Title: SUBSTITUTED BENZHYDRYLETHERS

Abstract: Disclosed herein are substituted benzhydrylethers of Formula (I), processes of preparation thereof, pharmaceutical compositions thereof, and methods of their use therof.

(51) International Patent Classification: C07D 207/10 (2006.01)

(21) International Application Number: PCT/US2009/031704

(22) International Filing Date: 22 January 2009 (22.01.2009)

(25) Filing Language: English

(26) Publication Language: English


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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published: without international search report and to be republished upon receipt of that report
SUBSTITUTED BENZHYDREL ETERS

[0001] This application claims the benefit of priority of United States provisional application No. 61/022,667, filed January 22, 2008, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[0002] Disclosed herein are substituted benzhydrel ether histamine receptor modulators and pharmaceutically acceptable salts and prodrugs thereof, the chemical synthesis thereof, and the medical use of such compounds for the treatment and/or management of allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, disorders ameliorated by bronchodilation, and/or or any disorder ameliorated, prevented or lessened by modulating histamine receptors.

6(4), 769-75. As compared with most antihistamine drugs, clemastine has less prominent central nervous system and anticholinergic side effects.

Clemastine is extensively metabolized in the human liver by O-dealkylation, direct oxidation, aromatic hydroxylation, aliphatic oxidation, and alcohol dehyration followed by enzymatic hydrolysis. Choi et al., *J Pharm Pharmacol* 1999, 51, 53-59. The main metabolites produced in humans are aromatic O-dealkylated metabolites formed after cleavage at the ether linkage. Other detected metabolites include fragments of the aliphatic region with one to two additional oxygens, as well as a glucuronidated metabolite. Tevell et al., *Rapid Comm in Mass Spec* 2004, 18, 2267-2272. Metabolism destroys the drug’s chirality and three-point geometry, which is thought to be required for its antihistamine activity. Naruto et al., *Eur J Med Chem Cmm Ther* 1985, 20, 529-532. In human subjects who received histamine injections over a 24 hour period, the antihistaminic activity of clemastine reached a peak at 5 to 7 hours, and generally persisted for 10 to 12 hours. In adults, the starting dose is 1 mg clemastine twice daily, with a maximum recommended dose of 2 mg three times daily. Medical Economics Data: Clemastine. *Physician’s Desk Reference for Prescription Drugs* 1996, 17th ed., 2297-2299. Clemastine’s major side effects include, but are not limited to, sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, and thickening of bronchial secretions. Clemastine was found to significantly impair driving performance after both one-time and repeated (daily) administration. Verster et al., *Ann Allergy Asthma Immunol* 2004, 92(3), 294-303. Clemastine is a potent inhibitor of the \( \text{P}_{450} \) cytochrome CYP2D6, and may cause clinically relevant drug-drug interactions with cardiovascular, antidepressant, and antipsychotic CYP2D6 substrates. Hamelin et al., *Drug Metabolism and Disposition* 1998, 26(6), 536-539.
Disclosed herein is a compound of Formula I:

I

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

- $R_1$ to $R_2$ are independently selected from the group consisting of hydrogen and deuterium;
- $R_{21}$ and $R_{22}$ are independently selected from the group consisting of $-\text{CD}_3$, $-\text{CD}_2\text{H}$, $-\text{CDH}_2$ and $\text{CH}_3$; and
- at least one of $R_{21}$ to $R_{22}$ is deuterium or contains deuterium.

Also disclosed herein are pharmaceutical compositions comprising at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof; in combination with one or more pharmaceutically acceptable excipients or carriers.

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) as 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.

Also disclosed herein are processes for preparing a compound as disclosed herein as a histamine receptor modulator.

In certain embodiments, a method for the treatment, prevention, or amelioration of one or more symptoms of a histamine receptor-mediated disorder in a subject by administering a therapeutically effective amount of a compound as disclosed herein.
In another aspect are processes for preparing a compound as disclosed herein as a histamine receptor modulator, or other pharmaceutically acceptable derivatives such as salts, solvates, or prodrugs.

