating muscarinic receptors.

## BACKGROUND

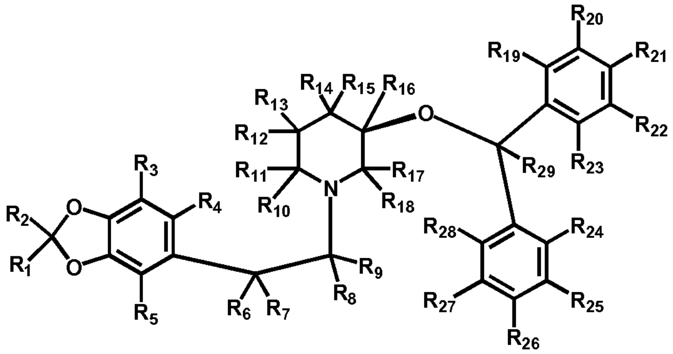


**Zamifenacin**

[0003] Zamifenacin (UK-76,654), 3-benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine, is an orally administered putative selective antagonist of the $M_3$ muscarinic receptor. It has been used as a therapy in a variety of physical and medical disorders, including disorders associated with altered smooth muscle contractility or tone, like IBS. Unlike other anticholinergics, such as hyoscyamine and dicyclomine, zamifenacin has much higher selecitivity for muscarinic $M_3$ receptors over muscarinic $M_2$ receptors. Other muscarinic $M_3$ receptor-selective anticholinergics include darifenacin and YM-905. (McRitchie et al, *British Journal of Pharmacology* **1993**, *109*, 38P Quinn et al, *British Journal of Pharmacology* **1993**, *109*, 37P; Wallis et al, *British Journal of Pharmacology* **1993**, *109*, 36P; Wallis, *Life Sciences* **1995**, *56*, 861-868; Beaumont et al, *Xenobiotica* **1996**, *26*, 459-471; Callahan, *Journal of Clinical Gastroenerology* **2002**, *35*(Suppl.), S58-S67).

## SUMMARY OF THE INVENTION

[0004] Disclosed herein is a compound having structural Formula I:



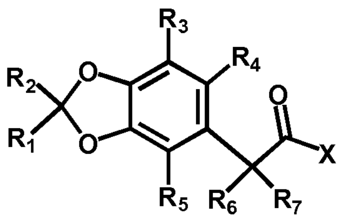
(I)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are selected from the group consisting of hydrogen or deuterium; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ is deuterium

[0005] Further disclosed herein is a compound having structural Formula II:



(II)

wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is selected from the group consisting of hydrogen or deuterium;

X is selected from the group consisting of hydroxyl, alkyloxy, and a leaving group; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is deuterium.

[0006] Also disclosed herein is a process for the manufacture of a compound having structural Formula I, comprising a reaction which contains a compound having structural Formula II.

[0007] Additionally, disclosed herein are methods of modulating muscarinic receptors.

[0008] Disclosed herein is a method for the treatment, prevention, or amelioration of one or more symptoms of a muscarinic-mediated disorder in a subject, comprising administering a therapeutically effective amount of a compound as disclosed herein.

[0009] Further disclosed herein is a method wherein the muscarinic-mediated disorder is selected from the group consisting of, but not limited to, irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, disorders associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by modulating muscarinic receptors.

[0010] Also disclosed herein are articles of manufacture and kits containing compounds as disclosed herein. By way of example only a kit or article of manufacture can include a container (such as a bottle) with a desired amount of at least one compound (or pharmaceutical composition of a compound) as disclosed herein. Further, such a kit or article of manufacture can further include instructions for using said compound (or pharmaceutical composition of a compound) disclosed herein. The instructions can be attached to the container, or can be included in a package (such as a box or a plastic or foil bag) holding the container.

[0011] In another aspect is the use of a compound as disclosed herein in the manufacture of a medicament for treating a disease or condition in an animal in which a muscarinic receptor contributes to the pathology and/or symptomology of the disorder. In a further embodiment, said disease or condition is irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, any disorders associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by modulating muscarinic receptors.

[0012] In another aspect are processes for preparing a compound as disclosed herein as a muscarinic receptor modulator.

[0013] Also disclosed herein are processes for formulating pharmaceutical compositions with a compound disclosed herein.

[0014] In certain embodiments said pharmaceutical composition comprises one or more release-controlling excipients.

[0015] In other embodiments said pharmaceutical composition further comprises one or more non-release controlling excipients.

[0016] In certain embodiments said pharmeaceutical composition is suitable for oral, parenteral, or intravenous infusion administration.

[0017] In yet other embodiments said pharmaceutical composition comprises a tablet, or capsule.

[0018] In certain embodiments the compounds as disclosed herein are administered in a dose of 0.5 milligram to 1000 milligram.

[0019] In yet further embodiments said pharmaceutical compositions further comprise another therapeutic agent.

[0020] In yet other embodiments said therapeutic agent is selected from the group consisting of prokinetics, tachykinins, anticholinergic agents, opioids, 5-$HT_3$ antagonists, alpha adrenergic agents, $CCK_A$ antagonists, NMDA receptor antagonists, serotoninergic agents, endothelin converting enzyme (ECE) inhibitors, thromboxane enzyme antagonists, potassium channel openers, thrombin inhibitors, growth factor inhibitors, platelet activating factor (PAF) antagonists, anti-platelet agents, Factor VIIa Inhibitors, Factor Xa Inhibitors, renin inhibitors, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, anti-atherosclerotic agents, MTP Inhibitors, calcium channel blockers, potassium channel activators, alpha-PDE5 agents, beta-PDE5 agents, antiarrhythmic agents, diuretics, anti-diabetic agents, PPAR-gamma agonists, mineralocorticoid enzyme antagonists, aP2 inhibitors, protein tyrosine kinase inhibitors, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-disruptor agents, microtubule-stablizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, antalarmin, Z-338, and platinum coordination complexes.

[0021] In yet other embodiments said therapeutic agent is a prokinetic.

[0022] In further embodiments said prokinetic is selected from the group consisting of cisapride, domperidone, lirexapride, metoclopramide, mosapride, neurotrophin-3, norcisapride, prucalipride, renzapride, tegaserod, TS-951, and YM-53389.

[0023] In yet other embodiments said therapeutic agent is a tachykinin.

[0024] In further embodiments said tachykinin is selected from the group consisting of exlopitant, nepadudant, and SR-140333.

[0025] In yet other embodiments said therapeutic agent is an anticholinergic agent.

[0026] In further embodiments said anticholinergic agent is selected from the group consisting of darifenacin, dicyclomine, hyoscyamine, and YM-905.

[0027] In yet other embodiments said therapeutic agent is an opioid.

[0028] In further embodiments said opioid is selected from the group consisting of morphine, codeine, thebain, diacetylmorphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, nicomorphine, fentanyl, 3-methylfentanyl, alfentanil, sufentanil, remifentanyl, carfentanyl, ohmefentanyl, pethidine, ketobemidone, propoxyphene, dextropropoxyphene, methadone, loperamide, pentazocine, buprenorphine, etorphine, butorphanol, nalbufine, levorphanol, naloxone, naltrexone, and tramadol.

[0029] In yet other embodiments said therapeutic agent a 5-$HT_3$ antagonist.

[0030] In further embodiments said 5-$HT_3$ antagonist is selected from the group consisting of alosetron, cilansetron, granisectron, and ondansetron.

[0031] In yet other embodiments said therapeutic agent a $CCK_A$ antagonist.

[0032] In further embodiments said $CCK_A$ antagonist is selected from the group consisting of dexloxigumide, loxiglumide, proglumide, and proxiglumide.

[0033] In yet other embodiments said therapeutic agent is a NMDA receptor antagonist.

[0034] In further embodiments said NMDA receptor antagonist is selected from the group consisting of dizocilpine, and memantine.

[0035] In yet other embodiments said therapeutic agent a serotoninergic agent.

[0036] In further embodiments said serotoninergic agent is selected from the group consisting of buspirone, piboserod, and sumatriptan.

[0037] In yet other embodiments said therapeutic is selected from the group consisting of antalarmin and Z-338.

[0038] In other embodiments, a method for the treatment, prevention, or amelioration of one or more symptoms of a muscarinic receptor-mediated disorder in a subject comprises administering a therapeutically effective amount of a compound as disclosed herein.

[0039] In yet other embodiments said muscarinic receptor-mediated disorder is selected from the group consisting of irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), and urinary incontinence.

[0040] In further embodiments said muscarinic receptor-mediated disorder is associated with smooth muscle tone or smooth muscle contractility.

[0041] In other embodiments said muscarinic receptor-mediated disorder can be lessened, alleviated, or prevented by administering a muscarinic receptor modulator.

[0042] In other embodiments said compound has at least one of the following properties:

**a)** decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;
**b)** increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
**c)** decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
**d)** increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
**e)** an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0043] In yet further embodiments said compound has at least two of the following properties:

**a)** decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;
**b)** increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
**c)** decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
**d)** increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
**e)** an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0044] In certain embodiments said compound has a decreased metabolism by at least one polymorphically-expressed cytochrome $P_{450}$ isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0045] In other embodiments said cytochrome $P_{450}$ isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0046] In yet further embodiments said compound is characterized by decreased inhibition of at least one cytochrome $P_{450}$ or monoamine oxidase isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0047] In certain embodiments said cytochrome $P_{450}$ or monoamine oxidase isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, $MAO_A$, and $MAO_B$.

[0048] In other embodiments said method method affects the treatment of the disorder while reducing or eliminating a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

[0049] In yet further embodiments said diagnostic hepatobiliary function endpoint is selected from the group consisting of alanine aminotransferase (“ALT”), serum glutamic-pyruvic transaminase (“SGPT”), aspartate aminotransferase (“AST,” “SGOT”), ALT/AST ratios, serum aldolase, alkaline phosphatase (“ALP”), ammonia levels, bilirubin, gamma-glutamyl transpeptidase (“GGTP,” “γ-GTP,” “GGT”), leucine aminopeptidase (“LAP”), liver biopsy, liver ultrasonography, liver nuclear scan, 5’-nucleotidase, and blood protein.

## INCORPORATION BY REFERENCE

[0050] All publications and references cited herein, including those in the background section, are expressly incorporated herein by reference in their entirety. However, with respect to any similar or identical terms found in both the incorporated publications or references and those expressly put forth or defined in this document, then those terms definitions or meanings expressly put forth in this document shall control in all respects.

## DETAILED DESCRIPTION

[0051] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

[0052] As used herein, the singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0053] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human monkey, chimpanzee, gorilla, and the like), rodents (e.g., rats, mice, gerbils, hamsters, ferrets, and the like), lagomorphs, swine (e.g., pig, miniature pig), equine, canine, feline, and the like. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human patient.

[0054] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder; or alleviating or abrogating one or more of the symptoms associated with the disorder; and/or alleviating or eradicating the cause(s) of the disorder itself.

[0055] The terms "prevent," "preventing," and "prevention" refer to a method of delaying or precluding the onset of a disorder; delaying or precluding its attendant symptoms; barring a subject from acquiring a disorder; and/or reducing a subject's risk of acquiring a disorder.

[0056] The term "therapeutically effective amount" refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0057] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenecity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. S*ee, Remington: The Science and Practice of Pharmacy*, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition; Rowe et al., Eds., The Pharmaceutical Press and the American

Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004).

[0058] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy.

[0059] The term "is/are deuterium," when used to describe a given position in a molecule such as $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ or the symbol "D," when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In an embodiment deuterium enrichment is of no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

[0060] The term "isotopic enrichment" refers to the percentage of incorporation of a less prevalent isotope of an element at a given position in a molecule in the place of the more prevalent isotope of the element.

[0061] The term "non-isotopically enriched" refers to a molecule in which the percentages of the various isotopes are substantially the same as the naturally occurring percentages.

[0062] The terms "substantially pure" and "substantially homogeneous" mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, or biological and pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, “substantially pure” or “substantially homogeneous” refers to a collection of molecules, wherein at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the molecules are a single compound, including a racemic mixture or single stereoisomer thereof, as determined by standard analytical methods.

[0063] The term “about” or “approximately” means an acceptable error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, “about” can mean 1 or more standard deviations.

[0064] The terms “active ingredient” and “active substance” refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients and/or carriers, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0065] The terms “drug,” “therapeutic agent,” and “chemotherapeutic agent” refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0066] The term “disorder” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disease,” “sydrome” and “condition” (as in medical condition), in that all reflect an abnormal condition of the body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

[0067] The term “release controlling excipient” refers to an excipient whose primary function is to modify the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0068] The term “nonrelease controlling excipient” refers to an excipient whose primary function do not include modifying the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0069] The term “muscarinic receptor” refers to the class of G-protein coupled receptors that facilitates neuroendocrine signaling through binding to its natural ligand, acetylcholine. Other acetylcholine-binding receptors exist, such as nicotinic receptors which are quite distinct, acting as ion-gated signaling proteins.

[0070] The terms “$M_3$ receptor” refers to a specific member of the class of muscaric G-protein coupled receptors.

[0071] The term "muscarinic receptor-mediated disorder" refers to a disorder that is characterized by abnormal muscarinic receptor activity or normal muscarinic receptor activity that, when that activity is modified, leads to the amelioration of other abnormal biological processes. A muscarinic receptor-mediated disorder may be completely or partially mediated by the muscarinic receptor. In particular, a muscarinic receptor-mediated disorder is one in which modulation of the muscarinic receptor activity results in some effect on the underlying disorder, e.g., a muscarinic receptor modulator results in some improvement in at least some of the patients being treated.

[0072] The term "muscarinic receptor modulator" or "modulation of muscarinic receptors" refers to the ability of a compound disclosed herein to alter the function of a muscarinic receptor. A modulator may activate the activity of a muscarinic receptor, may activate or inhibit the activity of a muscarinic receptor depending on the concentration of the compound exposed to the muscarinic receptor, or may inhibit the activity of a muscarinic receptor. Such activation or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types. The term "muscarinic receptor modulator" or "modulation of muscarinic receptors" also refers to altering the function of a muscarinic receptor by increasing or decreasing the probability that a complex forms between a muscarinic receptor and a natural binding partner. A muscarinic receptor modulator may increase the probability that such a complex forms between the muscarinic receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the muscarinic receptor and the natural binding partner depending on the concentration of the compound exposed to the muscarinic receptor, and or may decrease the probability that a complex forms between the muscarinic receptor and the natural binding partner. In some embodiments, modulation of the muscarinic receptor may be assessed using Receptor Selection and Amplification Technology (R-SAT) as described in U.S. Pat. No. 5,707,798, the disclosure of which is incorporated herein by reference in its entirety.

[0073] The term "protecting group" or "removable protecting group" refers to a group which, when bound to a functionality, such as the oxygen atom of a hydroxyl or carboxyl group, or the nitrogen atom of an amino group, prevents reactions from occurring at that functional group, and which can be removed by a conventional chemical or enzymatic step to reestablish the functional group (Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999).

[0074] The term "halogen", "halide" or "halo" includes fluorine, chlorine, bromine, and iodine.

[0075] The term "leaving group" (LG) refers to any atom (or group of atoms) that is stable in its anion or neutral form after it has been displaced by a nucleophile and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "leaving group" includes but is not limited to: water, methanol, ethanol, chloride, bromide, iodide, an alkylsulfonate, for example methanesulfonate, ethanesulfonate and the like, an arylsulfonate, for example benzenesulfonate, tolylsulfonate and the like, a perhaloalkanesulfonate, for example trifluoromethanesulfonate, trichloromethanesulfonate and the like, an alkylcarboxylate, for example acetate and the like, a perhaloalkylcarboxylate, for example trifluoroacetate, trichloroacetate and the like, an arylcarboxylate, for example benzoate and the like, an N-hydroxyimide anion, for example N-hydroxymaleimide anion, N-hydroxysuccinimide anion, N-hydroxyphthalimide anion, N-hydroxysulfosuccinimide anion and the like.

[0076] The term "coupling reagent" refers to any reagent that will activate the carbonyl of a carboxylic acid and facilitate the formation of an ester or amide bond. The definition of "coupling reagent" includes but is not limited to: acetyl chloride, ethyl chloroformate, dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino- phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like.

[0077] The terms "alkyl" and "substituted alkyl" are interchangeable and include substituted, optionally substituted and unsubstituted $C_1$-$C_{10}$ straight chain saturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted $C_2$-$C_{10}$ straight chain unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted $C_2$-$C_{10}$ branched saturated aliphatic hydrocarbon groups, substituted and unsubstituted $C_2$-$C_{10}$ branched unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted $C_3$-$C_8$ cyclic saturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted $C_5$-$C_8$ cyclic unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, the definition of "alkyl" shall include but is not limited to: methyl (Me), trideuteromethyl (-$CD_3$), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, adamantyl, norbornyl and the like. Alkyl substituents are independently selected from the group consisting of hydrogen, deuterium, halogen, -OH, -SH, -$NH_2$, -CN, -$NO_2$, =O, =$CH_2$, trihalomethyl, carbamoyl, aryl$C_{0-10}$alkyl, heteroaryl$C_{0-10}$alkyl, $C_{1-10}$alkyloxy, aryl$C_{0-10}$alkyloxy, $C_{1-10}$alkylthio, aryl$C_{0-10}$alkylthio, $C_{1-10}$alkylamino, aryl$C_{0-10}$alkylamino, N-aryl-N-$C_{0-10}$alkylamino, $C_{1-10}$alkylcarbonyl, aryl$C_{0-10}$alkylcarbonyl, $C_{1-10}$alkylcarboxy, aryl$C_{0-10}$alkylcarboxy, $C_{1-10}$alkylcarbonylamino, aryl$C_{0-10}$alkylcarbonylamino, tetrahydrofuryl, morpholinyl, piperazinyl, hydroxypyronyl, -$C_{0-10}$alkylCOO$R_{30}$ and -$C_{0-10}$alkylCON$R_{31}R_{32}$ wherein $R_{30}$, $R_{31}$ and $R_{32}$ are independently selected from the group consisting of hydrogen, deuterium, alkyl, aryl, or $R_{32}$ and $R_{33}$ are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined herein.

[0078] The term "aryl" represents an unsubstituted, mono-, or polysubstituted monocyclic, polycyclic, biaryl aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-phenyl, 4-naphthyl and the like). The aryl substituents are independently selected from the group consisting of hydrogen, deuterium, halogen, -OH, -SH, -CN, -$NO_2$, trihalomethyl, hydroxypyronyl, $C_{1-10}$alkyl, aryl$C_{0-10}$alkyl, $C_{0-10}$alkyloxy$C_{0-10}$alkyl, aryl$C_{0-10}$alkyloxy$C_{0-10}$alkyl, $C_{0-10}$alkylthio$C_{0-10}$alkyl, aryl$C_{0-10}$alkylthio$C_{0-10}$alkyl, $C_{0-10}$alkylamino$C_{0-10}$alkyl, aryl$C_{0-10}$alkylamino$C_{0-10}$alkyl, N-aryl-N-$C_{0-10}$alkylamino$C_{0-10}$alkyl, $C_{1-10}$alkylcarbonyl$C_{0-10}$alkyl, aryl$C_{0-10}$alkylcarbonyl$C_{0-10}$alkyl, $C_{1-10}$alkylcarboxy$C_{0-10}$alkyl, aryl$C_{0-10}$alkylcarboxy$C_{0-10}$alkyl, $C_{1-10}$alkylcarbonylamino$C_{0-10}$alkyl, aryl$C_{0-10}$alkylcarbonylamino$C_{0-10}$alkyl, –$C_{0-10}$alkylCOO$R_{30}$, and –$C_{0-10}$alkylCON$R_{31}R_{32}$ wherein $R_{30}$, $R_{31}$ and $R_{32}$ are independently selected from the group consisting of hydrogen, deuterium, alkyl, aryl or $R_{31}$ and $R_{32}$ are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

[0079] The definition of "aryl" includes but is not limited to phenyl, pentadeuterophenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl, indanyl, azulenyl, anthryl, phenanthryl, fluorenyl, pyrenyl and the like.

[0080] In light of the purposes described in the present disclosure, all references to "alkyl" and "aryl" groups or any groups ordinarily containing C-H bonds may include partially or fully deuterated versions as required to affect the improvements outlined herein.

**Deuterium Kinetic Isotope Effect**

[0081] In an attempt to eliminate foreign substances, such as therapeutic agents, from its circulation system, the animal body expresses various enzymes, such as the cytochrome $P_{450}$ enzymes or CYPs, esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C-H) bond to either a carbon-oxygen (C-O) or carbon-carbon (C-C) $\pi$-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses.

[0082] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, $k = Ae^{-Eact/RT}$, where $E_{act}$ is the activation energy, T is temperature, R is the molar gas constant, k is the rate constant for the reaction, and A (the frequency factor) is a constant specific to each reaction that depends on the probability that the molecules will collide with the correct orientation. The Arrhenius equation states that the fraction of molecules that have enough energy to overcome an energy barrier, that is, those with energy at least equal to the activation energy, depends exponentially on the ratio of the activation energy to thermal energy (RT), the average amount of thermal energy that molecules possess at a certain temperature.

[0083] The transition state in a reaction is a short lived state (on the order of $10^{-14}$ sec) along the reaction pathway during which the original bonds have stretched to their limit. By definition, the activation energy $E_{act}$ for a reaction is the energy required to reach the transition state of that reaction. Reactions that involve multiple steps will necessarily have a number of transition states, and in these instances, the activation energy for the reaction is equal to the energy difference between the reactants and the most unstable transition state. Once the transition state is reached, the molecules can either revert, thus reforming the original reactants, or the new bonds form giving rise to the products. This dichotomy is possible because both pathways, forward and reverse, result in the release of energy. A catalyst facilitates a reaction process by lowering the activation energy leading to a transition state. Enzymes are examples of biological catalysts that reduce the energy necessary to achieve a particular transition state.

[0084] A carbon-hydrogen bond is by nature a covalent chemical bond. Such a bond forms when two atoms of similar electronegativity share some of their valence electrons, thereby creating a force that holds the atoms together. This force or bond strength can be quantified and is expressed in units of energy, and as such, covalent bonds between various atoms can be classified according to how much energy must be applied to the bond in order to break the bond or separate the two atoms.

[0085] The bond strength is directly proportional to the absolute value of the ground-state vibrational energy of the bond. This vibrational energy, which is also known as the zero-point vibrational energy, depends on the mass of the atoms that form the bond. The absolute value of the zero-point vibrational energy increases as the mass of one or both of the atoms making the bond increases. Since deuterium (D) is two-fold more massive than hydrogen (H), it follows that a C-D bond is stronger than the corresponding C-H bond. Compounds with C-D bonds are frequently indefinitely stable in $H_2O$, and have been widely used for isotopic studies. If a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), then substituting a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE) and can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small size of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. A deuterium is larger and statistically has a much lower probability of undergoing this phenomenon. Substitution of tritium for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects.

[0086] Discovered in 1932 by Urey, deuterium (D) is a stable and non-radioactive isotope of hydrogen. It was the first isotope to be separated from its element in pure form and is twice as massive as hydrogen, and makes up about 0.02% of the total mass of hydrogen (in this usage meaning all hydrogen isotopes) on earth. When two deuteriums bond with one oxygen, deuterium oxide ($D_2O$ or "heavy water") is formed. $D_2O$ looks and tastes like $H_2O$, but has different physical properties. It boils at 101.41 °C and freezes at 3.79 °C. Its heat capacity, heat of fusion, heat of vaporization, and entropy are all higher than $H_2O$. It is also more viscous and is not as powerful a solvent as $H_2O$.

[0087] When pure $D_2O$ is given to rodents, it is readily absorbed and reaches an equilibrium level that is usually about eighty percent of the concentration of what was consumed. The quantity of deuterium required to induce toxicity is extremely high. When 0% to as much as 15% of the body water has been replaced by $D_2O$, animals are healthy but are unable to gain weight as fast as the control (untreated) group. When about 15% to about 20% of the body water has been replaced with $D_2O$, the animals become excitable. When about 20% to about 25% of the body water has been replaced with $D_2O$, the animals are so excitable that they go into frequent convulsions when stimulated. Skin lesions, ulcers on the paws and muzzles, and necrosis of the tails appear. The animals also become very aggressive; males becoming almost unmanageable. When about 30%, of the body water has been replaced with $D_2O$, the animals refuse to eat and become comatose. Their body weight drops sharply and their metabolic rates drop far below normal, with death occurring at about 30 to about 35% replacement with $D_2O$. The effects are reversible unless more than thirty percent of the previous body weight has been lost due to $D_2O$. Studies have also shown that the use of $D_2O$ can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

[0088] Tritium (T) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Mixing tritium with a phosphor provides a continuous light source, a technique that is commonly used in wristwatches, compasses, rifle sights and exit signs. It was discovered by Rutherford, Oliphant and Harteck in 1934, and is produced naturally in the upper atmosphere when cosmic rays react with $H_2$ molecules. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as $T_2O$, a colorless and odorless liquid. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level.

[0089] Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. For example, DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching which may even give rise to an oxidative intermediate with a faster off-rate from an activating Phase I enzyme (e.g., cytochrome $P_{450}$ 3A4). The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and have not been heretofore sufficiently predictable *a priori* for any drug class.

**Deuterated Piperidine Derivatives**

[0090] Zamifenacin is a substituted piperidine-based muscarinic receptor modulator. The carbon-hydrogen bonds of zamifenacin contain a naturally occurring distribution of hydrogen isotopes, namely $^{1}H$ or protium (about 99.9844%), $^{2}H$ or deuterium (about 0.0156%), and $^{3}H$ or tritium (in the range between about 0.5 and 67 tritium atoms per $10^{18}$ protium atoms). Increased levels of deuterium incorporation may produce a detectable Kinetic Isotope Effect (KIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic profiles of such muscarinic receptor modulators in comparison with the compound having naturally occurring levels of deuterium.

[0091] The zamifenacin chemical structure contains a number of moieties that we posit will produce inactive (at best) and toxic (at worst) metabolites, the formation of which can be prevented or diminished by the approach described herein.

[0092] The C-H bonds of the methylene group alpha to the oxygen atom of the dioxolane moiety are enzymatically oxidized. The resultant metabolite may further break down to the catechol or close variant that can then be further transformed to a reactive ortho quinone. Reactive ortho quinones are known to produce hepato- and other toxicities.

[0093] The two distinct benzylic positions are susceptible to enzymatic oxidation and such oxidation can shorten the half-life and produce metabolites with as-yet-unknown pharmacology/toxicology.

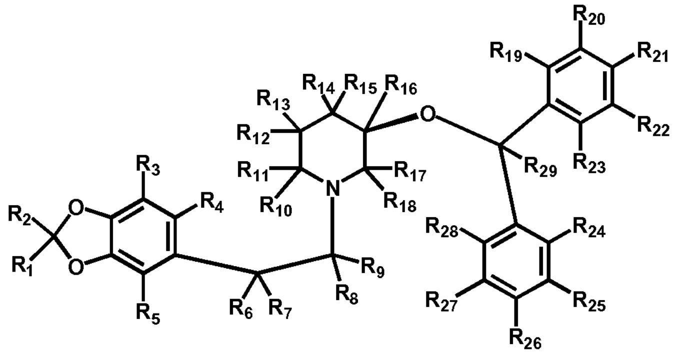
[0094] The C-H bonds alpha to the piperidinyl ring nitrogen are also highly susceptible to oxidation, whether by $P_{450}$ enzymes or other oxidative processes.

[0095] The toxicity and pharmacology of the resultant aforementioned metabolite/s are not known with certainty but oxidation of C-H may lead to the formation of reactive metabolites which can be toxic. Limiting the production of such metabolites has the potential to decrease the danger of the administration of such drugs and may even allow increased dosage and concomitant increased efficacy.

[0096] All of these transformations, among other potential transformations, can occur through polymorphically-expressed enzymes thus exacerbating the interpatient variability for the compound. Further, it is quite typical for disorders ameliorated by the present disclosure, such as irritable bowel syndrome, to produce chronic symptoms best medicated around the clock, thus supporting the likelihood that a longer half-life medicine will diminish these problems with greater efficacy.

[0097] Various deuteration patterns can be used to a) reduce or eliminate unwanted metabolites, b) increase the half-life of the parent drug, c) decrease the number of doses needed to achieve a desired effect, d) decrease the amount of a dose needed to achieve a desired effect, e) increase the formation of active metabolites, if any are formed, and/or f) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for polypharmacy, whether the polypharmacy be intentional or not. The deuteration approach has strong potential to slow metabolism via various oxidative mechanisms and attenuate interpatient variatability.

[0098] In one embodiment, disclosed herein is a compound having structural Formula I:



(I)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are selected from the group consisting of hydrogen or deuterium; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ is deuterium.

[0099] In another embodiment, at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[00100] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[00101] In other embodiments, $R_1$ is hydrogen. In yet other embodiments, $R_2$ is hydrogen. In still other embodiments, $R_3$ is hydrogen. In yet other embodiments, $R_4$ is hydrogen. In some embodiments, $R_5$ is hydrogen. In yet other embodiments, $R_6$ is hydrogen. In still other embodiments, $R_7$ is hydrogen. In still other embodiments, $R_8$ is hydrogen. In some embodiments, $R_9$ is hydrogen. In other embodiments, $R_{10}$ is hydrogen. In yet other embodiments, $R_{11}$ is hydrogen. In still other embodiments, $R_{12}$ is hydrogen. In yet other

embodiments, $R_{13}$ is hydrogen. In other embodiments, $R_{14}$ is hydrogen. In certain embodiments, $R_{15}$ is hydrogen. In other embodiments, $R_{16}$ is hydrogen. In yet other embodiments, $R_{17}$ is hydrogen. In some embodiments, $R_{18}$ is hydrogen. In other embodiments, $R_{19}$ is hydrogen. In yet other embodiments, $R_{20}$ is hydrogen. In yet other embodiments, $R_{21}$ is hydrogen. In yet other embodiments, $R_{22}$ is hydrogen. In yet other embodiments, $R_{23}$ is hydrogen. In yet other embodiments, $R_{24}$ is hydrogen. In yet other embodiments, $R_{25}$ is hydrogen. In yet other embodiments, $R_{26}$ is hydrogen. In yet other embodiments, $R_{27}$ is hydrogen. In yet other embodiments, $R_{28}$ is hydrogen. In yet other embodiments, $R_{29}$ is hydrogen.

[00102] In other embodiments, $R_1$ is deuterium. In yet other embodiments, $R_2$ is deuterium. In still other embodiments, $R_3$ is deuterium. In yet other embodiments, $R_4$ is deuterium. In some embodiments, $R_5$ is deuterium. In yet other embodiments, $R_6$ is deuterium. In still other embodiments, $R_7$ is deuterium. In still other embodiments, $R_8$ is deuterium. In some embodiments, $R_9$ is deuterium. In other embodiments, $R_{10}$ is deuterium. In yet other embodiments, $R_{11}$ is deuterium. In still other embodiments, $R_{12}$ is deuterium. In yet other embodiments, $R_{13}$ is deuterium. In other embodiments, $R_{14}$ is deuterium. In certain embodiments, $R_{15}$ is deuterium. In other embodiments, $R_{16}$ is deuterium. In yet other embodiments, $R_{17}$ is deuterium. In some embodiments, $R_{18}$ is deuterium. In other embodiments, $R_{19}$ is deuterium. In yet other embodiments, $R_{20}$ is deuterium. In yet other embodiments, $R_{21}$ is deuterium. In yet other embodiments, $R_{22}$ is deuterium. In yet other embodiments, $R_{23}$ is deuterium. In yet other embodiments, $R_{24}$ is deuterium. In yet other embodiments, $R_{25}$ is deuterium. In yet other embodiments, $R_{26}$ is deuterium. In yet other embodiments, $R_{27}$ is deuterium. In yet other embodiments, $R_{28}$ is deuterium. In yet other embodiments, $R_{29}$ is deuterium.

[00103] In yet another embodiment, at least one of $R_1$ and $R_2$ is deuterium.

[00104] In yet another embodiment, $R_1$ and $R_2$ are deuterium.

[00105] In yet another embodiment, at least one of $R_3$, $R_4$, and $R_5$ is deuterium.

[00106] In yet another embodiment, $R_3$, $R_4$, and $R_5$ are deuterium.

[00107] In yet another embodiment, at least one of $R_6$ and $R_7$ is deuterium.

[00108] In yet another embodiment, $R_6$ and $R_7$ are deuterium.

[00109] In yet another embodiment, at least one of $R_8$ and $R_9$ is deuterium.

[00110] In yet another embodiment, $R_8$ and $R_9$ are deuterium.

[00111] In yet another embodiment, at least one of $R_{10}$ and $R_{11}$ is deuterium.

[00112] In yet another embodiment, $R_{10}$ and $R_{11}$ are deuterium.

[00113] In yet another embodiment, at least one of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, and $R_{16}$ is deuterium.

[00114] In yet another embodiment, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, and $R_{16}$ are deuterium.

[00115] In yet another embodiment, at least one of $R_{17}$ and $R_{18}$ is deuterium.

[00116] In yet another embodiment, $R_{17}$ and $R_{18}$ are deuterium.

[00117] In yet another embodiment, at least one of $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$ and $R_{28}$ is deuterium.

[00118] In yet another embodiment, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$ and $R_{28}$ are deuterium.

[00119] In yet another embodiment, $R_{29}$ is deuterium.

[00120] In yet another embodiment, at least one of $R_1$ and $R_2$ is deuterium; and $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00121] In yet another embodiment, $R_1$ and $R_2$ are deuterium; and $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00122] In yet another embodiment, at least one of $R_3$, $R_4$, and $R_5$ is deuterium; and $R_1$, $R_2$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00123] In yet another embodiment, $R_3$, $R_4$, and $R_5$ are deuterium; and $R_1$, $R_2$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00124] In yet another embodiment, at least one of $R_6$ and $R_7$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00125] In yet another embodiment, $R_6$ and $R_7$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00126] In yet another embodiment, at least one of $R_8$ and $R_9$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00127] In yet another embodiment, $R_8$ and $R_9$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00128] In yet another embodiment, at least one of $R_{10}$ and $R_{11}$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00129] In yet another embodiment, $R_{10}$ and $R_{11}$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00130] In yet another embodiment, at least one of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00131] In yet another embodiment, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

[00132] In yet another embodiment, at least one of $R_{17}$ and $R_{18}$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

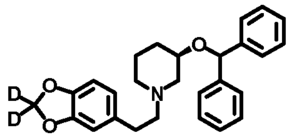
[00133] In yet another embodiment, $R_{17}$ and $R_{18}$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are hydrogen.

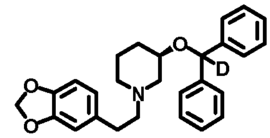
[00134] In yet another embodiment, at least one of $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$ and $R_{28}$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$ and $R_{29}$ are hydrogen.

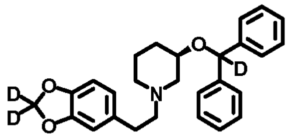
[00135] In yet another embodiment, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$ and $R_{28}$ are deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$ and $R_{29}$ are hydrogen.

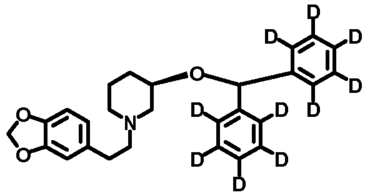
[00136] In yet another embodiment, $R_{29}$ is deuterium; and $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$ and $R_{28}$ are hydrogen.

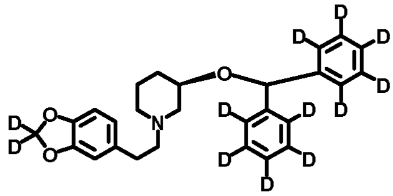
[00137] In yet another embodiment, the compound as disclosed herein is selected from the group consisting of:

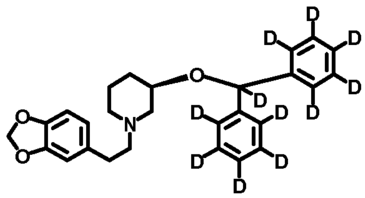


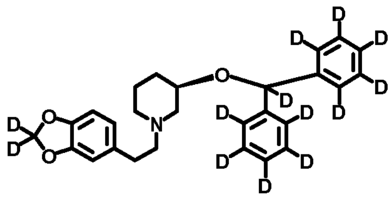


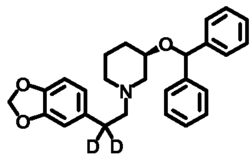


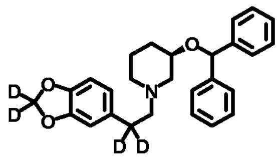


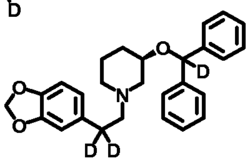


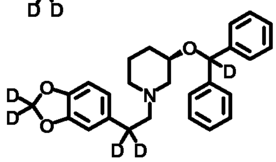


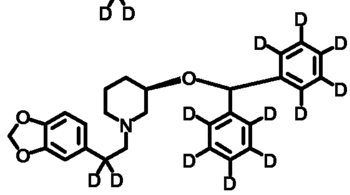


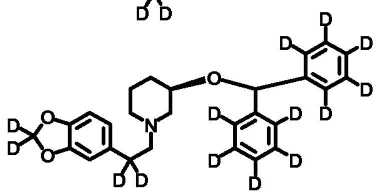


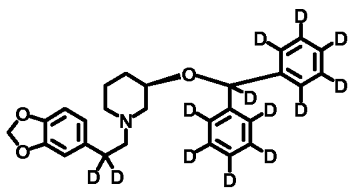


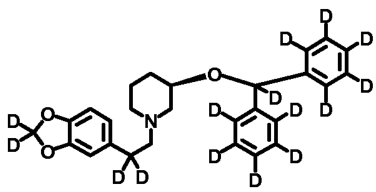


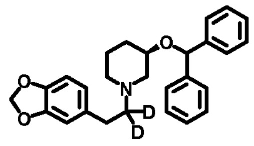
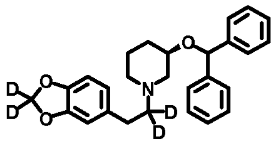
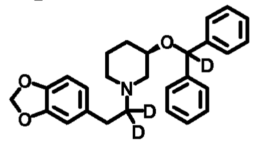
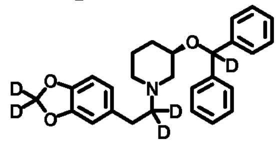
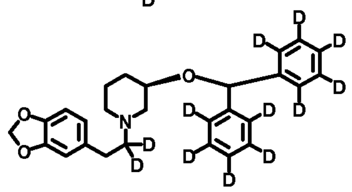
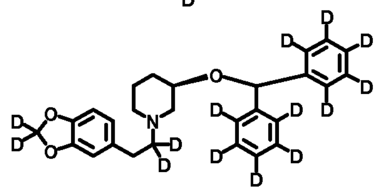
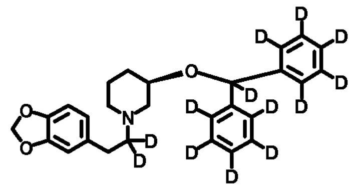
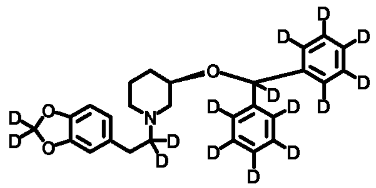
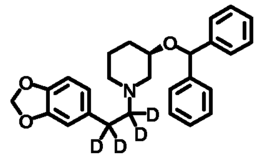
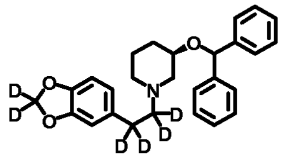
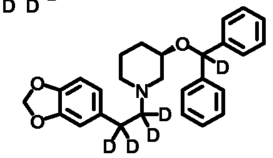
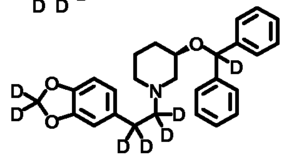
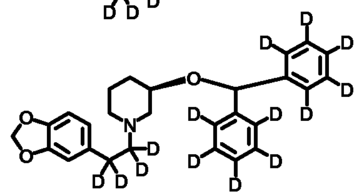
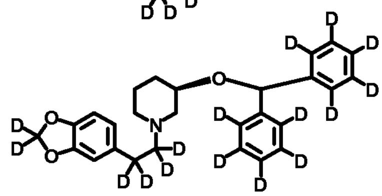
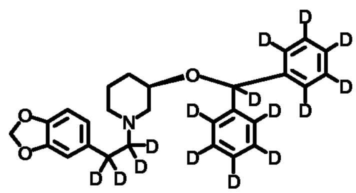
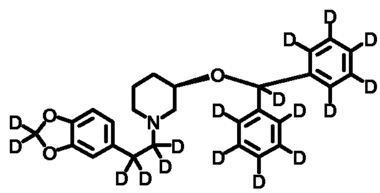