In certain embodiments, a method for the treatment, prevention, or amelioration of one or more symptoms of a histamine receptor-mediated disorder in a subject by administering a therapeutically effective amount of a compound as disclosed herein.

In other embodiments said histamine receptor-mediated disorder is selected from the group consisting of allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and any disorder ameliorated by bronchodilation.

In certain embodiments said histamine receptor-mediated disorder can be ameliorated by modulating histamine receptors.

In further embodiments, said method comprises a compound disclosed herein and one or more pharmaceutically acceptable carriers.

In yet further embodiments said method further comprises administering another therapeutic agent.

In certain embodiments, the compounds disclosed herein can be combined with one or more therapeutic agents, including, but not limited to, decongestant treatments, antitussive treatments, mucolytic treatments, expectorant treatments, antiallergic non-steroidal treatments, steroidal drugs, antihistamine treatments, leukotriene receptor antagonists, phosphodiesterase inhibitors, CYP3A inhibitors, CYP3A inducers, protease inhibitors, antifungal agents, antibacterials, antimycobacterial agents, sepsis treatments, steroidal drugs, anticoagulants, thrombolytics, non-steroidal anti-inflammatory agents, antiplatelet 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 Vila 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, antiinflammatory drugs, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-
disruptor agents, microtubule-stabilizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, and platinum coordination complexes.

In certain embodiments, the compounds disclosed herein can be combined with one or more antitussive treatments known in the art, including, but not limited to, dextromethorphan, ethylmorphine, hydrocodone, codeine, normetahdone, noscapine, pholcodine, thebacon, dimemorfan, acetylhydrocodeine, benzonatate, benproperine, clobutinol, isoaminile, pentoxyverine, oxolamine, oxeladin, clofedanol, pipazetate, bibenzonium bromide, butamirate, fedrilate, zipeprol, dibunate, droxypropine, prenoxidazine, dropropizine, cloperastine, meprotixol, piperidione, tipepidine, morclofone, nepinalone, levodropropizine, and dimethoxanate.

In certain embodiments, the compounds disclosed herein can be combined with one or more mucolytic treatments known in the art, including, but not limited to, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, dornase alfa, neltenezine, and erdosteine.

In certain embodiments, the compounds disclosed herein can be combined with one or more expectorant treatments known in the art, including, but not limited to, tyloxapol, potassium iodide, guaifenesin, ipecacuanha, althea root, senega, antimony pentasulfide, creosote, guaiacolsulfonate, and levoverbenone.

In certain embodiments, the compounds disclosed herein can be combined with one or more antiallergic non-steroidal treatments known in the art, including, but not limited to, cromoglicic acid, levocabastine, azelastine, antazoline, spaglumic acid, thonzylamine, nedocromil, and olopatadine.

In certain embodiments, the compounds disclosed herein can be combined with one or more steroidal drugs known in the art, including, but not limited to, aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone acetate, hydrocortisone (Cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone, flunisolide, flucicasone, mometasone furoate, tiocortol, and budesonide.

In certain embodiments, the compounds disclosed herein can be combined with one or more antihistamine treatments known in the art, including, but not limited to, mepyramine, antazoline, diphenhydramine, carbinoxamine, doxylamine, dimenhydrinate, pheniramine, chlorophenamine, brompheniramine, triprolidine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, promethazine, alimemazine, cyproheptadine, azatadine, and ketotifen.
In yet other embodiments, the compounds disclosed herein can be combined with one or more leukotriene receptor antagonists known in the art, including, but not limited to, montelukast, pranlukast, and zafirlukast.

In certain embodiments, the compounds disclosed herein can be combined with one or more non-steroidal anti-inflammatory agents known in the art, including, but not limited to, aceclofenac, acemetacin, amoxicillin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoracoxib, fainstalmine, fenbuten, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, suprofen, tenoxicam, tiaprofenic acid, and tolmetin.