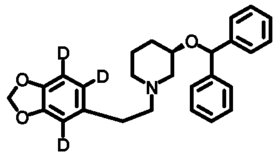
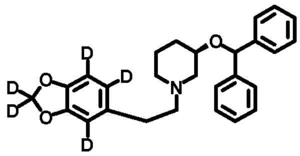
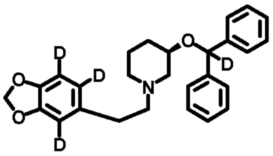
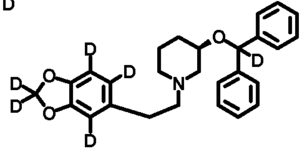
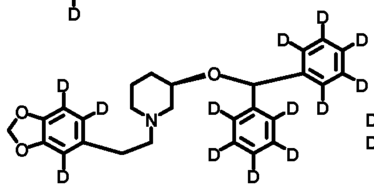
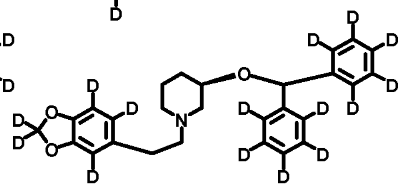
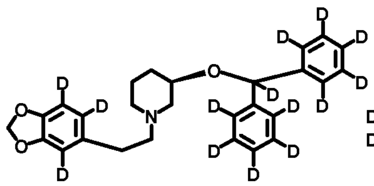
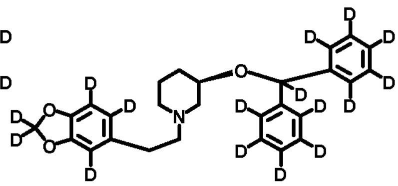
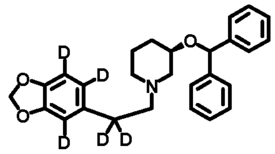
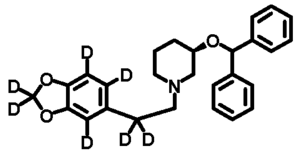
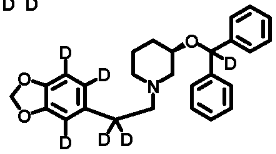
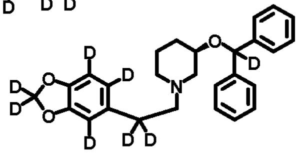
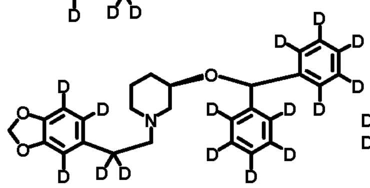
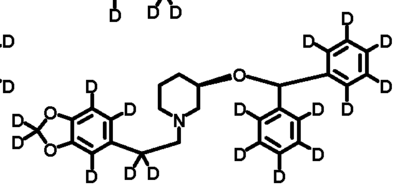
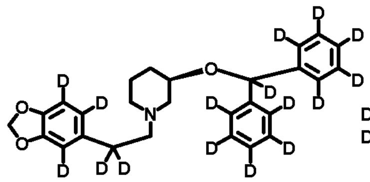
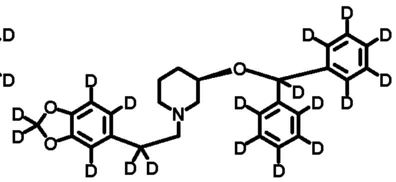


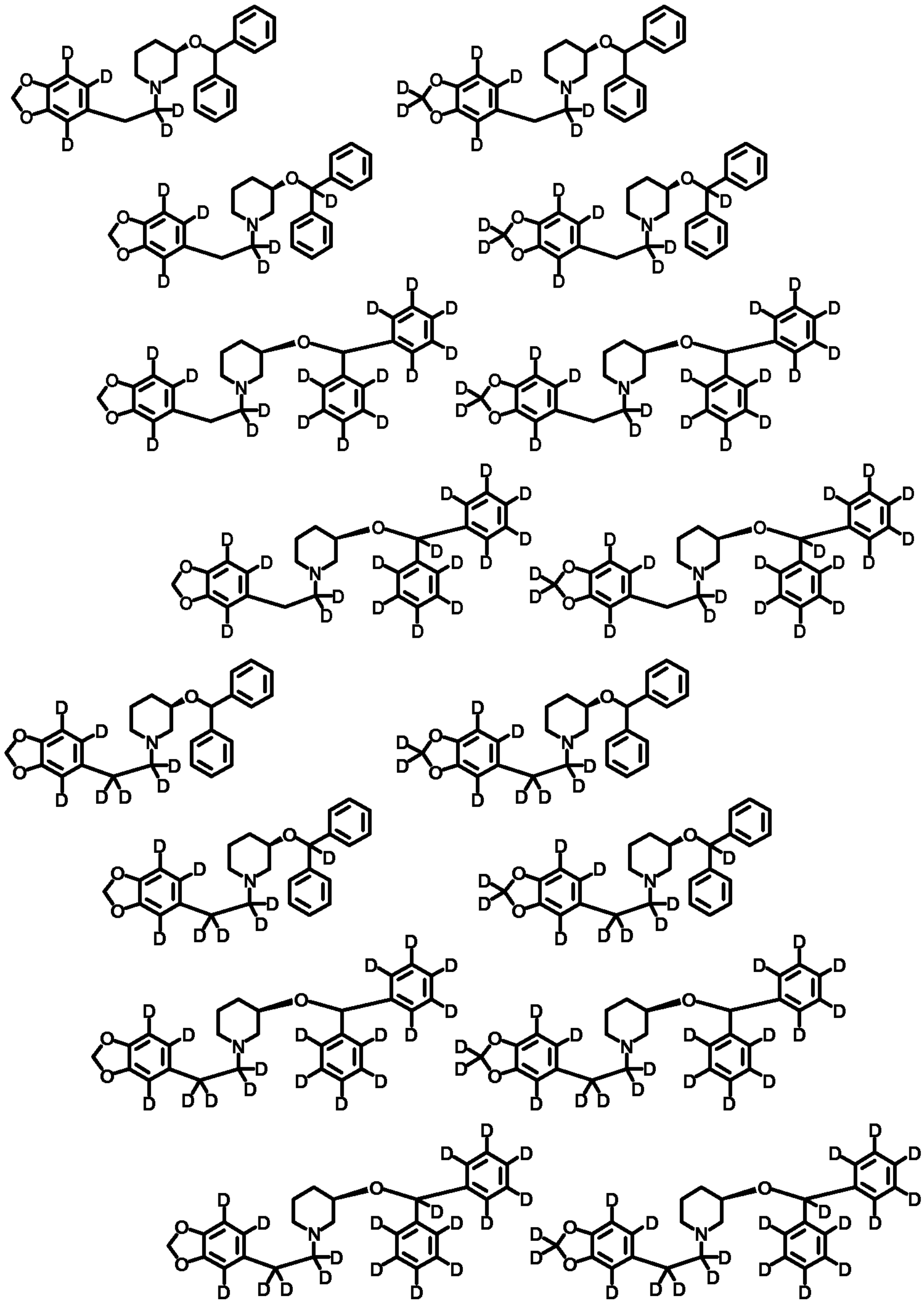






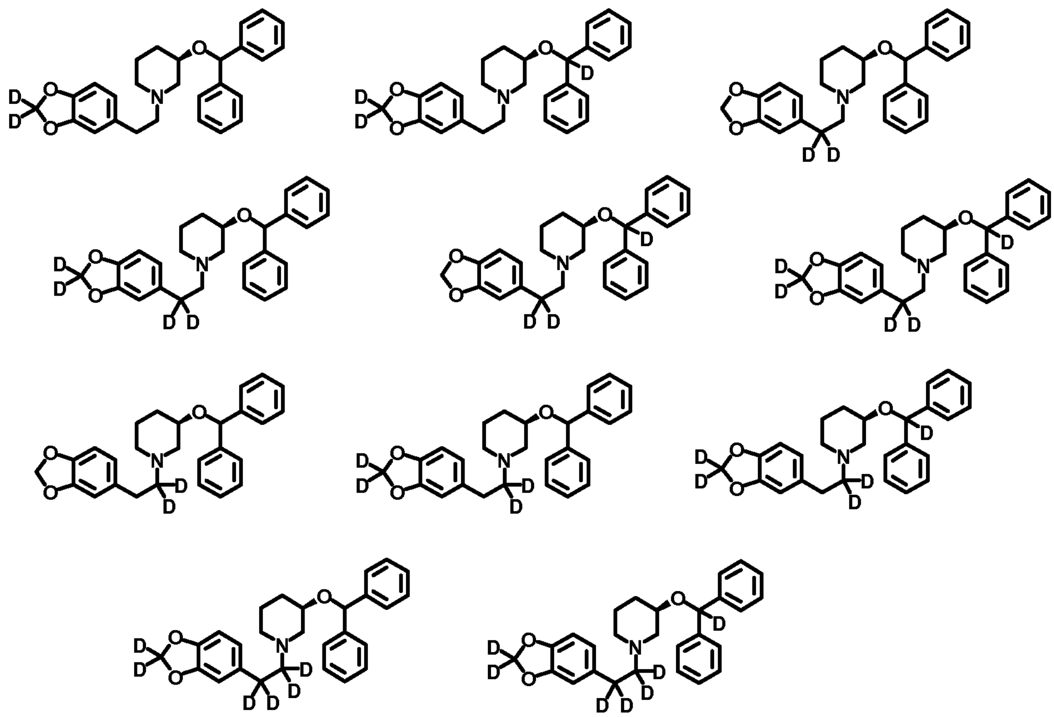


or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00138] In another embodiment, at least one of the positions represented as D independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[00139] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[00140] In yet another embodiment, the compound as disclosed herein is selected from the group consisting of:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00141] In another embodiment, at least one of the positions represented as D independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

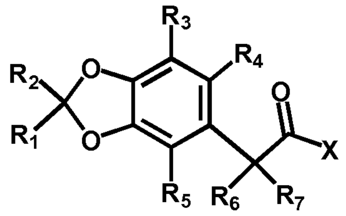
[00142] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[00143] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (-)-enantiomer of the compound and about 40% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (-)-enantiomer of the compound and about 30% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (-)-enantiomer of the compound and about 20% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (-)-enantiomer of the compound and about 10% or less by weight of the (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of the (-)-enantiomer of the compound and about 5% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of the (-)-enantiomer of the compound and about 1% or less by weight of (+)-enantiomer of the compound.

[00144] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (+)-enantiomer of the compound and about 40% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (+)-enantiomer of the compound and about 30% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (+)-enantiomer of the compound and about 20% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (+)-enantiomer of the compound and about 10% or less by weight of the (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein

contains about 95% or more by weight of the (+)-enantiomer of the compound and about 5% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of the (+)-enantiomer of the compound and about 1% or less by weight of (-)-enantiomer of the compound.

[00145] In another embodiment is a compound having structural Formula II:



(II)

wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ are independently selected form the group consisting of hydrogen or deuterium;

X is selected from the group consisting of hydroxyl, alkyloxy, and a leaving group; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is deuterium.

[00146] In another embodiment, at least one of the positions represented as D independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[00147] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[00148] In another embodiment, a process for the manufacture of a compound having structural Formula I comprises a reaction which contains a compound having structural Formula II.

[00149] A deuterated compound disclosed herein may also contain less prevalent isotopes for other elements, including, but not limited to, $^{13}C$ or $^{14}C$ for carbon, $^{33}S$, $^{34}S$, or $^{36}S$ for sulfur, $^{15}N$ for nitrogen, and $^{17}O$ or $^{18}O$ for oxygen.

[00150] In certain embodiments, without being bound by any theory, the compound disclosed herein may expose a patient to a maximum of about 0.000005% $D_2O$ or about 0.00001% DHO, assuming that all of the C-D bonds in the compound of a compound disclosed herein are metabolized and released as $D_2O$ or DHO. This quantity is a small fraction of the naturally occurring background levels of $D_2O$ or DHO in circulation. In certain embodiments, the levels of $D_2O$ shown to cause toxicity in animals is much greater than even the maximum limit of exposure because of the deuterium enriched compound of a compound disclosed herein. Thus, in certain embodiments, the deuterium-enriched compound disclosed herein should not cause any additional toxicity because of the use of deuterium.

[00151] In one embodiment, the deuterated compounds disclosed herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration ($C_{max}$) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

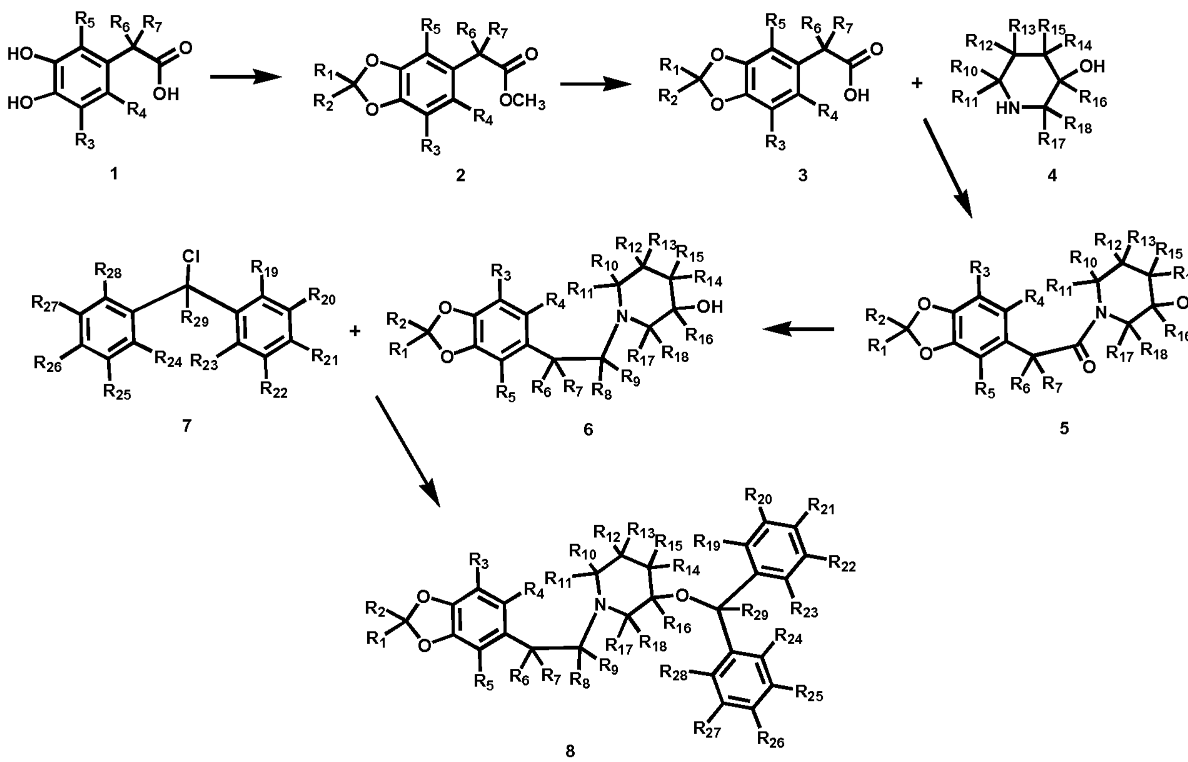
[00152] Isotopic hydrogen can be introduced into a compound of a compound disclosed herein as disclosed herein by synthetic techniques that employ deuterated reagents, whereby incorporation rates are pre-determined; and/or by exchange techniques, wherein incorporation rates are determined by equilibrium conditions, and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. In addition, the molecule being labeled may be changed, depending upon the severity of the synthetic reaction employed. Exchange techniques, on the other hand, may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule, but offer the advantage that they do not require separate synthetic steps and are less likely to disrupt the structure of the molecule being labeled.

[00153] The compounds as disclosed herein can be prepared by methods known to one of skill in the art and routine modifications thereof, and/or following procedures similar to those described in the Example section herein and routine modifications thereof, and/or procedures found in Khan, *J. Am. Chem. Soc.* **1952**, *74*, 3018-3022, Cabedo et al, *J. Med. Chem.* **2001**, *44*, 1794-1801, Cossy et al *Biorganic Medicinal Chemistry Letters* **1997**, *7(10)*, 1343-1344, Mavromoustakos et al *Bioorganic & Medicinal Chemistry* **2006**, *14*, 4353–4360,

Cossy et al *Biorganic Medicinal Chemistry Letters* **1997**, *7(10)*, 1343-1344, and Pojer *Tetrahedron Letters* **1984**, *25(23)*, 2507-2508, and references cited therein and routine modifications thereof. Compounds as disclosed herein can also be prepared as shown in any of the following schemes and routine modifications thereof.

[00154] For example, certain compounds as disclosed herein can be prepared as shown in Scheme 1.

**Scheme 1**



[00155] Carboxylic acid **1** is treated with an acid, such as sulfuric acid, in an appropriate solvent, such as methanol, at an elevated temperature to afford a methyl ester, which when reacted with dichloromethane, in the presence of a base, such as cesium chloride, in an appropriate solvent, such as dimethylformamide, at an elevated temperature affords methylenedioxy **2**. Compound **2** is treated with a base, such as potassium hydroxide, in an appropriate solvent, such as methanol, at an elevated temperature to give carboxylic acid **3**, which then reacts with 3-piperidinol **4**, in the presence of a coupling agent, such as O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, in the presence of a base, such as triethylamine, in an appropriate solvent, such as *N,N*-dimethylformamide, to afford amide **5**. Compound **5** is reacted with an appropriate reducing agent, such as lithium aluminum hydride, in an appropriate solvent, such as tetrahydrofuran, at an elevated

temperature to amine **6**, which then reacts with diphenyl methylchloride **7** in an appropriate solvent, such as dimethyl sulfoxide, at an elevated termperature to give piperidine **8** of Formula I.

[00156] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 1, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions selected from $R_1$, and $R_2$, dichloromethane with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions selected from $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$, 3,4-dihydroxyphenylacetic acid with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions selected from $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, and $R_{18}$, 3-piperidinol with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of $R_8$, and $R_9$, lithium aluminum hydride with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$, diphenyl methyl chloride with the corresponding deuterium substitutions can be used. These deuterated intermediates are either commercially available, or can be prepared by methods known to one of skill in the art or following procedures similar to those described in the Example section herein and routine modifications thereof.

[00157] Deuterium can also be incorporated to various positions having an exchangeable proton, via proton-deuterium equilibrium exchange. Such protons may be replaced with deuteriums selectively or non-selectively through proton-deuterium exchange methods known in the art.

[00158] It is to be understood that the compounds disclosed herein may contain one or more chiral centers, chiral axes, and/or chiral planes, as described in "Stereochemistry of Carbon Compounds" Eliel and Wilen, John Wiley & Sons, New York, 1994, pp. 1119-1190. Such chiral centers, chiral axes, and chiral planes may be of either the (R) or (S) configuration, or may be a mixture thereof.

[00159] Another method for characterizing a composition containing a compound having at least one chiral center is by the effect of the composition on a beam of polarized light. When a beam of plane polarized light is passed through a solution of a chiral compound, the plane of polarization of the light that emerges is rotated relative to the original plane. This phenomenon is known as optical activity, and compounds that rotate the plane of polarized light are said to be optically active. One enantiomer of a compound will rotate the beam of polarized light in one direction, and the other enantiomer will rotate the beam of

light in the opposite direction. The enantiomer that rotates the polarized light in the clockwise direction is the (+) enantiomer, and the enantiomer that rotates the polarized light in the counterclockwise direction is the (-) enantiomer. Included within the scope of the compositions described herein are compositions containing between 0 and 100% of the (+) and/or (-) enantiomer of compounds disclosed herein.

[00160] Where a compound as disclosed herein contains an alkenyl or alkenylene group, the compound may exist as one or mixture of geometric *cis*/*trans* (or Z/E) isomers. Where structural isomers are interconvertible *via* a low energy barrier, the compound disclosed herein may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound disclosed herein that contains for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00161] The compounds disclosed herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, a racemic mixture, or a diastereomeric mixture. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00162] When the compound disclosed herein contains an acidic or basic moiety, it may also disclosed as a pharmaceutically acceptable salt (*See*, Berge et al., *J. Pharm. Sci.* **1977**, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

[00163] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid,

α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[00164] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00165] The compound as disclosed herein may also be designed as a prodrug, which is a functional derivative of the compound as disclosed herein and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich et al. in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang et al., *Curr. Pharm. Design* 1999, *5*, 265-287; Pauletti et al., *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen et al., *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault et al., *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon et al., Ed., Marcell Dekker,

185-218, 2000; Balant et al., *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher et al., *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher et al., *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar et al., *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman et al., *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar et al., *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella et al., *Drugs* **1985**, *29*, 455-73; Tan et al., *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; Waller et al., *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507.

**Pharmaceutical Composition**

[00166] Disclosed herein are pharmaceutical compositions comprising a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as an active ingredient, combined with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; in combination with one or more pharmaceutically acceptable excipients or carriers.

[00167] Disclosed herein are pharmaceutical compositions in modified release dosage forms, which comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients or carriers as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multiparticulate devices, and combinations thereof. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[00168] Further disclosed herein are pharmaceutical compositions in enteric coated dosage forms, which comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients or carriers for use in an enteric coated dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[00169] Further disclosed herein are pharmaceutical compositions in effervescent dosage forms, which comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients or carriers for use in an effervescent dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[00170] Additionally disclosed are pharmaceutical compositions in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling and non-release controlling excipients or carriers, such as those excipients or carriers suitable for a disruptable semi-permeable membrane and as swellable substances.

[00171] Disclosed herein also are pharmaceutical compositions in a dosage form for oral administration to a subject, which comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[00172] Disclosed herein are pharmaceutical compositions that comprise about 0.1 to about 1000 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg of one or more compounds as disclosed herein in the form of extended-release tablet, and contains the following inactive ingredients: dibasic calcium phosphate (anhydrous), hydroxypropyl methylcellulose (hypromellose), lactose monohydrate, magnesium stearate, titanium dioxide and triacetin.

[00173] The pharmaceutical compositions disclosed herein may be disclosed in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include ampouls, syringes, and individually packaged tablets and capsules. Unit-dosage forms may be administered in fractions or multiples thereof. A multiple-dosage form

is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of multiple-dosage forms include vials, bottles of tablets or capsules, or bottles of pints or gallons.

[00174] The compound as disclosed herein may be administered alone, or in combination with one or more other compounds disclosed herein, one or more other active ingredients. The pharmaceutical compositions that comprise a compound disclosed herein may be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions may also be formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

[00175] The pharmaceutical compositions disclosed herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[00176] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00177] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday").

[00178] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

**A. Oral Administration**

[00179] The pharmaceutical compositions disclosed herein may be formulated in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also include buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00180] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions disclosed herein.

[00181] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[00182] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions disclosed herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions disclosed herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00183] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions disclosed herein may contain about 0.1 to about 5% by weight of a lubricant.

[00184] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying

agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00185] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00186] The pharmaceutical compositions disclosed herein may be formulated as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00187] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00188] The pharmaceutical compositions disclosed herein may be formulated as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms disclosed herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00189] The pharmaceutical compositions disclosed herein may be formulated in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00190] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) disclosed herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate

average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00191] The pharmaceutical compositions disclosed herein for oral administration may be also formulated in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00192] The pharmaceutical compositions disclosed herein may be formulated as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00193] Coloring and flavoring agents can be used in all of the above dosage forms.

[00194] The pharmaceutical compositions disclosed herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00195] The pharmaceutical compositions disclosed herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action, such as drotrecogin-α, and hydrocortisone.

## B. Parenteral Administration

[00196] The pharmaceutical compositions disclosed herein may be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[00197] The pharmaceutical compositions disclosed herein may be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for

solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00198] The pharmaceutical compositions intended for parenteral administration may include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00199] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

[00200] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium

hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00201] The pharmaceutical compositions disclosed herein may be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00202] In one embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are formulated as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are formulated as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile emulsions.

[00203] The pharmaceutical compositions disclosed herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00204] The pharmaceutical compositions may be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions disclosed herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00205] Suitable inner matrixes include polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00206] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

**C. Topical Administration**

[00207] The pharmaceutical compositions disclosed herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, include (intra)dermal, conjuctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, uretheral, respiratory, and rectal administration.

[00208] The pharmaceutical compositions disclosed herein may be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches. The topical formulation of the pharmaceutical compositions disclosed herein may also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00209] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations disclosed herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryopretectants, lyoprotectants, thickening agents, and inert gases.

[00210] The pharmaceutical compositions may also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00211] The pharmaceutical compositions disclosed herein may be formulated in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including such as lard, benzoinated lard, olive oil, cottonseed oil, and

other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00212] Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00213] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, Carbopol®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00214] The pharmaceutical compositions disclosed herein may be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00215] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening

agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions disclosed herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00216] The pharmaceutical compositions disclosed herein may be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00217] The pharmaceutical compositions disclosed herein may be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions may be formulated in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions may also be formulated as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00218] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer may be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient disclosed herein, a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00219] The pharmaceutical compositions disclosed herein may be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes may be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00220] Capsules, blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the pharmaceutical compositions disclosed herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-

leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions disclosed herein for inhaled/intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00221] The pharmaceutical compositions disclosed herein for topical administration may be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

**D. Modified Release**

[00222] The pharmaceutical compositions disclosed herein may be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00223] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

**1. Matrix Controlled Release Devices**

[00224] The pharmaceutical compositions disclosed herein in a modified release dosage form may be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999).

[00225] In one embodiment, the pharmaceutical compositions disclosed herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00226] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00227] In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene,

polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00228] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00229] The pharmaceutical compositions disclosed herein in a modified release dosage form may be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

## 2. Osmotic Controlled Release Devices

[00230] The pharmaceutical compositions disclosed herein in a modified release dosage form may be fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s) and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00231] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as “osmopolymers” and “hydrogels,” including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol

(PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00232] The other class of osmotic agents are osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00233] Osmotic agents of different dissolution rates may be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00234] The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00235] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and

reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxlated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00236] Semipermeable membrane may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00237] The delivery port(s) on the semipermeable membrane may be formed post-coating by mechanical or laser drilling. Delivery port(s) may also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports may be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00238] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00239] The pharmaceutical compositions in an osmotic controlled-release dosage form may further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00240] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00241] In certain embodiments, the pharmaceutical compositions disclosed herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00242] In certain embodiments, the pharmaceutical compositions disclosed herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

### 3. Multiparticulate Controlled Release Devices

[00243] The pharmaceutical compositions disclosed herein in a modified release dosage form may be fabricated a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates may be made by the processes know to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00244] Other excipients or carriers as described herein may be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate device or may be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

**4. Targeted Delivery**

[00245] The pharmaceutical compositions disclosed herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

## Methods of Use

[00246] Disclosed are methods for treating, preventing, or ameliorating one or more symptoms of a muscarinic receptor-mediated disorder, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00247] Muscarinic receptor-mediated disorders include, but are not limited to, irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, any disorder associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by muscarinic receptor modulation.

[00248] Also disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder associated with muscarinic receptors, by administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00249] Further disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder responsive to modulation of muscarinic receptors, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00250] Furthermore, disclosed herein are methods of modulating the activity of muscarinic receptors, comprising contacting the receptors with at least one compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the muscarinic receptor is expressed by a cell.

[00251] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect decreased inter-individual variation in plasma levels of the compound or a metabolite thereof, during the treatment of the disease as compared to the corresponding non-isotopically enriched compound.

[00252] In certain embodiments, the inter-individual variation in plasma levels of the compounds disclosed herein, or metabolites thereof, is decreased by greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or by greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[00253] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect increased average plasma levels of the compound or decreased average plasma levels of at least one metabolite of the compound per dosage unit as compared to the corresponding non-isotopically enriched compound.

[00254] In certain embodiments, the average plasma levels of the compound disclosed herein are increased by greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

[00255] In certain embodiments, the average plasma levels of a metabolite of the compound disclosed herein are decreased by greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds

[00256] Plasma levels of the compound disclosed herein, or metabolites thereof, are measured using the methods described by Li et al. (*Rapid Communications in Mass Spectrometry* **2005**, *19*, 1943-1950).

[00257] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect a decreased inhibition of, and/or metabolism by at least one cytochrome $P_{450}$ or monoamine oxidase isoform in the subject during the treatment of the disease as compared to the corresponding non-isotopically enriched compound.

[00258] Examples of cytochrome $P_{450}$ isoforms in a mammalian subject include, but are not limited to, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[00259] Examples of monoamine oxidase isoforms in a mammalian subject include, but are not limited to, $MAO_A$, and $MAO_B$.

[00260] In certain embodiments, the decrease in inhibition of the cytochrome $P_{450}$ or monoamine oxidase isoform by a compound disclosed herein is greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

[00261] The inhibition of the cytochrome $P_{450}$ isoform is measured by the method of Ko et al. (*British Journal of Clinical Pharmacology*, **2000**, *49*, 343-351). The inhibition of the $MAO_A$ isoform is measured by the method of Weyler et al. (*J. Biol Chem.* **1985**, *260*, 13199-13207). The inhibition of the $MAO_B$ isoform is measured by the method of Uebelhack et al. (*Pharmacopsychiatry*, **1998**, *31*, 187-192).

[00262] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such disease in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically

acceptable salt, solvate, or prodrug thereof, so as to affect a decreased metabolism via at least one polymorphically-expressed cytochrome $P_{450}$ isoform in the subject during the treatment of the disease as compared to the corresponding non-isotopically enriched compound.

[00263] Examples of polymorphically-expressed cytochrome $P_{450}$ isoforms in a mammalian subject include, but are not limited to, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[00264] In certain embodiments, the decrease in metabolism of the compound disclosed herein by at least one polymorphically-expressed cytochrome $P_{450}$ isoforms cytochrome $P_{450}$ isoform is greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[00265] The metabolic activities of the cytochrome $P_{450}$ isoforms are measured by the method described in Example 7. The metabolic activities of the monoamine oxidase isoforms are measured by the methods described in Examples 9 and 10.

[00266] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect at least one statistically-significantly improved disorder-control and/or disorder-eradication endpoint, as compared to the corresponding non-isotopically enriched compound.

[00267] Examples of improved disorder-control and/or disorder-eradication endpoints include, but are not limited to, statistically-significant improvement in pain indices, reduction in diarrhea, and/or constipation, and/or vomiting events, reduction in fever, normalization of bowel movement frequency to about 2.5 to about 4 bowel movements per 48 hours, improvement in "Rome II" criteria or the "Rome Process" outcomes, normalization of control of continence and micturation, reduction in dyspnea and/or tachypnea, improvement of forced expiratory volume over about 1 second ($FEV_1$) to about $\geq$ 70% of predicted value for an individual, improvement of forced vital capacity (FVC) to about $\geq$ 0.7, reduction in toxicological adverse events including but not limited to, hepatotoxicity, as compared to the corresponding non-isotopically enriched compound.

[00268] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a

therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect an improved clinical effect as compared to the corresponding non-isotopically enriched compound. Examples of improved disorder-control and/or disorder-eradication endpoints include, but are not limited to, statistically-significant improvement in pain indices, reduction in diarrhea, and/or constipation, and/or vomiting events, reduction in fever, normalization of bowel movement frequency to about 2.5 to 4 bowel movements per 48 hours, improvement in “Rome II” criteria or the “Rome Process” outcomes, normalization of control of continence and micturation, reduction in dyspnea and/or tachypnea, improvement of forced expiratory volume over about 1 second ($FEV_1$) to about $\geq$ 70% of predicted value for an individual, improvement of forced vital capacity (FVC) to about $\geq$ 0.7, reduction in toxicological adverse events including but not limited to, hepatotoxicity, as compared to the corresponding non-isotopically enriched compound.

[00269] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect prevention of recurrence, or delay of decline or appearance, of abnormal alimentary or hepatic parameters as the primary clinical benefit, as compared to the corresponding non-isotopically enriched compound.

[00270] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a muscarinic receptor-mediated disorder, or for preventing such a disorder in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to allow the treatment of, but not limited to, irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, any disorder associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by muscarinic receptor modulation while reducing or eliminating deleterious changes in any diagnostic hepatobiliary function endpoints as compared to the corresponding non-isotopically enriched compound.

[00271] Examples of diagnostic hepatobiliary function endpoints include, but are not limited to, alanine aminotransferase (“ALT”), serum glutamic-pyruvic transaminase (“SGPT”), aspartate aminotransferase (“AST” or “SGOT”), ALT/AST ratios, serum aldolase, alkaline phosphatase (“ALP”), ammonia levels, bilirubin, gamma-glutamyl transpeptidase

("GGTP," "□-GTP," or "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein. Hepatobiliary endpoints are compared to the stated normal levels as given in "Diagnostic and Laboratory Test Reference", 4th edition, Mosby, 1999. These assays are run by accredited laboratories according to standard protocol.

[00272] Depending on the disorder to be treated and the subject's condition, the compound disclosed herein disclosed herein may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration, and may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[00273] The dose may be in the form of one, two, three, four, five, six, or more sub-doses that are administered at appropriate intervals per day. The dose or sub-doses can be administered in the form of dosage units containing from about 0.1 to about 1000 milligram, from about 0.1 to about 500 milligrams, or from 0.5 about to about 100 milligram active ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of example only, be administered as a continuous infusion.

[00274] In certain embodiments, an appropriate dosage level is about 0.01 to about 100 mg per kg patient body weight per day (mg/kg per day), about 0.01 to about 50 mg/kg per day, about 0.01 to about 25 mg/kg per day, or about 0.05 to about 10 mg/kg per day, which may be administered in single or multiple doses. A suitable dosage level may be about 0.01 to about 100 mg/kg per day, about 0.05 to about 50 mg/kg per day, or about 0.1 to about 10 mg/kg per day. Within this range the dosage may be about 0.01 to about 0.1, about 0.1 to about 1.0, about 1.0 to about 10, or about 10 to about 50 mg/kg per day.

## Combination Therapy

[00275] The compounds disclosed herein may also be combined or used in combination with other agents useful in the treatment, prevention, or amelioration of one or more symptoms of irritable bowel syndrome (IBS), chronic obstructive pulmonary disease (COPD), urinary incontinence, any disorder associated with smooth muscle tone and/or contractility, and/or any disorder ameliorated by muscarinic receptor modulation. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may

be enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced).

[00276] Such other agents, adjuvants, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a compound disclosed herein. When a compound disclosed herein disclosed herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound disclosed herein may be utilized, but is not required. Accordingly, the pharmaceutical compositions disclosed herein include those that also contain one or more other active ingredients or therapeutic agents, in addition to the compound disclosed herein.

[00277] In certain embodiments, the compounds disclosed herein can be combined with one or more prokinetics known in the art, including, but not limited to, cisapride, domperidone, lirexapride, metoclopramide, mosapride, neurotrophin-3, norcisapride, prucalipride, renzapride, tegaserod, TS-951, and YM-53389.

[00278] In certain embodiments, the compounds disclosed herein can be combined with one or more tachykinins known in the art, including, but not limited, exlopitant, nepadudant, and SR-140333.

[00279] In certain embodiments, the compounds disclosed herein can be combined with one or more other anticholinergic agents known in the art, including, but not limited, darifenacin, dicyclomine, hyoscyamine, and YM-905.

[00280] In certain embodiments, the compounds disclosed herein can be combined with one or more other opioids known in the art, including, but not limited to, morphine, codeine, thebain, diacetylmorphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, nicomorphine, fentanyl, 3-methylfentanyl, alfentanil, sufentanil, remifentanyl, carfentanyl, ohmefentanyl, pethidine, ketobemidone, propoxyphene, dextropropoxyphene, methadone, loperamide, pentazocine, buprenorphine, etorphine, butorphanol, nalbufine, levorphanol, naloxone, naltrexone, and tramadol.

[00281] In certain embodiments, the compounds disclosed herein can be combined with one or more 5-$HT_3$ antagonists known in the art, including, but not limited to, alosetron, cilansetron, granisectron, and ondansetron.

[00282] In certain embodiments, the compounds disclosed herein can be combined with one or more alpha adrenergic agents known in the art, including, but not limited to, lidamidine, and clonidine.

[00283] In certain embodiments, the compounds disclosed herein can be combined with one or more $CCK_A$ antagonists known in the art, including, but not limited to, dexloxigumide, loxiglumide, proglumide, and proxiglumide.

[00284] In certain embodiments, the compounds disclosed herein can be combined with one or more NMDA receptor antagonists known in the art, including, but not limited to, dizocilpine, and memantine.

[00285] In certain embodiments, the compounds disclosed herein can be combined with one or more serotoninergic agents known in the art, including, but not limited to, buspirone, piboserod, and sumatriptan.

[00286] In certain embodiments, the compounds disclosed herein can be combined with one or more agents not fitting the aforementioned categories known in the art, including, but not limited to the group including antalarmin, and Z-338.

[00287] The compounds disclosed herein can also be administered in combination with other classes of compounds, including, but not limited to, endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists, such as ifetroban; potassium channel openers; thrombin inhibitors, such as hirudin; growth factor inhibitors, such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents, such as GPIIb/IIIa blockers (e.g., abdximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants, such as warfarin; low molecular weight heparins, such as enoxaparin; Factor VIIa Inhibitors and Factor Xa Inhibitors; renin inhibitors; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants, such as questran; niacin; anti-atherosclerotic agents, such as ACAT inhibitors; MTP Inhibitors; calcium channel blockers, such as amlodipine besylate; potassium channel activators; alpha-adrenergic agents; beta-adrenergic agents, such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothlazide, hydrochiorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichioromethiazide, polythiazide, benzothlazide, ethacrynic acid, tricrynafen, chlorthalidone, furosenilde, musolimine, bumetanide, triamterene, amiloride, and spironolactone; thrombolytic agents, such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator

complex (APSAC); anti-diabetic agents, such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, and glipizide), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; growth hormone secretagogues; aP2 inhibitors; phosphodiesterase inhibitors, such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., sildenafil, tadalafil, vardenafil); protein tyrosine kinase inhibitors; antiinflammatories; antiproliferatives, such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil; chemotherapeutic agents; immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes); antimetabolites, such as folate antagonists, purine analogues, and pyrridine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone anatagonists, and octreotide acetate; microtubule-disruptor agents, such as ecteinascidins; microtubule-stablizing agents, such as pacitaxel, docetaxel, and epothilones A-F; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and cyclosporins; steroids, such as prednisone and dexamethasone; cytotoxic drugs, such as azathiprine and cyclophosphamide; TNF-alpha inhibitors, such as tenidap; anti-TNF antibodies or soluble TNF receptor, such as etanercept, rapamycin, and leflunimide; and cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, gold compounds, platinum coordination complexes, such as cisplatin, satraplatin, and carboplatin.

**Kits/Articles of Manufacture**

[00288] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00289] For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

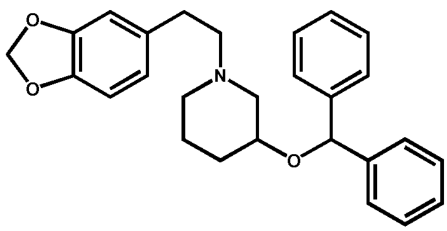
[00290] A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but are not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00291] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein. These other therapeutic agents may be used, for example, in the amounts indicated in the Physicians' Desk Reference (PDR).