In certain embodiments, the compounds disclosed herein can be combined with one or more decongestant treatments known in the art, including, but not limited to, phenylpropanolamine hydrochloride, pseudoephedrine, phenylephrine, ephedrine, ephedrine, pseudooxymetanoxylamine, xylometazoline, tetryzoline, naphazoline, cyclopentamine, tramazoline, metizoline, fenoxazoline, tymazoline, and oxymetazoline.

In certain embodiments said method has at least one effect selected from the group consisting of:

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.

In other embodiments said method has at least two effects selected from the group consisting of:

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.

[0029] In certain embodiments said method 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.

[0030] In other embodiments said cytochrome P_{450} isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0031] In yet further embodiments said method 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.

[0032] 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, CYP1B1, CYP1B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAOA, and MAO_B.

[0033] In yet other embodiments said 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.

[0034] In 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.

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 explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.

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. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

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

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.

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

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

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.

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

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 known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

When values are disclosed as ranges and the notation "from ni ... to n₂" or "ni-n₂" is used, wherein ni and n₂ are numbers, then unless otherwise specified, this notation includes these numbers themselves and the range between them. This range may be integral or continuous between and including the end values.

The term "is/are deuterium," when used to describe a given position in a molecule such as R₁-R₂₂ 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 another embodiment deuterium enrichment is no less than about 10%, in another no less than about 50%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

The term "contains deuterium," when used to describe a given position in a molecule such as R₂₁-R₂₂ means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In an another embodiment deuterium enrichment is no less than about 10%, in another no less than about 50%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.
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.

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.

The terms "substantially pure" and "substantially homogeneous" mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods used by one of ordinary skill in the art, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), infrared spectroscopy (IR), gas chromatography (GC), Ultraviolet Spectroscopy (UV), nuclear magnetic resonance (NMR), atomic force spectroscopy and mass spectroscopy (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.

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.

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 or carriers, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

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.

The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease," "syndrome," 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.

[0054] 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.

[0055] 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.

[0056] The term "histamine receptor" refers to metabotropic G-protein-coupled receptors expressed throughout the body, specifically in smooth muscles, on vascular endothelial cells, in the heart, and in the central nervous system. The histamine receptor is linked to an intracellular G-protein (Gq) which activates phospholipase C and the phosphatidylinositols (PIP2) signalling pathways. Histamine receptors are activated by endogenous histamine, which is released by neurons which have their cell bodies in the tuberomamillary neurons of the hypothalamus. A histamine receptor antagonist serves to reduce or eliminate effects mediated by histamine. A histamine receptor agonist serves to enhance or replicate the effects mediated by histamine.

[0057] The term "histamine receptor-mediated disorder," refers to a disorder that is characterized by abnormal histamine receptor activity or normal histamine receptor activity that, when that activity is modified, leads to the amelioration of other abnormal biological processes. A histamine receptor-mediated disorder may be completely or partially mediated by modulation of the histamine receptor. In particular, a histamine receptor-mediated disorder is one in which modulation of the histamine receptor activity results in some effect on the underlying disorder, e.g., a histamine receptor modulator results in some improvement in at least some of the patients being treated.

[0058] The term "modulating histamine receptors" or "histamine receptor modulator" refers to the ability of a compound disclosed herein to alter the function of a histamine receptor. A modulator may activate the activity of a histamine receptor, may activate or inhibit the activity of a histamine receptor depending on the concentration of the compound exposed to the histamine receptor, or may inhibit the activity of a histamine 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 "modulating histamine receptors" or "histamine receptor modulator" also
refers to altering the function of a histamine receptor by increasing or decreasing the probability that a complex forms between a histamine receptor and a natural binding partner. A modulator may increase the probability that such a complex forms between the histamine receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the histamine receptor and the natural binding partner depending on the concentration of the compound exposed to the histamine receptor, and or may decrease the probability that a complex forms between the histamine receptor and the natural binding partner.

[0059] 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).

[0060] 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.

[0061] The term "chlorinating reagent" refers to a reactive chemical reagent used in chlorination reactions, whereby chlorine is transferred to a substrate. Examples of chlorinating agents include, but are not limited to, thionyl chloride, chlorine gas, carbon tetrachloride, cyanuric chloride, hexachloro-2-propanone, N-chlorosuccinimide, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, phosphorus (V) oxychloride, and sulfuryl chloride.

[0062] The term "resolving reagent" refers to optically pure reagents used to resolve a racemic compound into its individual stereoisomers. The racemic compound and the resolving agent must have suitable functional groups capable of interacting with each other. Resolution of racemic compounds is possible when the optically pure resolving agent binds to the
racemic compound, usually by salt formation, to form pairs of diastereomers. It is essential that the configuration of the chiral centers remains unchanged during the formation of the diastereomers as well as during the regeneration of the optically pure reagent. The different diastereomeric pairs can then be separated by conventional techniques in physical chemistry, such as fractional crystallization. Once separated, simple deprotonation affords the pure enantiomer. Examples of resolving agents include, but is not limited to, (-)-3 β-Acetoxy-5- eteniacid, L-(−) α-Amino-ε-caprolactam hydrochloride, (R)-(−)-l-Amino-2-propanol, (S)-(+)l-Amino-2-propanol, (R)-(−)-l-(9-Anthryl)-2,2,2-trifluoroethanol, (5)-(+)l-(9-Anthryl)-2,2,2-trifluoroethanol, L-Aspartic, (R)-l,4-Benzodioxane-2-carboxylic acid, (S)-l,4- Benzodioxane-2-carboxylic acid, cis-(1R,2S)-(+)2-(Benzylamino)cyclohexanemethanol, cis-(IS,2R)-(−)-2-(Benzyaminocyclohexanemethanol, (S)-N-Benzyl-l-(1-naphthyl)ethylamine hydrochloride, (R)-(−)-N-Benzyl 1-(1-naphthyl)ethylamine hydrochloride, (R)-(−)-l,l′-Binaphthalene-2,2′-diyl hydrogen phosphate, (S)-(+) l,l′-Binaphthalene-2,2′-diyl hydrogen phosphate, (R)-(−)-l,l′-Binaphthalene-2,2′-diyl hydrogen phosphate, (5)-(+)l,l′-Binaphthalene-2,2′-diyl hydrogen phosphate, (+)l,4-Bis-O-(4-chlorobenzyl)-D-threitol, (−)-l,4-Bis-O-(4-chlorobenzyl)-L-threitol, (+)l,6-Bis-(2-chlorophenyl)-1,6-diphenyl-2,4-hexadiyne-1,6-diol, (+)-Bis[(R)-(−)-1-phenylethyl] amine hydrochloride, N,N-Bis[(R)-(−)-1-phenylethyl]phthalamic acid, N,N-Bis[(5)-(−)-l-phenylethyl]phthalamic acid, (+)-3-Bromocamphor-10-sulfonic acid hydrate, (lS)-(−)-3-Bromocamphor-10-sulfonic acid hydrate, (R)-(−)-l-(4-Bromophenylethyl)amin e, (E)-(−)l-(4-Bromophenylethyl)amine, Brucine, Brucine sulfate salt, (R)-(−)-2-Butanol, (S)-(+)2-Butanol, (1R)-(−)-Camphanic acid, (15H−)Camphanic acid, (IR,3S)-(++)-Camphoric acid, (IS,3R)-(−)-Camphoric acid, (+)-Camphoric acid, (−)-Camphoric acid, (1R)-(−)-10-Camphorsulfonic acid, (IS)-(−)-10-Camphorsulfonic acid, (15)-(+)10-Camphorsulfonic acid, chloride, (IR)-(−)-10-Camphorsulfonic acid, chloride, (R)-4-Chloro-α-methylbenzylamine, (S)-4-Chloro-α-methylbenzylamine, Cinchonidine, (+)-Cinchonine, (+)-Dehydroabietylamine, (+)-O,O′-Diacetyl-l-laric