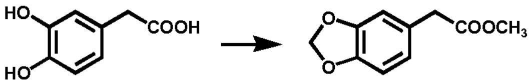
[00292] The invention is further illustrated by the following examples:

## EXAMPLE 1

**3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine**



Step 1

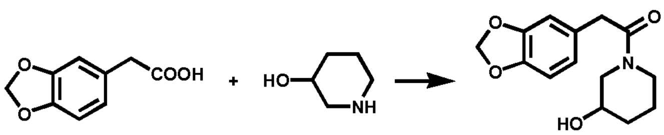


[00293] Benzo[1,3]dioxol-5-yl-acetic acid methyl ester: 3,4-Dihydroxyphenylacetic acid (13 g, 77.3 mmol) was heated with methanol (260 mL) and concentrated sulfuric acid (6.5 mL) at reflux for about 3 hours. The solvent was removed *in vacuo*, and the resulting residue was dissolved in anhydrous dimethylformamide (50 mL). Dichloromethane (19.5 mL, 304 mmol) and cesium fluoride (60 g, 395 mmol) were then added, and the mixture was heated to about 90 °C for about 12 hours. After cooling to ambient temperature, standard extractive workup was performed with dichloromethane, and the crude product was then purified by column chromatography on silica gel (5x20 cm, petroleum ether/ethyl acetate=10/1 elution) to yield the title product (6.3 g, 42%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.77-6.69 (m, 3H), 5.93 (s, 2H), 3.69 (s, 3H), 3.53 (s, 2H); LC-MS: *m/z*=195$(MH)^+$.

Step 2


[00294] Benzo[1,3]dioxol-5-yl-acetic acid: A mixture of benzo[1,3]dioxol-5-yl-acetic acid methyl ester (1 g, 5.15 mmol) in methanol (2 mL) and 20% aqueous potassium hydroxide (10 mL) were heated at reflux for about 3 hours. Methanol was removed by evaporation, and the aqueous solution was acidified to pH=1 with 5% aqueous hydrochloric acid. Standard extractive workup was performed to yield the title product. (910 mg, 99%). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.78-6.70 (m, 3H), 5.94 (s, 2H), 3.57 (s, 2H); LC-MS: *m/z*=179$(M-1)^-$.

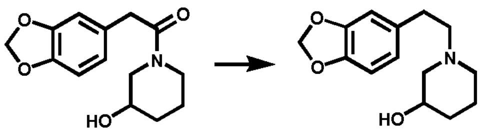
Step 3




[00295] 2-Benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone: At about 0 °C, benzo[1,3]dioxol-5-yl-acetic acid (1.5 g, 8.3 mmol), triethylamine (3.5 mL, 25.4 mmol) and O-(benzotriazol-1-yl)- *N,N,N',N'*-tetramethyluronium tetrafluoroborate (2.96 g, 9.22 mmol) were sequentially added to 3-piperidinol (848 mg, 8.4 mmol) in 30 mL of *N,N*-dimethylformamide. The reaction mixture was slowly warmed to ambient temperature. Under continuous stirring, the mixture was maintained at ambient temperature for about 16 hours, and then diluted with water (50 mL). Following standard extractive workup, the

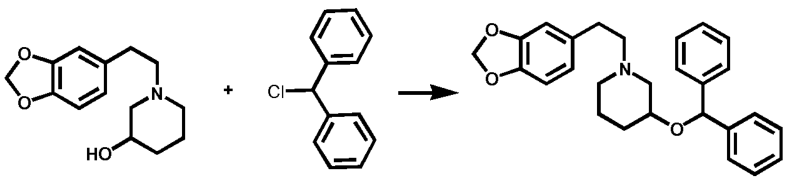
crude residue was purified by flash column chromatography on silica gel (4x 15 cm, dichloromethane/methanol=50/1 elution) to give the title product. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.76-6.66 (m, 3H), 5.93 (s, 2H), 3.88-3.58(m, 5H), 3.31-3.25 (m, 2H), 1.68-1.26 (m, 4H). LC-MS: *m/z*=264(MH)$^+$.

Step 4



[00296] 1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol: At about 0 °C, a solution of 2-benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone (1.5 g, 5.7 mmol) in tetrahydrofuran (2 mL) was added dropwise to a suspension of lithium aluminum hydride (433 mg, 11.4 mmol) in anhydrous tetrahydrofuran (2 mL). Under continous stirring, the mixture was maintained at about 56 °C for about 12 hours, cooled to ambient temperature, and quenched with water (10 mL). The resulting precipitate was removed by filtration. Following standard extractive workup, the crude product was purified by flash column chromatography on silica gel (4 x 15 cm, dichloromethane/methanol/triethylamine=100/1/0.5 elution) to give the title product (1.4 g, 98%). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.73-6.61 (m, 3H), 5.92 (s, 2H), 3.81 (br. s, 1H), 1.76-1.64 (m, 2H), 2.84-2.44 (m, 8H), 1.98-1.53 (m, 4H); LC-MS: *m/z*=250(MH)$^+$.

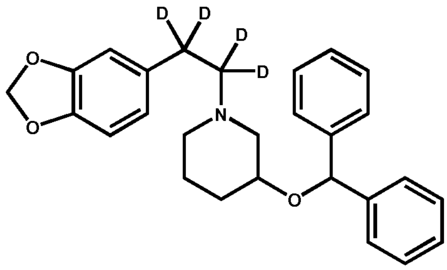
Step 5



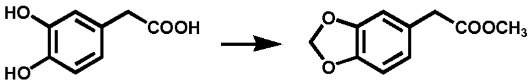
[00297] 3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: A mixture of 1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol (1.42 g, 5.7 mmol), dimethyl sulfoxide (3 mL) and diphenyl methylchloride (2.2 mL, 12.4 mmol) was heated at about 110 °C for about 12 hours to give a crude product which was then purified by alumina column chromatography (1x15 cm, dichloromethane/triethylamine=833/1 elution) to afford the title compound (230 mg, 10%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 7.37-7.21 (m, 10H), 6.78-6.61 (m, 3H), 5.94 (s, 2H), 5.66 (s, 1H), 3.01-2.99 (m, 1H), 2.67-2.60 (m, 3H), 2.46-2.42 (m, 2H), 1.98-1.92 (m, 3H), 1.61 (s, 1H), 1.31-1.19 (m, 3H); LC-MS: *m/z*=416 (MH)$^+$ ; HPLC: 98.9% (Purity).

## EXAMPLE 2

## *$d_4$*-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine

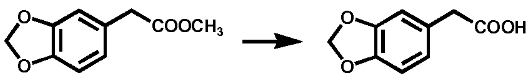


Step 1



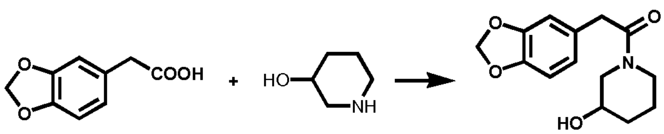
[00298] Benzo[1,3]dioxol-5-yl-acetic acid methyl ester: The title product was made by following the procedure set forth in Example 1, step 1.

Step 2



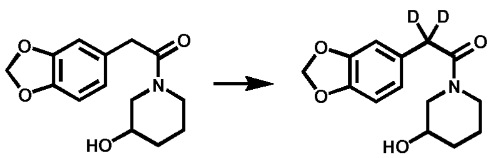
[00299] Benzo[1,3]dioxol-5-yl-acetic acid: The title product was made by following the procedure set forth in Example 1, step 2.

Step 3



[00300] 2-Benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone: The title product was made by following the procedure set forth in Example 1, step 3.

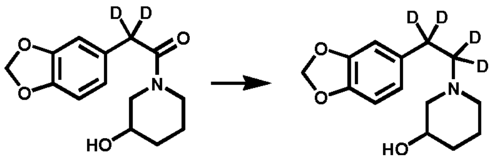
Step 4



[00301] *$d_2$*-1-(3-Hydryloxy-piperidin-1-yl)-2-benzo[1,3]dioxol-5-yl-ethanone: A mixture of 2-benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone (2.3 g, 8.75

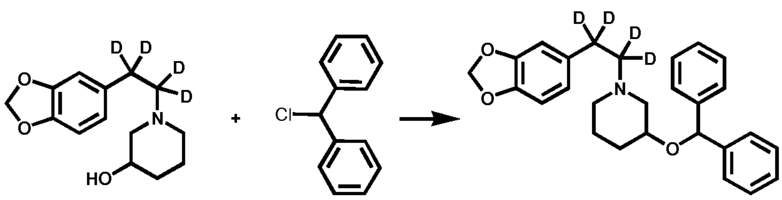
mmol), deuterium oxide (38 mL), and potassium carbonate (2 g, 14.5 mmol) was heated at about 100°C for about 12 hours. Following standard extractive workup the crude product was purified by flash column chromatography on silica gel (2 x 16 cm, dichloromethane/methanol=30/1 elution) to give the title product (1 g, 43%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 6.84-6.65 (m, 3H), 5.97 (s, 2H), 3.68-3.59 (m, 2H), 3.42-3.38 (m, 1H), 3.05-2.93 (m, 2H), 1.78 (m, 1H), 1.62-1.61 (m, 1H), 1.44-1.15 (m, 2H); LC-MS: *m/z*=266(MH)$^+$.

Step 5



[00302] $d_4$-1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol: At about 0 °C, a solution of $d_2$-1-(3-hydryloxy-piperidin-1-yl)-2-benzo[1,3]dioxol-5-yl-ethanone (1.0 g, 3.77 mmol) in tetrahydrofuran (2 mL) was added dropwise to a suspension of lithium aluminum deuteride (317 mg, 7.54 mmol) in anhydrous tetrahydrofuran (2 mL). Under continuous stirring, the mixture was maintained at about 56 °C for about 12 hours. After cooling to ambient temperature, the reaction was quenched with water (10 mL), and the resulting precipitate was removed by filtration. Following standard extractive workup the crude product was purified by flash column chromatography on silica gel (1 x 16 cm, dichloromethane/methanol/triethylamine=100/1/0.5 elution) to give the title product (960 mg, 100%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 6.79-6.76 (m, 2H), 6.65-6.62 (m, 1H), 5.91 (s, 2H), 4.56 (d, 1H, *J*=4.8 Hz), 3.44-3.37 (m, 1H), 3.15 (d, 1H, *J*=5.4 Hz), 2.87-2.84 (m, 1H), 2.70-2.66 (m, 1H), 1.87-0.96 (m, 5H); LC-MS: *m/z*=254(MH)$^+$.

Step 5

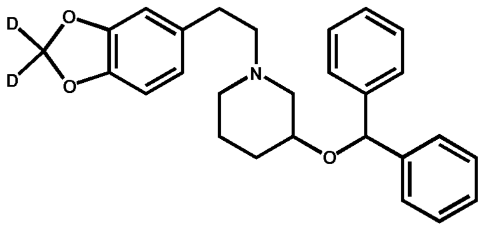


[00303] $d_4$-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: A mixture of $d_4$-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol (390 mg, 3.78 mmol), diphenyl methylchloride (3 mL, 16.9 mmol), and potassium carbonate (900 mg, 6.52mmol) was

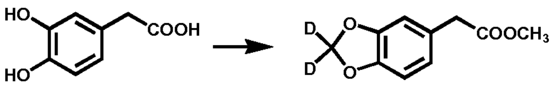
heated at about 80 °C for about 12 hours to give a crude product which was purified by alumina column chromatography (1 x 15 cm, dichloromethane/methanol/triethylamine=500/1/1 elution) to give the title compound. $^1$H NMR (300 MHz, $d_6$-DMSO) δ 7.97-7.22 (m, 10H), 6.78-6.61 (m, 3H), 5.94 (s, 2H), 5.66 (s, 1H) , 3.01-2.99 (m, 1H), 2.67-2.63 (m, 1H), 1.94-1.91 (m, 3H), 1.62-1.61 (m, 1H), 1.44-1.15 (m, 3H); LC-MS: *m/z*=420 $(MH)^+$ ; HPLC: 99% (Purity).

## EXAMPLE 3

## $d_2$-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine

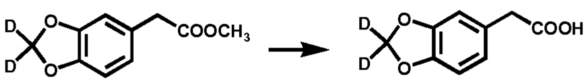


Step 1



[00304] $d_2$-Benzol[1,3]dioxol-5-yl-acetic acid methyl ester: 3,4-Dihydroxyphenylacetic acid (19 g, 112.4 mmol) was heated with methanol (380 mL) and concentrated sulfuric acid (9.5 mL) at reflux for about 3 hours. The solvent was removed *in vacuo*, and the resulting residue was dissolved in anhydrous dimethylformamide (200 mL). $d_2$-Dichloromethane (15 mL, 228.8 mmol) and cesium fluoride (98 g, 644.7 mmol) were then added, and the mixture was heated at about 100 °C for about 12 hours. After cooling to ambient temperature, standard extractive workup was performed with dichloromethane, and the resulting crude product was then purified by flash column chromatography on silica gel (4 x 15 cm, petroleum ether/ethyl acetate=10/1elution) to yield the title product as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.79-6.71 (m, 3H), 3.71 (s, 3H), 3.55 (s, 2H); LC-MS: *m/z*=197 $(MH)^+$.

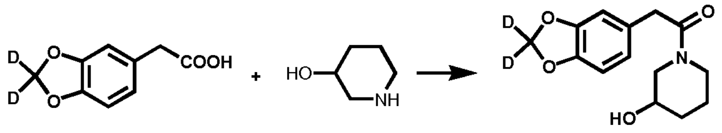
Step 2



[00305] $d_2$-Benzo[1,3]dioxol-5-yl-acetic acid: A mixture of $d_2$-benzol[1,3]dioxol-5-yl-acetic acid methyl ester (4 g, 20.4 mmol) in methanol (8 mL) and 20% aqueous potassium

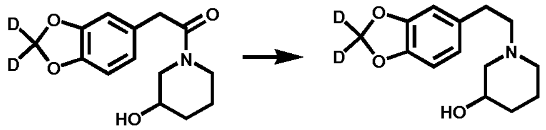
hydroxide (40 mL) was heated at reflux for 3 hours. Methanol was removed by evaporation, and the aqueous solution was acidified to pH 1 with 5% aqueous hydrochloric acid. Standard extractive workup was performed to yield the title product. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.78-6.70 (m, 3H), 3.56 (s, 2H); LC-MS: *m/z*=181(M-H).

Step 3



[00306] $d_2$-2-Benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone: At about 0 °C, 3-piperidinol (2.05 g, 20.3 mmol) was added to a mixture of $d_2$-benzo[1,3]dioxol-5-yl-acetic acid (3.7 g, 20.3 mmol), triethylamine (8.5 mL, 61 mmol), and O-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (7.17 g, 22.33 mmol) in *N*,*N*-dimethylformamide (100 mL). Under continuous stirring, the reaction mixture was maintained at ambient temperature for about 16 hours. Following strandard extractive workup, the crude product purified by flash column chromatography on silica gel (4 x 16 cm, dichloromethane/methanol=65/1 elution) to give the title product (3.36 g, 62%). 1H NMR (300 MHz, CDCl3) δ 6.78-6.69 (m, 3H), 3.93-3.32 (m, 7H), 1.99-1.27 (m, 5H); LC-MS: *m/z*=266(MH)$^+$.

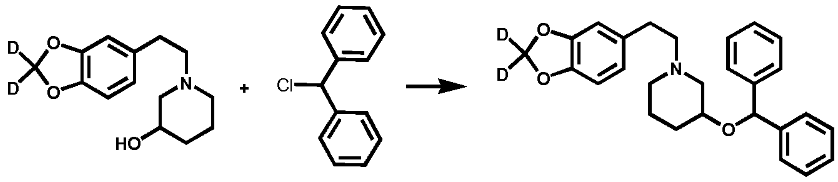
Step 4



[00307] $d_2$-1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol: At about 0°C, $d_2$-2-benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone (1.12 g, 4.23 mmol) in tretrahydrofuran (5 mL) was added dropwise to a suspension of lithium aluminum hydride (322 mg, 8.47 mmol) in anhydrous tetrahydrofuran (5 mL). Under continuous stirring, the mixture was maintained at about 56 °C for about 12 hours. The mixture was cooled to ambient temperature and quenched with water (10 mL). The resulting precipitate was removed by filtration. Following standard extractive workup, the crude residue was purified

by flash column chromatography on silica gel (2 x 16 cm, dichloromethane/methanol/triethylamine=100/1/0.5 elution) to give the title product (1.08 g, 100%). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.73-6.61 (m, 3H), 3.81 (br.s, 1H), 1.76-1.64 (m, 2H), 2.84-2.44 (m, 8H), 1.98-1.53 (m, 4H); LC-MS: $m/z$=252$(MH)^+$.

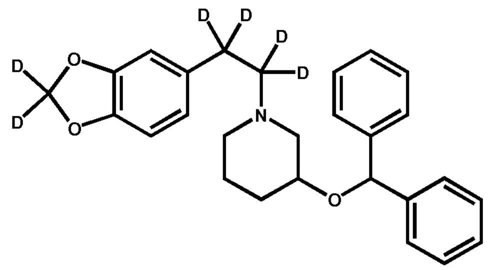
Step 5



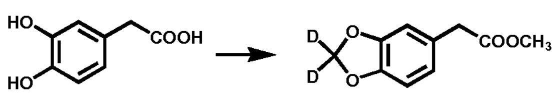
[00308] $d_2$-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: A mixture of $d_2$-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol (1.08 g, 4.3 mmol), diphenyl methylchloride (3 mL, 16.9 mmol), and potassium carbonate (900 mg, 6.5 mmol) was heated at about 80 °C for about 12 hours to give a crude product, which was then purified by alumina column chromatography (1 x 16 cm, dichloromethane/methanol/triethylamine=600/1/1elution) to afford the title compound (260 mg, 15%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 7.37-7.21 (m, 10H), 6.78-6.61 (m, 3H), 5.66 (s, 1H), 3.01-2.99 (m, 1H), 2.67-2.60 (m, 3H), 2.46-2.42 (m, 2H), 1.98-1.92 (m, 3H), 1.61 (s, 1H), 1.31-1.19 (m, 3H); LC-MS: $m/z$=418 $(MH)^+$ ; HPLC: 95.2% (Purity).

## EXAMPLE 4

## $d_6$-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine

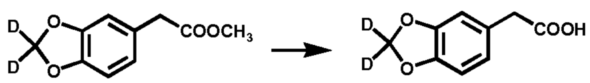


Step 1



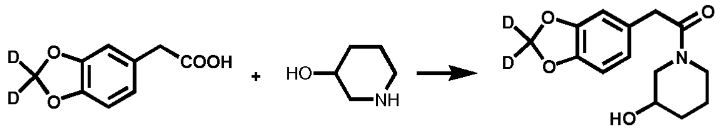
[00309] $d_2$-Benzol[1,3]dioxol-5-yl-acetic acid methyl ester: The title product was made by following the procedure set forth in Example 3, step 1.

Step 2



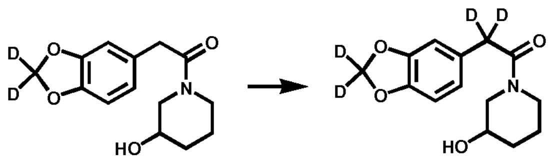
[00310] $d_2$-Benzo[1,3]dioxol-5-yl-acetic acid: The title product was made by following the procedure set forth in Example 3, step 2.

Step 3



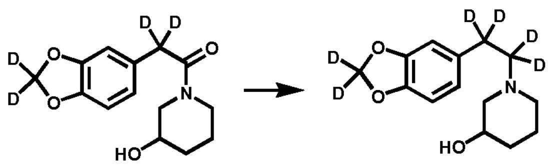
[00311] $d_2$-2-Benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone: The title product was made by following the procedure set forth in Example 3, step 3.

Step 4



[00312] $d_4$-2-Benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone: A mixture of $d_2$-2-benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone (2.24 g, 8.45 mmol), deuterium oxide (40 mL), and potassium carbonate (2 g, 14.5 mmol) was heated at about 100 °C for about 12 hours in a sealed tube. Following standard extractive workup the crude prodct was purified by flash column chromatography on silica gel (4 x 15 cm, dichloromethane/methanol=30/1elution) to yield the title product (1.23 g, 61%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 6.84-6.65 (m, 3H), 3.68-3.59 (m, 2H), 3.42-3.38 (m, 1H), 3.05-2.93 (m, 2H), 1.78 (m, 1H), 1.62-1.61 (m, 1H), 1.44-1.15 (m, 2H); LC-MS: $m/z$=268(MH)$^+$.

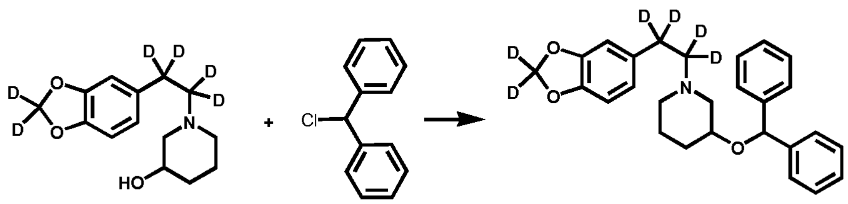
Step 5



[00313] $d_6$-1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol: At about 0 °C, a solution of $d_4$-2-benzo[1,3]dioxol-5-yl-1-(3-hydroxy-piperidin-1-yl)-ethanone (1.23 g, 4.6 mmol) in tetrahydrofuran (2 mL) was added dropwise to a suspension of lithium aluminum

deuteride (406 mg, 9.7 mmol) in anhydrous tetrahydrofuran (2 mL). Under continuous stirring, the mixture was maintained at about 56 °C for about 12 hours, and then cooled to ambient temperature and quenched with water (10 mL). The resulting precipitate was removed by filtration. Following standard extractive workup, the crude product was purified by flash column chromatography on silica gel (2 x 16 cm, dichloromethane/methanol/triethylamine=100/1/0.5 elution) to give the title product (1.12 g, 95%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 6.79-6.76 (m, 2H), 6.65-6.62 (m, 1H), 4.56 (d, 1H, $J$=4.8 Hz), 3.44-3.37 (m, 1H), 3.15 (d, 1H, $J$=5.4 Hz), 2.85-2.84 (m, 1H), 2.70-2.66 (m, 1H), 1.87-0.964 (m, 5H); LC-MS: $m/z$=256(MH)$^+$.

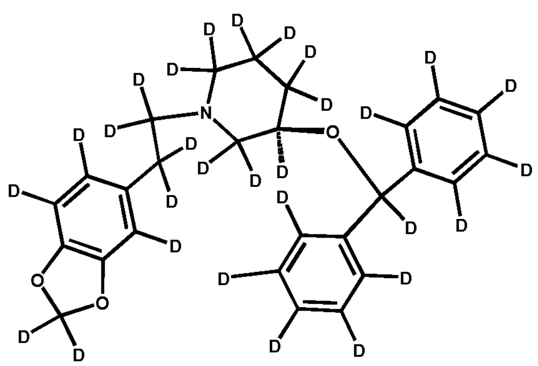
Step 6



[00314] $d_6$-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: A mixture of $d_6$-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol (1.18 g, 4.63 mmol), diphenyl methylchloride (3 mL, 16.9 mmol) and potassium carbonate (1.1 g, 7.97 mmol) was heated at about 80 °C for about 12 hours to give a crude product, which was then purified by alumina column chromatography (1 x 16 cm, dichloromethane/methanol/t=500/1.2/1.2 elution) to afford the title compound (400 mg, 43%). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 7.97-7.22 (m, 10H), 6.78-6.61 (m, 3H), 5.66 (s, 1H) , 3.01-2.99 (m, 1H), 2.67-2.63 (m, 1H), 1.94-1.91 (m, 3H), 1.62-1.61 (m, 1H), 1.44-1.15 (m, 3H); LC-MS: $m/z$=422 (MH)$^+$ ; HPLC: 99% (Purity).

EXAMPLE 5

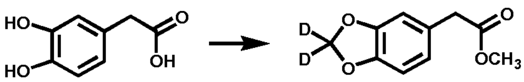
**$d_{29}$-(3R)-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine**



Step 1

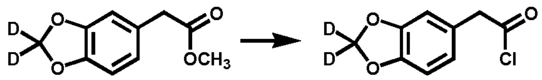
[00315] Deuterated Raney Nickel: The procedure is carried out using the methods described by Khan, *J. Am. Chem. Soc.* **1952**, *74*, 3018-3022. Raney nickel (25 g, still wet with dioxane) is washed once with a 25 mL portion of dioxane by centrifugation, suspended in 10 mL of deuterium oxide, and then allowed to stand in a stoppered tube for 48 hours with periodic stirring. The nickel is then washed with three 25 mL portions of dioxane and transferred to the reaction vessel of a Joshel apparatus (250 mL) with about 125 mL of dioxane. In the reaction vessel 5 mL of deuterium oxide is added to the catalyst. The stopcock above the reaction vessel is then closed, the system evacuated, and deuterium gas is introduced until about 100 mL of deuterium gas is collected in the 500 mL reservoir. After closing all stopcocks, the stopcock over the reaction vessel is opened and the catalyst in dioxane is agitated in the presence of deuterium gas under slight pressure for about two hours. The system is then flushed with dry oxygen-free nitrogren. The process is then repeated three more times with fresh deuterium. Nickel prepared in this manner is stored in purified dioxane with a small amount of deuterium oxide.

Step 2



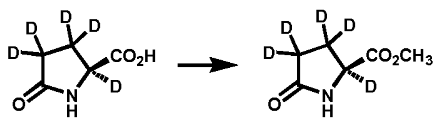

[00316] *$d_2$*-Benzo[1,3]dioxol-5-yl-acetic acid methyl ester: The procedure of Step 2 is carried out using the methods described by Cabedo et al, *J. Med. Chem.* **2001**, *44*, 1794-1801 and references cited therein. 3,4-Dihydroxyphenylacetic acid (2.0 g, 11.9 mmol), methanol (40 mL) and concentrated sulfuric acid (0.5 mL), are heated at reflux for about 3 hours. The solvent is removed under reduced pressure, and the resulting residue is then dissolved in anhydrous dimethylformamide (40 mL). *$d_2$*-Dichloromethane (3 mL, 46.7 mmol) and cesium fluoride (8.4 g, 55.3 mmol) are then added, and the mixture is heated at reflux for about 3 hours. Following standard extractive workup the crude product is purified by flash column chromatography to yield the title product as a pale yellow oil

Step 3



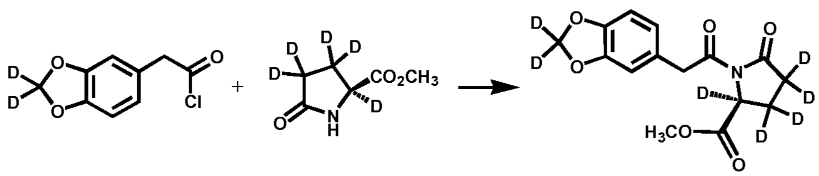

$d_2$-Benzo[1,3]dioxol-5-yl-acetyl chloride: The procedure is carried out using the methods described by Cabedo et al, *J. Med. Chem.* **2001**, *44*, 1794-1801 and references cited therein. A mixture of $d_2$-benzo[1,3]dioxol-5-yl-acetic acid methyl ester (1.0 g, 5.15 mmol) in methanol (2 mL) and 20% aqueous potassium hydroxide (10 mL) is heated at reflux for about 3 hours. Methanol is removed by evaporation, and the aqueous solution is acidified by the addition of 5% aqueous hydrochloric aid. Standard extractive workup is performed to yield $d_2$-benzo[1,3]dioxol-5-yl-acetic acid, which is then treated with excess thionyl chloride in anhydrous dichloromethane at reflux for about 3 hours. The solvent is removed *in vacuo* to give the title product.

Step 4




[00317] (S)-$d_5$-Pyroglutamic acid methyl ester: The procedure is carried out using the methods described by Mavromoustakos et al *Bioorganic & Medicinal Chemistry* **2006**, *14*, 4353–4360 and references cited therein. $d_5$-(S)- Pyroglutamic acid (C/D/N isotopes Inc., Pointe-Claire, Quebec) is treated with thionyl chloride in methanol. The crude residue is purified by flash column chromatography to yield the title product.

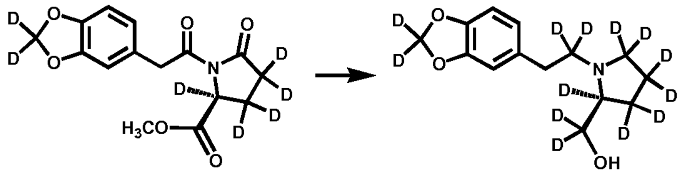
Step 5




[00318] $d_7$-(2S)-1-(2-Benzo[1,3]dioxol-5-yl-acetyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester: The procedure is carried out using the methods described by Cossy et al *Biorganic Medicinal Chemistry Letters* **1997**, *7(10)*, 1343-1344 and references cited therein.

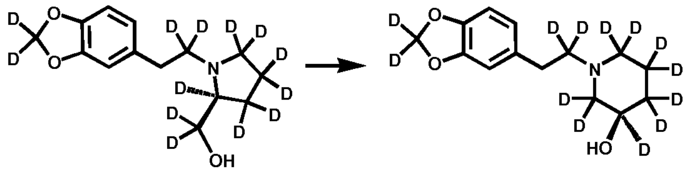
$d_2$-Benzo[1,3]dioxol-5-yl-acetyl chloride is coupled with $d_5$-(S)-pyroglutamic acid methyl ester under standard conditions. The crude residue is purified by flash column chromatography to yield the title product.

Step 6



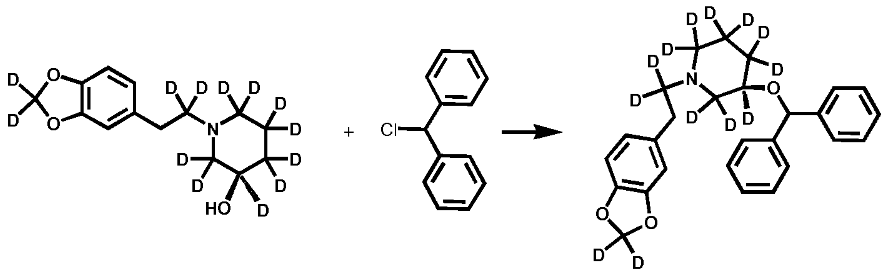
[00319] $d_{13}$-(2S)-[1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-pyrrolidin-2-yl]-methanol: The procedure is carried out using the methods described by Cossy et al *Biorganic Medicinal Chemistry Letters* **1997**, *7(10)*, 1343-1344 and references cited therein. $d_7$-(2S)-1-(2-Benzo[1,3]dioxol-5-yl-acetyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester is reduced with lithium aluminum deuteride (Sigma-Aldrich, St. Louis MO 63103) in tetrahydrofuran. Following standard extractive workup the crude product is purifed by flash column chromatography to yield the title product..

Step 7



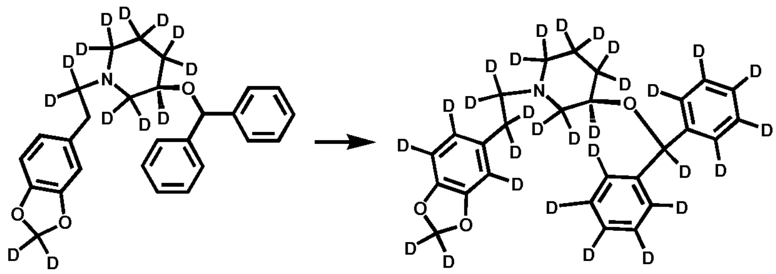
[00320] $d_{13}$-(3R)-1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol: The procedure is carried out using the methods described by Cossy et al *Tetrahedron Letters* **1995**, *36(4)*, 549-552 and references cited therein. At about -78°C and under nitrogen, trifluoroacetic anhydride (l.l equiv) is added dropwise to a solution of $d_{13}$-[1-(2-benzo[1,3]dioxol-5-yl-ethyl)-pyrrolidin-2-yl]-methanol (l equiv) in tetrahydrofuran. Under continuous stirring, the mixture is maintained at about -78°C for about 3 hours, triethylamine (4 equiv) is added dropwise, the reaction mixture is maintained at -78°C for an additional 15 minutes, and then heated at reflux for about 20 hours. Under continuous stirring, aqueous sodium hydroxide (2.5 M, 3.3 equiv) is added and the mixture maintained at about 3 hours at reflux. Following standard extractive workup with dichloromethane, the crude product is purified by flash column chromatography to afford the title product.

Step 8



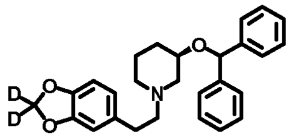
[00321] $d_{13}$-(3R)-3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: The procedure is carried out using the methods described by Cossy et al *Biorganic Medicinal Chemistry Letters* **1997**, *7(10)*, 1343-1344 and references cited therein. $d_{13}$-1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidin-3-ol is heated neat with diphenyl methylchloride for about 2 hours to give a crude residue which is purified by flash column chromatography to give the title product.

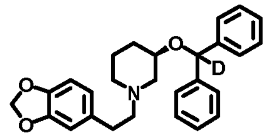
Step 9

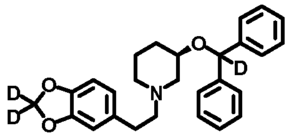


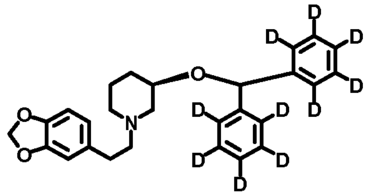
[00322] $d_{29}$-(3R)- 3-Benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine: The procedure is carried out using the methods described by Pojer *Tetrahedron Letters* **1984**, *25(23)*, 2507-2508 and references cited therein. A stirred solution of $d_{13}$-(3R)-3-benzhydryloxy-1-(2-benzo[1,3]dioxol-5-yl-ethyl)-piperidine (0.1 g) is heated at 70-100°C for about 18 hours with deuterated Raney nickel (2 mL wet) in tetrahydrofuran or deuterium oxide (5 mL). The reaction is cooled, Raney nickel is removed by filtration, and the filtrate is then diluted with $d_1$-hydrochlric acid in deuterium oxide. Standard extractive workup is performed to yield the title product. .

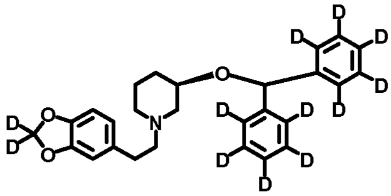
[00323] The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

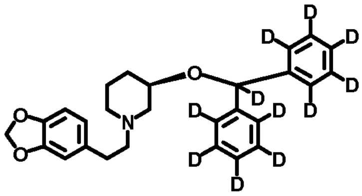


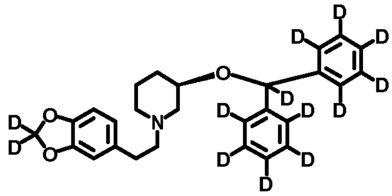


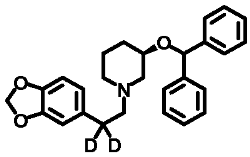


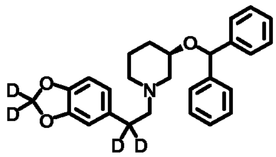


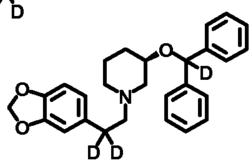


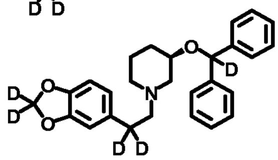


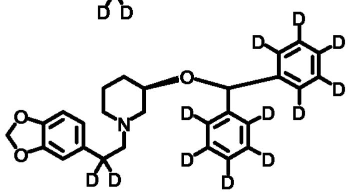


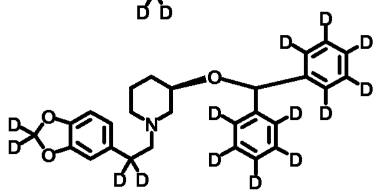


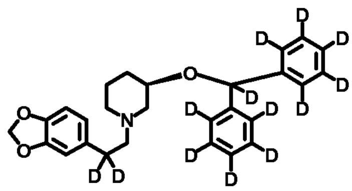


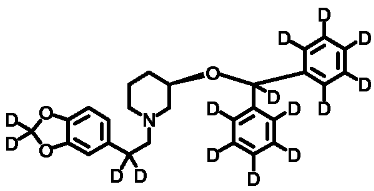


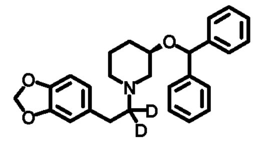
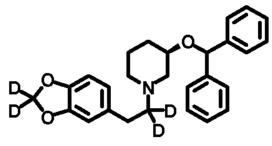
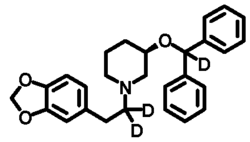
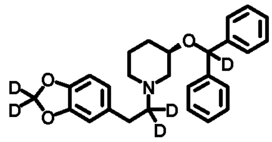
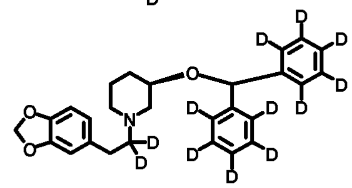
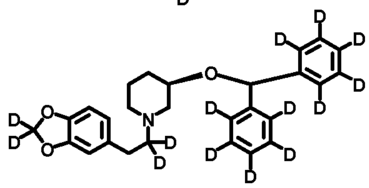
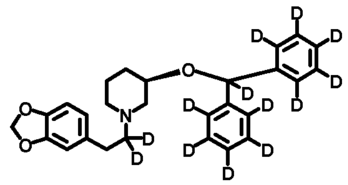
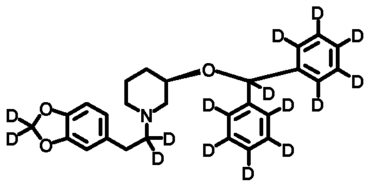
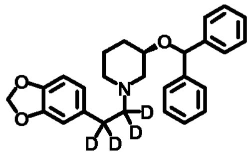
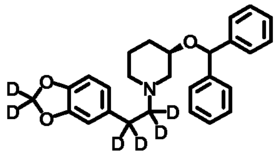
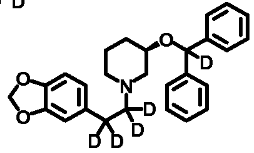
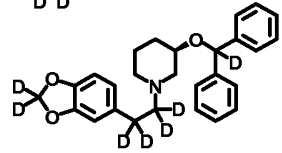
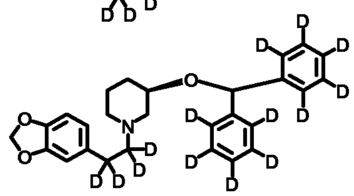
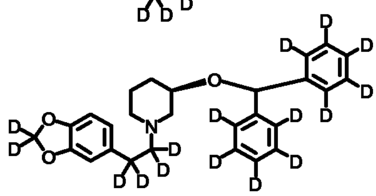
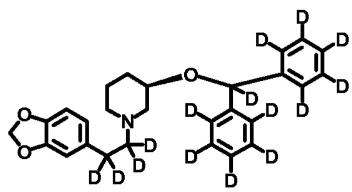
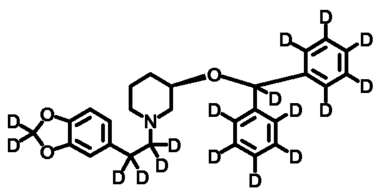