acid anhydride, (+)-2,3-Dibenzoyl-D-tartaric acid, (+)-2,3-Dibenzoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid, (-)-O,O′-Dibenzoyl-l-tartaric acid monohydrate, (−)-O,O′-Dibenzoyl-l-tartaric acid mono(dimethylamide), (−)-N,N′-Dibenzyl-D-tartaric diamide, (+)-Diethyl D-tartrate, (−)-Diisopropyl D-tartrate, (R)-(−)-N,α-Dimethylbenzylamine, (S)-(−)-N,α-Dimethylbenzylamine, (R)-(−)-N,N-Dimethyl-1-phenylethylamine, (S)-(−)-N,N-Dimethyl-1-phenylethylamine, (R)-(−)-3,5-Dinitro-N-(l-phenylethyl)benzamide, (5)-(+)3,5- Dinitro-N-(l-phenylethyl)benzamide, (−S)-(−)-3,5-Dinitro-N-(l-phenylethyl)benzamide, Dip- toluoyl-D-tartaric acid monohydrate, (+)-O,O′-Di-p-toluoyl-D-tartaric acid, (+)-O,O′-Di-p-
toluoyl-D-tartaric acid, (-)-0,(7-Di-p-toluoyl-L-tartaric acid, (-)-O,O’-Di-p-toluoyl-L-tartaric, (1R,2S>(-)-Ephedrine, (1S,2R>(-)-Ephedrine hydrochloride, (+)-Ephedrine hydrochloride, (-)-Ephedrine, (+)-l-(9-Fluorenyl)ethyl chloroformate solution 18 mM in acetone, D-Glutamic acid, L-Glutamic acid, (4R)-2-Hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan, D-(+) Malic acid, L-(+) Malic acid, (R)-(+) Mandelic acid, (E)-(+) Mandelic acid, D-(+) Mandelic acid, L-(+) Mandelic acid, (-)(1 R)-Menthol chloroformate, (15H +)Menthol chloroformate, (+)-Menthoxyacetic acid, (-)Menthoxyacetic acid, (R)-(+) α-Methoxyphenylacetic acid, (5)-(+)α-Methoxyphenylacetic acid, (R)-(+)α-Methoxy-α-trifluoromethylphenylacetic, (5)-(+)α-Methoxy-α-trifluoromethylphenylacetic acid, (R)-(+)α-Methoxy-α-trifluoromethylphenylacetyl chloride, (5)-(+)α-Methoxy-α-trifluoromethylphenylacetyl chloride, (R)-(+)α-Methoxybenzylamine, (5)-(+)α-Methylbenzylamine, (R)-(+)α-Methylbenzyl isocyanate, (5)-(+)α-Methylbenzyl isocyanate, (R)-(+)N-(α-Methylbenzyl)succinamidic acid, (5)-(+)2-Methylbutanol, Methyl (R)-(--)mandelate, (+)-Methyl L-mandelate, (+)-Methyl D-mandelate, Methyl (5)-(+)mandelate, (R)-α-Methyl-4-nitrobenzylamine hydrochloride, (5)-α-Methyl-4-nitrobenzylamine hydrochloride, (5)-α-Methyl-4-nitrobenzylamine hydrochloride, (R)-(+)α-Methyl-4-pyridinemethanol, (5)-α-Methyl-2-pyridinemethanol, (5)-(--)α-Methyl-4-pyridinemethanol, (--)-mono-(1 R)-Menthol phthalate, (R)-(++)l-2-Naphthyl ethylamine, (5)-(--)l-2-Naphthyl ethylamine, (R)-(--)N-[l-(1-Naphthyl)ethyl]-3,5-dinitrobenzamide, (S)-(++)N-[l-(1-Naphthyl)ethyl]-3,5-dinitrobenzamide, (R)-(++)l-(1-Naphthyl)ethyl isocyanate, (R)-(++)N-[l-(1-Naphthyl)ethyl]succinic acid, (5)-(--)N-[l-(1-Naphthyl)ethyl]succinic acid, (R)-(++)2-Octanol, (R)-(++)5-Oxo-2-tetrahydrofurancarboxylic acid, (S)-(++)5-Oxo-2-tetrahydrofurancarboxylic acid, (S)-(++)2-(Phenylcarbamoyloxy)propionic acid, (R)-(++)l-Phenylethanol, (S>)(-)l-Phenylethanol, (R)-(++)N-(l-Phenylethyl)phthalamic acid, (S)-(--)N-(1-Phenylethyl)phthalamic acid, (R)-(++)N-(l-Phenylethyl)succinic acid, (S)-(--)N-(1-Phenylethyl)succinic acid, (R)-(++)2-Phenylpropionic acid, (5)-(++)2-Phenylpropionic acid, Potassium L-tartrate, L-Pyroglutamic acid, D-(--)Quinic acid, Quinidine, Strychnine, D-(--)Tartaric acid, L-(++)Tartaric acid, (R)-(++)α-(Trifluoromethyl)benzyl alcohol, (5)-(++)α-(Trifluoromethyl)benzyl alcohol, (5)-(--)N,N,α’-Trimethylbenzylamine, D-Valine, and L-Valine.