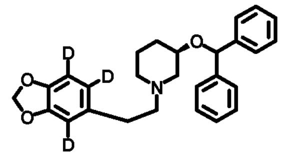
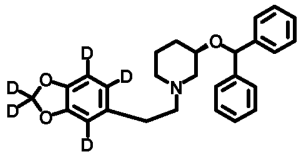
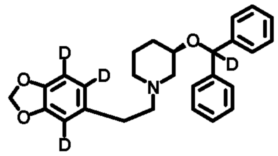
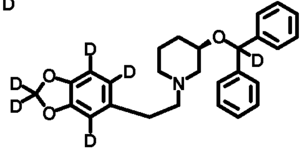
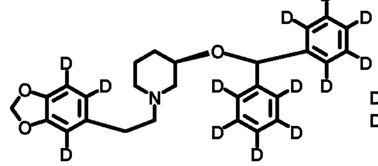
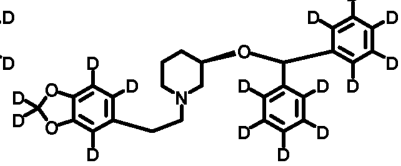
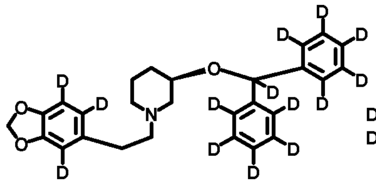
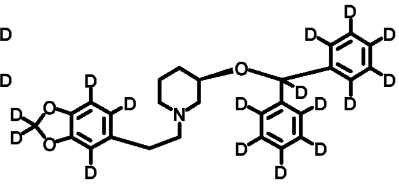
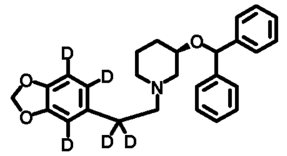
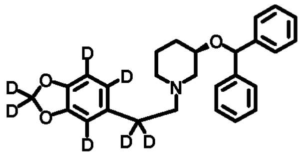
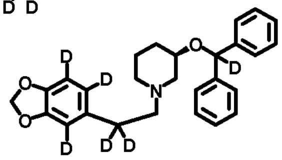
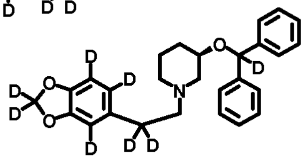
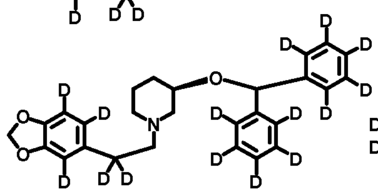
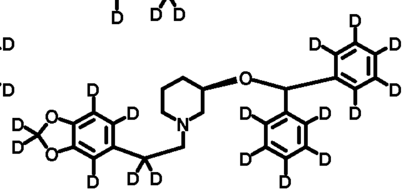
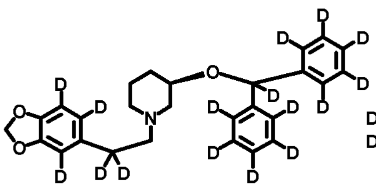
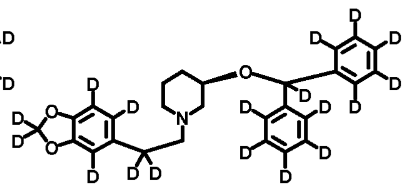


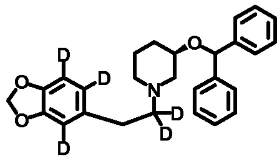
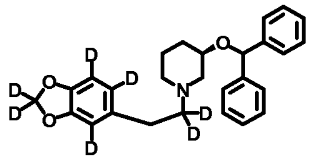
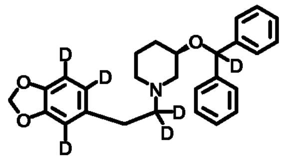
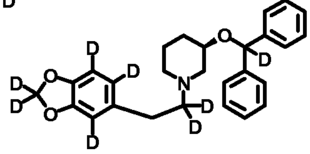
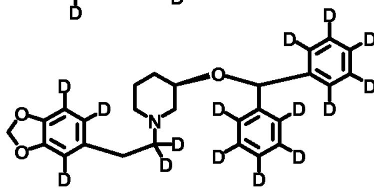
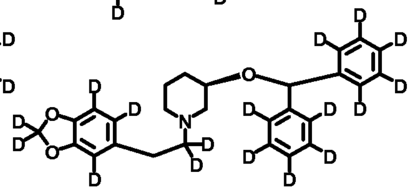
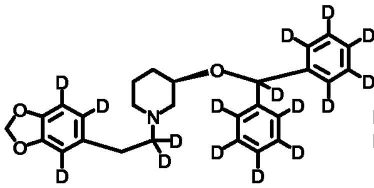
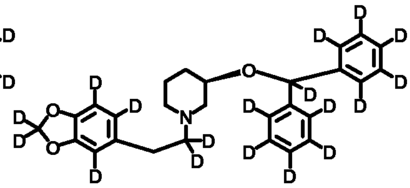
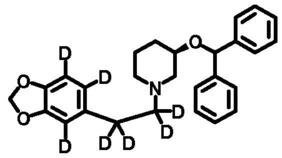
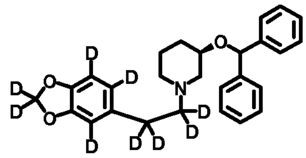
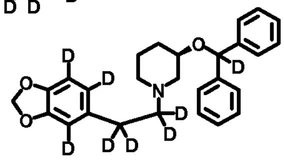
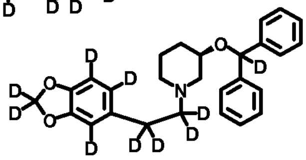
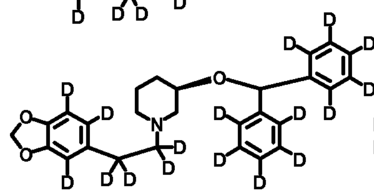
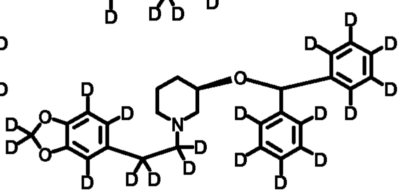
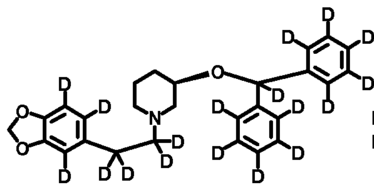
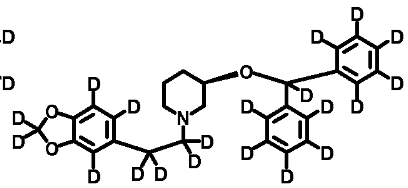






or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00324] Changes in the metabolic properties of the compounds of Examples 2-5 and their analogs as compared to its non-isotopically enriched analogs can be shown using the following assays. Other compounds listed above, which have not yet been made and/or tested, are predicted to have changed metabolic properties as shown by one or more of these assays as well.

## EXAMPLE 6

### *In vitro* Liver Microsomal Stability Assay

[00325] Liver microsomal stability assays are conducted at 1 mg per mL liver microsome protein with an NADPH-generating system in 2% $NaHCO_3$ (2.2 mM NADPH, 25.6 mM glucose 6-phosphate, 6 units per mL glucose 6-phosphate dehydrogenase and 3.3 mM $MgCl_2$). Test compounds are prepared as solutions in 20% acetonitrile-water and added to the assay mixture (final assay concentration 5 microgram per mL) and incubated at 37 °C. Final concentration of acetonitrile in the assay should be <1%. Aliquots (50µL) are taken out at times 0, 15, 30, 45, and 60 min, and diluted with ice cold acetonitrile (200 µL) to stop the reactions. Samples are centrifuged at 12,000 RPM for 10 min to precipitate proteins. Supernatants are transferred to microcentrifuge tubes and stored for LC/MS/MS analysis of the degradation half-life of the test compounds.

## EXAMPLE 7

### *In vitro* metabolism using human cytochrome $P_{450}$ enzymes

[00326] The cytochrome $P_{450}$ enzymes are expressed from the corresponding human cDNA using a baculovirus expression system (BD Biosciences, San Jose, CA). A 0.25 milliliter reaction mixture containing 0.8 milligrams per milliliter protein, 1.3 millimolar $NADP^+$, 3.3 millimolar glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 millimolar magnesium chloride and 0.2 millimolar of a compound of Formula I, the corresponding non-isotopically enriched compound or standard or control in 100 millimolar potassium phosphate (pH 7.4) is incubated at 37 °C for 20 min. After incubation, the reaction is stopped by the addition of an appropriate solvent (e.g., acetonitrile, 20% trichloroacetic acid, 94% acetonitrile/6% glacial acetic acid, 70% perchloric acid, 94% acetonitrile/6% glacial acetic acid) and centrifuged (10,000 g) for 3 min. The supernatant is analyzed by HPLC/MS/MS.

| Cytochrome $P_{450}$ | Standard |
|---|---|
| CYP1A2 | Phenacetin |
| CYP2A6 | Coumarin |
| CYP2B6 | [$^{13}C$]-(S)-mephenytoin |
| CYP2C8 | Paclitaxel |
| CYP2C9 | Diclofenac |
| CYP2C19 | [$^{13}C$]-(S)-mephenytoin |
| CYP2D6 | (+/-)-Bufuralol |
| CYP2E1 | Chlorzoxazone |
| CYP3A4 | Testosterone |
| CYP4A | [$^{13}C$]-Lauric acid |

## EXAMPLE 8

*In vitro* inhibition of human cytochrome $P_{450}$ enzymes

**CYP2C19**

Solution A: NADPH-regenerating system

[00327] To a glass tube on ice were added sequentially: Water (8 mL) in NADP+ (20 mg), glucose-6-phosphate (20 mg), magnesium chloride hexahydrate (13.3 mg) and glucose-6-phosphate dehydrogenase (60 units).

Solution B

[00328] To a glass tube on ice were added sequentially: 0.5 M $KH_2PO_4$ (pH 7.4, 2.4 mL), water (9 mL), CYP2C19 (480 μL of 1 picomol/microliter), and 3-cyano-7-ethoxycoumarin (5mM in 2% acetonitrile-water, 120 microliter).

[00329] Solution A was transferred to a 96-well black plate (80 microliter per well), followed by various concentrations of a solution of paroxetine in 20% acetonitrile-water (20 microliter per well). The reaction was initiated by adding 100 microliter of solution B to each well of the 96-well plate. The plate was incubated for 30 minutes at 37°C in the dark. The reaction was stopped by adding 75 microliter of stop buffer (4:1 acetonitrile-0.5 M Tris base) to each well, and the end point was measured in a fluorometer plate reader at $\lambda_{ex}$ = 409 nm and $\lambda_{em}$ = 460 nm. Tranylcypromine was used as positive control ($IC_{50}$ = 2.4 micromolar). Compounds having structural Formula (I) that have been tested in this assay, demonstrate that

it takes at least 1.1 times to 1.5 times the amount of deuterated compound to inhibit CYP2C19, as compared to the non-isotopically enriched drug. For example, it took 1.1 times the amount of the compound of Example 2 ($IC_{50}$ 4.0 μM), 1.4 times the amount of compound Example 3 ($IC_{50}$ 5.1 μM), and 1.5 times the amount of Example 4 ($IC_{50}$ 5.3 μM), to inhibit CYP2C19 than non-isotopically enriched zamifenacin ($IC_{50}$ 3.6 μM).

**CYP2D6**

Solution A: NADPH-regenerating system

[00330] To a glass tube on ice were added sequentially: Water (8.664 mL), 0.5 M KH2PO4 (1 mL) in NADP+ (0.136 mg), glucose-6-phosphate (2.72 mg), magnesium chloride hexahydrate (1.81 mg) and glucose-6-phosphate dehydrogenase (60 units).

Solution B

[00331] To a glass tube on ice were added sequentially: 0.5 M $KH_2PO_4$ (pH 7.4, 3 mL), water (6.725 mL), CYP2D6 (175 μL of 4 picomol/microliter), and 3-[2-(N,N diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (1 mM in 50 mM $KH_2PO_4$ pH 7.4, 100 microliter).

[00332] Solution A was transferred to a 96-well black plate (92 microliter per well), followed by various concentrations of a solution of Compound in 25% acetonitrile-water (8 microliter per well). The reaction was initiated by adding 100 microliter of solution B to each well of the 96-well plate. The plate was incubated for 40 minutes at 37°C in the dark. The reaction was stopped by adding 75 microliter of stop buffer (4:1 acetonitrile-0.5 M Tris base) to each well, and the end point was measured in a fluorometer plate reader at $\lambda_{ex}$ = 360 nm and $\lambda_{em}$ = 460 nm. Furafylline was used as positive control ($IC_{50}$ = 14.5 nanomolar). Compounds having structural Formula (I) that have been tested in this assay, demonstrate that it takes at least 1.2 times to 1.3 times the amount of deuterated compound to inhibit CYP2D6, as compared to the non-isotopically enriched drug. For example, it took 1.2 times the amount of the compound of Example 3 ($IC_{50}$ 0.4 μM), and 1.3 times the amount of compound Example 4 ($IC_{50}$ 0.42 μM), to inhibit CYP2D6 than non-isotopically enriched zamifenacin ($IC_{50}$ 0.33 μM).

**CYP3A4**

Solution A: NADPH-regenerating system

[00333] To a glass tube on ice were added sequentially: Water (8 mL) in NADP+ (20 mg), glucose-6-phosphate (20 mg), magnesium chloride hexahydrate (13.3 mg) and glucose-6-phosphate dehydrogenase (60 units).

Solution B

[00334] To a glass tube on ice were added sequentially: 0.5 M $KH_2PO_4$ (pH 7.4, 9.6 mL), water (2.328 mL), CYP3A4 (60 μL of 1 picomol/microliter), and dibenzylfluorescein (2 mM in 100% acetonitrile, 12 microliter). Solution A was transferred to a 96-well black plate (80 microliter per well), followed by various concentrations of a solution of Compound in 20% acetonitrile-water (20 microliter per well). The reaction was initiated by adding 100 microliter of solution B to each well of the 96-well plate. The plate was incubated for 10 minutes at 37°C in the dark. The reaction was stopped by adding 75 microliter of stop buffer (2 N NaOH) to each well, and incubated at 37°C for 2 hours and the end point was measured in a fluorometer plate reader at $\lambda_{ex}$ = 485 nm and $\lambda_{em}$ = 538 nm. Ketoconazole was used as positive control ($IC_{50}$ = 5.7 nanomolar). Compounds having structural Formula (I) that have been tested in this assay, demonstrate that it takes at least 1.6 times to 1.7 times the amount of deuterated compound to inhibit CYP3A4, as compared to the non-isotopically enriched drug. For example, it took 1.6 times the amount of the compound of Example 3 ($IC_{50}$ 1.48 μM), and 1.64 times the amount of compound Example 4 ($IC_{50}$ 1.53 μM), to inhibit CYP3A4 than non-isotopically enriched zamifenacin ($IC_{50}$ 0.93 μM).

## EXAMPLE 9

### Monoamine Oxidase A Inhibition and Oxidative Turnover

[00335] The procedure is carried out using the methods described by Weyler, *Journal of Biological Chemistry* **1985**, *260*, 13199-13207. Monoamine oxidase A activity is measured spectrophotometrically by monitoring the increase in absorbance at 314 nm on oxidation of kynuramine with formation of 4-hydroxyquinoline. The measurements are carried out, at 30 °C, in 50mM $NaP_i$ buffer, pH 7.2, containing 0.2% Triton X-100 (monoamine oxidase assay buffer), plus 1 mM kynuramine, and the desired amount of enzyme in 1 mL total volume.

## EXAMPLE 10

## Monoamine Oxidase B Inhibition and Oxidative Turnover

[00336] The procedure is carried out using the methods described by Uebelhack, *Pharmacopsychiatry* **1998**, *31*, 187-192.

## EXAMPLE 11

## Muscarinic $M_3$ Receptor Modulation

[00337] The procedure is carried out using the methods described by Smith et al, *Journal of Receptor and Signal Transduction Research* **1997**, 17(1-3), 177-184.

## EXAMPLE 12

## Stimulation of Jejunal Motility with ECG and Salivary Secretion Monitoring in Concious and Anesthetized Dog

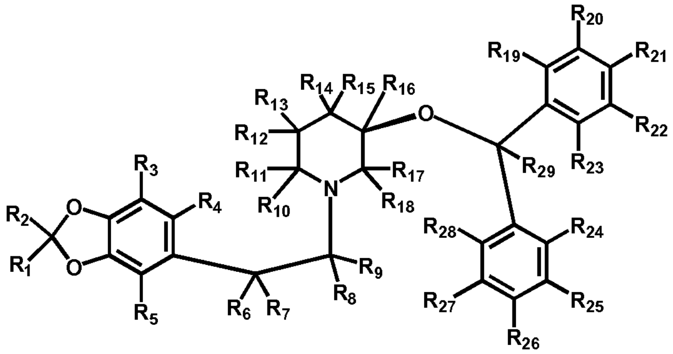
[00338] The procedure is carried out using the methods described by Wallis, R. M., *Life Sciences* **1995**, *56*(11/12), 861-868 and references cited therein.

* * * * *

[00339] The examples set forth above are disclosed to give a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what the inventors regard as what is disclosed herein. Modifications that are obvious are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A compound having structural Formula I



(I)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ are independently selected from the group consisting of hydrogen and deuterium; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ is deuterium.

2. The compound as recited in Claim 1, wherein said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

3. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 98%.

4. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 90%.

5. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 50%.

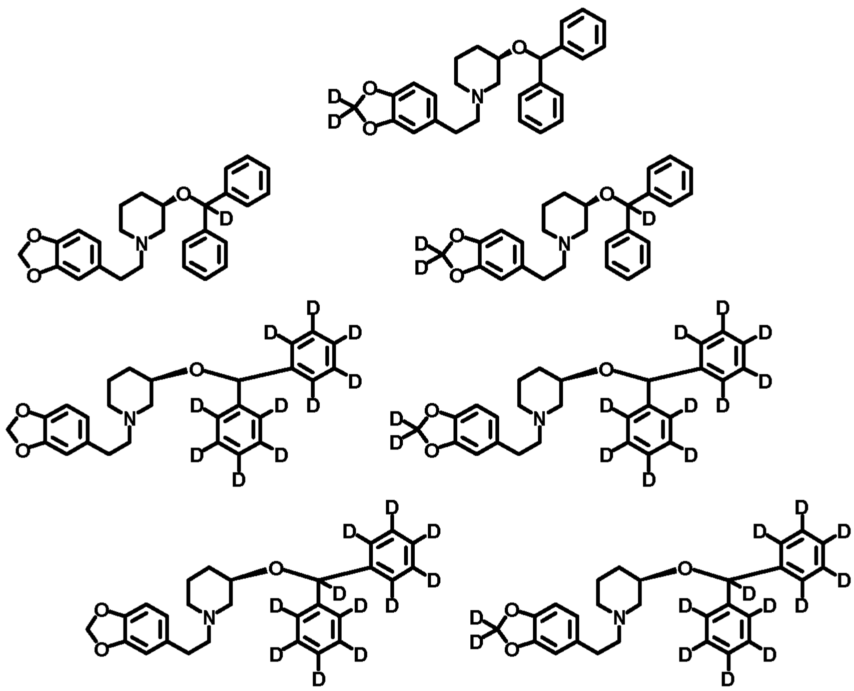
6. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 20%.

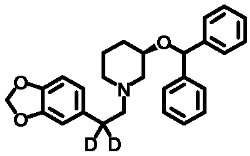
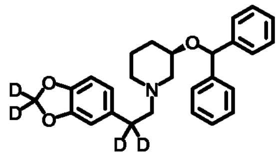
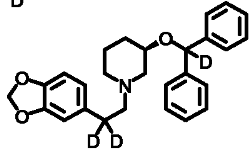
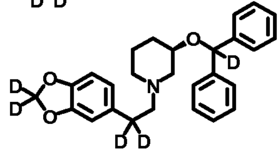
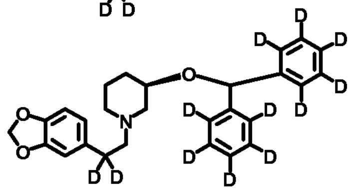
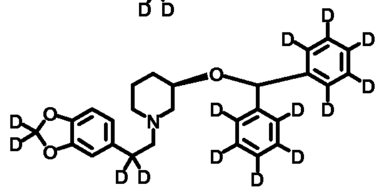
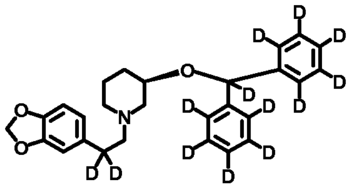
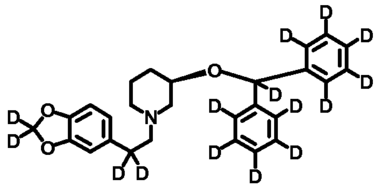
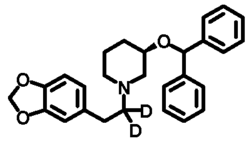
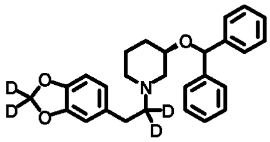
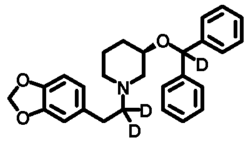
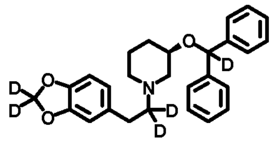
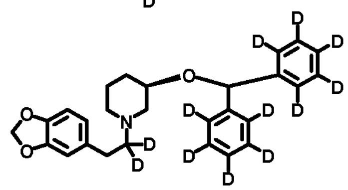
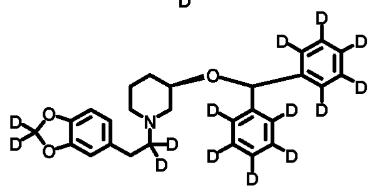
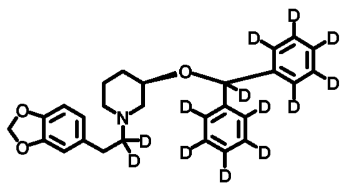
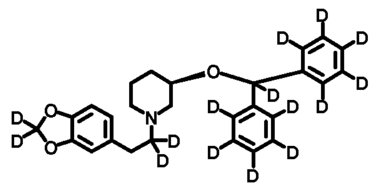
7. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 10%.

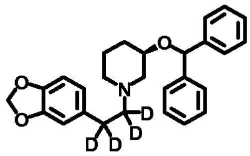
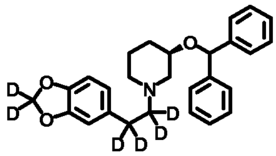
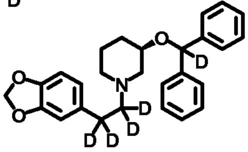
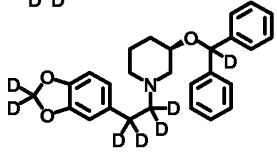
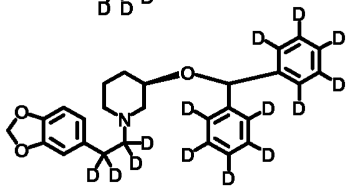
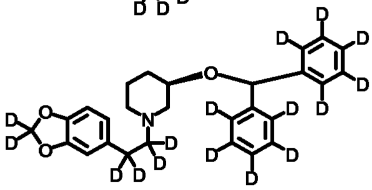
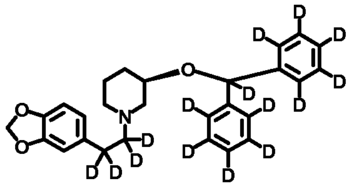
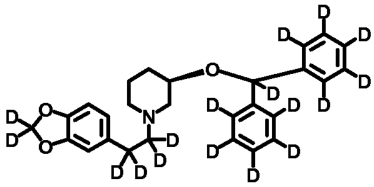
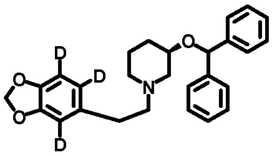
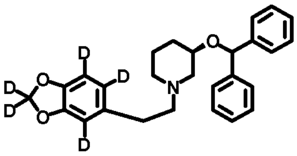
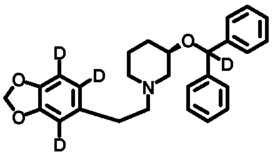
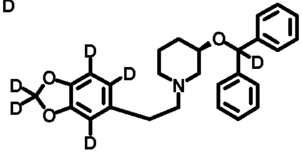
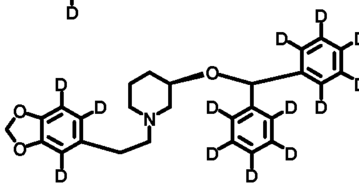
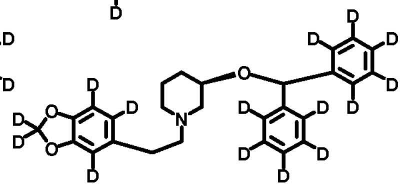
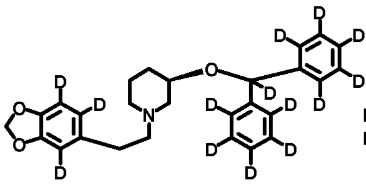
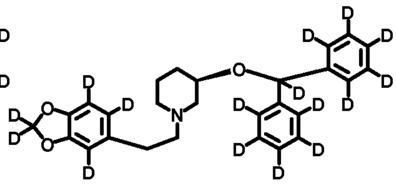
8. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 5%.

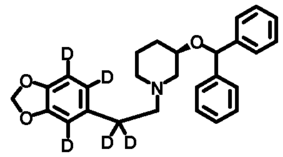
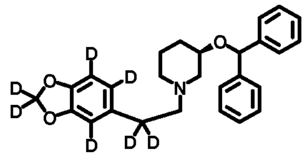
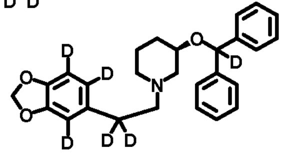
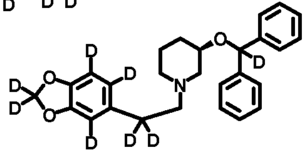
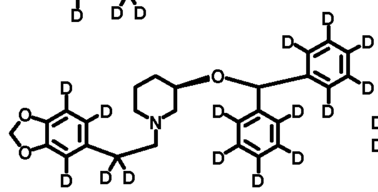
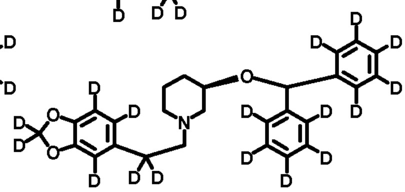
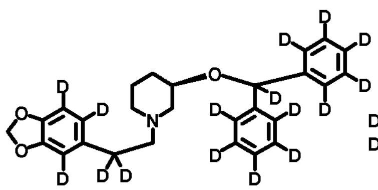
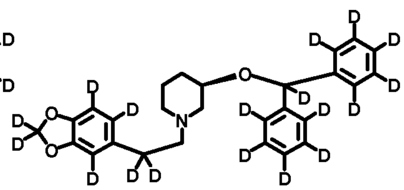
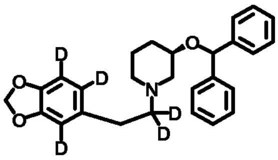
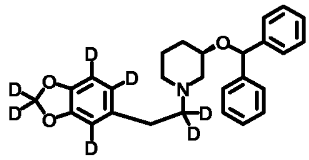
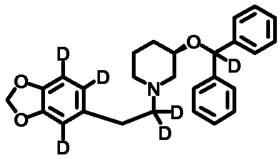
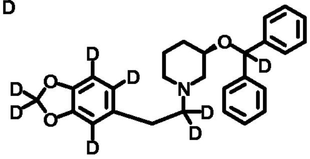
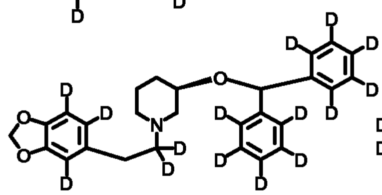
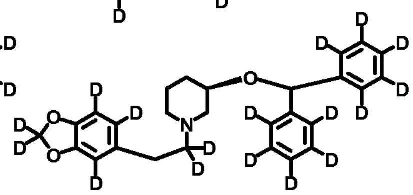
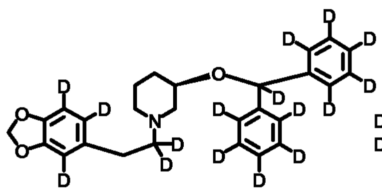
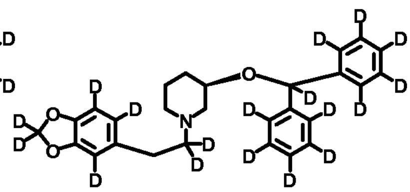
9. The compound as recited in Claim 1, wherein at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, and $R_{29}$ independently has deuterium enrichment of no less than about 1%.

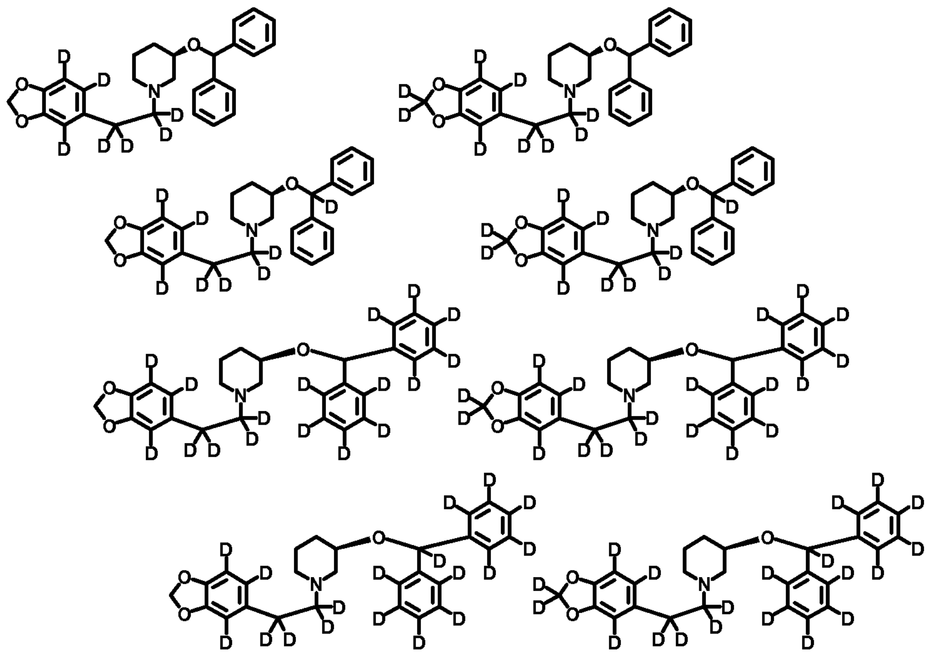
10. The compound as recited in Claim 1, wherein the compound is selected from the group consisting of:



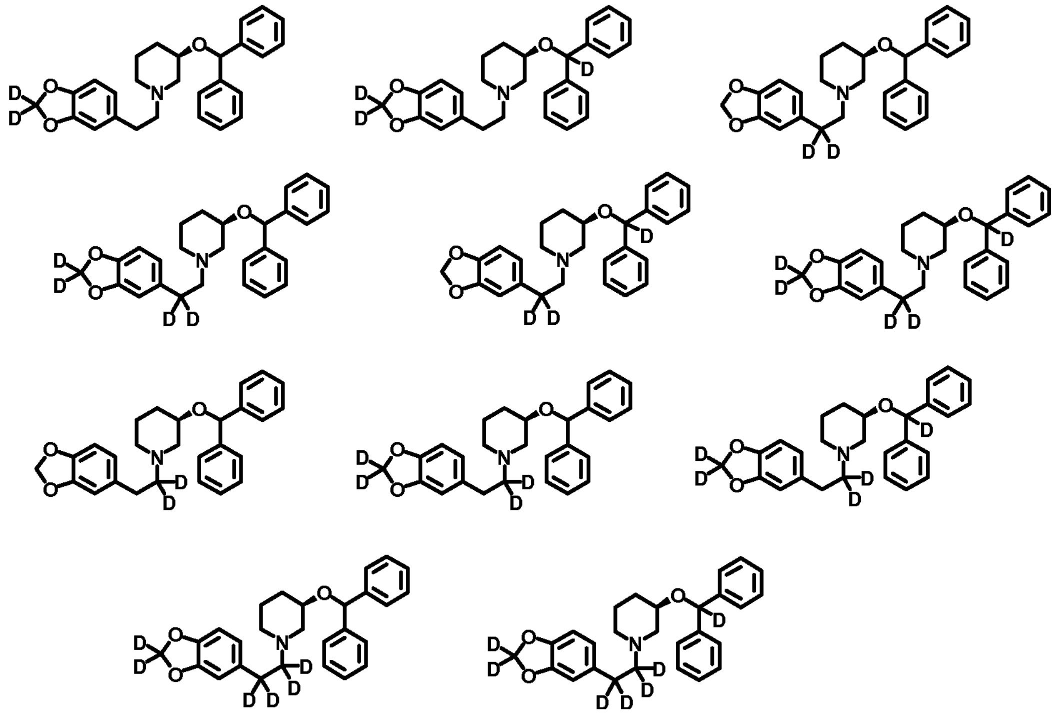


or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

11. The compound as recited in Claim 10, wherein said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.
12. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 98%.
13. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 90%.
14. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 50%.
15. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 20%.
16. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 10%.
17. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 5%.

18. The compound as recited in Claim 10, wherein each of said positions represented as D have deuterium enrichment of at least 1%.

19. The compound as recited in Claim 1, wherein the compound is selected from the group consisting of:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

20. The compound as recited in Claim 19, wherein said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

21. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 98%.

22. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 90%.

23. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 50%.

24. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 20%.
25. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 10%.
26. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 5%.
27. The compound as recited in Claim 19, wherein each of said positions represented as D have deuterium enrichment of at least 1%.
28. A pharmaceutical composition comprising the compound as recited in Claim 1 and one or more pharmaceutically acceptable carriers.
29. A pharmaceutical composition as recited in Claim 28, further comprising one or more release-controlling excipients.
30. The pharmaceutical composition as recited in Claim 28, further comprising one or more non-release controlling excipients.
31. The pharmaceutical composition as recited in Claim 28, wherein the composition is suitable for oral, parenteral, or intravenous infusion administration.
32. The pharmaceutical composition as recited in Claim 31, wherein the oral dosage form is a tablet or capsule.
33. The pharmaceutical composition as recited in Claim 31, wherein the compound is administered in a dose of about 0.5 milligram to about 1,000 milligram.
34. The pharmaceutical composition as recited in Claim 28, further comprising another therapeutic agent.
35. The pharmaceutical composition as recited in Claim 34, wherein the therapeutic agent is selected from the group consisting of prokinetics, tachykinins, anticholinergic agents, opioids, 5-$HT_3$ antagonists, alpha adrenergic agents, $CCK_A$ antagonists, NMDA receptor antagonists, serotoninergic agents, endothelin converting enzyme (ECE) inhibitors, thromboxane enzyme antagonists, potassium channel openers, thrombin inhibitors, growth factor inhibitors, platelet activating factor (PAF) antagonists, anti-platelet agents, Factor VIIa Inhibitors, Factor Xa Inhibitors, renin inhibitors, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, anti-atherosclerotic agents, MTP Inhibitors, calcium channel blockers, potassium channel activators, alpha-PDE5 agents, beta-PDE5 agents, antiarrhythmic agents, diuretics,

anti-diabetic agents, PPAR-gamma agonists, mineralocorticoid enzyme antagonists, aP2 inhibitors, protein tyrosine kinase inhibitors, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-disruptor agents, microtubule-stablizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, antalarmin, Z-338 and platinum coordination complexes.

36. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a prokinetic.

37. The pharmaceutical composition as recited in Claim 36, wherein the prokinetic is selected from the group consisting of cisapride, domperidone, lirexapride, metoclopramide, mosapride, neurotrophin-3, norcisapride, prucalipride, renzapride, tegaserod, TS-951, and YM-53389.

38. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a tachykinin.

39. The pharmaceutical composition as recited in Claim 38, wherein the tachykinin is selected from the group consisting of exlopitant, nepadudant, and SR-140333.

40. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is an anticholinergic agent.

41. The pharmaceutical composition as recited in Claim 40, wherein the anticholinergic agent is selected from the group consisting of darifenacin, dicyclomine, hyoscyamine, and YM-905.

42. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is an opioid.

43. The pharmaceutical composition as recited in Claim 42, wherein the opioid is selected from the group consisting of morphine, codeine, thebain, diacetylmorphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, nicomorphine, fentanyl, 3-methylfentanyl, alfentanil, sufentanil, remifentanyl, carfentanyl, ohmefentanyl, pethidine, ketobemidone, propoxyphene, dextropropoxyphene, methadone, loperamide, pentazocine, buprenorphine, etorphine, butorphanol, nalbufine, levorphanol, naloxone, naltrexone, and tramadol.

44. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a 5-$HT_3$ antagonist.
45. The pharmaceutical composition as recited in Claim 44, wherein the 5-$HT_3$ antagonist is selected from the group consisting of alosetron, cilansetron, granisectron, and ondansetron.
46. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a $CCK_A$ antagonist.
47. The pharmaceutical composition as recited in Claim 46, wherein the $CCK_A$ antagonist is selected from the group consisting of dexloxigumide, loxiglumide, proglumide, and proxiglumide.
48. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a NMDA receptor antagonist.
49. The pharmaceutical composition as recited in Claim 48, wherein the NMDA receptor antagonist is selected from the group consisting of dizocilpine and memantine.
50. The pharmaceutical composition as recited in Claim 35, wherein the therapeutic agent is a serotoninergic agent.
51. The pharmaceutical composition as recited in Claim 50, wherein the serotoninergic agent is selected from the group consisting of buspirone, piboserod, and sumatriptan.
52. The pharmaceutical composition as recited in Claim 34, wherein the therapeutic agent is selected from the group consisting of antalarmin and Z-338.
53. A method for the treatment, prevention, or amelioration of one or more symptoms of a muscarinic receptor-mediated disorder, in a subject, comprising administering a therapeutically effective amount of a compound as recited in Claim 1.
54. The method as recited in Claim 53, wherein the muscarinic receptor-mediated disorder is selected from the group consisting of irritable bowel syndrome, chronic obstructive pulmonary disease, and urinary incontinence.
55. The method as recited in Claim 53, wherein the muscarinic receptor-mediated disorder is associated with smooth muscle tone or smooth muscle contractility.
56. The method as recited in Claim 53, wherein the muscarinic receptor-mediated disorder can be lessened, alleviated, or prevented by administering a muscarinic receptor modulator.

57. The method as recited in Claim 53, wherein said compound has at least one of the following properties:
    **a)** decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;
    **b)** increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
    **c)** decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
    **d)** increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
    **e)** an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.
58. The method as recited in Claim 53, wherein said compound has at least two of the following properties:
    **a)** decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;
    **b)** increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
    **c)** decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;
    **d)** increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
    **e)** an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.
59. The method as recited in Claim 53, wherein the method affects a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed cytochrome P450 isoform in the subject, as compared to the corresponding non-isotopically enriched compound.

60. The method as recited in Claim 59, wherein the cytochrome $P_{450}$ isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

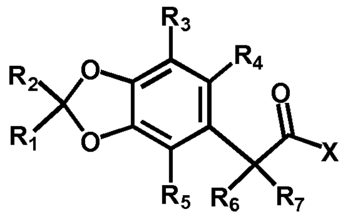
61. The method as recited in Claim 53, wherein said compound is characterized by decreased inhibition of at least one cytochrome $P_{450}$ or monoamine oxidase isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

62. The method as recited in Claim 61, wherein said cytochrome $P_{450}$ or monoamine oxidase isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, $MAO_A$, and $MAO_B$.

63. The method as recited in Claim 53, wherein the method affects the treatment of the disease while reducing or eliminating a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

64. The method as recited in Claim 63, wherein the diagnostic hepatobiliary function endpoint is selected from the group consisting of alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGTP," "γ-GTP," "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein.

65. A compound having structural Formula II:



(II)

wherein:

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is selected from the group consisting of hydrogen or deuterium;

X is selected from the group consisting of hydroxyl, alkyloxy, and a leaving group; and

at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is deuterium.

66. A process for the manufacture of a compound as recited in Claim 1, comprising a reaction which contains the compound as recited in Claim 65.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/064031

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. C07D405/06 A61K31/4525 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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 |
|---|---|
| 12 August 2008 | 21/08/2008 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kollmannsberger, M |

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