Deuterium Kinetic Isotope Effect

[0063] 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
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) π-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.

The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, \( k = A e^{E_{\text{act}}/RT} \), where \( E_{\text{act}} \) 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.

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 \( E_{\text{act}} \) 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 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.

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.

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) has twice the mass of 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 H₂O, 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). The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C-H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE 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 mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it 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.

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 has twice the mass of hydrogen, and makes up about 0.02% of the total mass of hydrogen (in this usage meaning all hydrogen isotopes) on earth. When two deuterium atoms bond with one oxygen, deuterium oxide (D₂O or "heavy water") is formed. D₂O looks and tastes like H₂O, 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 H₂O. It is more viscous and has different solubilizing properties than H₂O.
When pure D$_2$O 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$_2$O, 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$_2$O, the animals become excitable. When about 20% to about 25% of the body water has been replaced with D$_2$O, 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$_2$O, 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$_2$O. The effects are reversible unless more than thirty percent of the previous body weight has been lost due to D$_2$O. Studies have also shown that the use of D$_2$O can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

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$_2$O, 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.

Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. For example, the 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. 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 are not predictable apriori for any drug class.

**Deuterated Benzhydrel ether Derivatives**

[0072] Clemastine is a substituted benzhydrel ether-based histamine receptor modulator. The carbon-hydrogen bonds of clemastine 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 histamine receptor modulators in comparison with the compound having naturally occurring levels of deuterium.

[0073] Based on discoveries made in our laboratory, as well as considering the KIE literature, clemastine is likely metabolized in humans at the methylene carbon alpha to the ether linkage. The current approach has the potential to prevent oxidation at this site. Oxidations of the aromatic and aliphatic portions of the structure have also been described. The molecule may undergo additional transformations leading to metabolites with as-yet-unknown pharmacology/toxicology. All of these transformations, among other potential transformations, can occur through polymorphically-expressed enzymes thus exacerbating the interpatient variability for such a compound. Clemastine is a rather potent inhibitor of the P_{450} cytochrome CYP2D6, and may cause clinically relevant drug-drug interactions with cardiovascular, antidepressant, and antipsychotic CYP2D6 substrates. Further, it is quite typical for diseases ameliorated by compounds disclosed herein such as allergic rhinitis to produce symptoms best medicated around the clock, thus supporting the likelihood that a longer half-life medicine will diminish these problems with greater efficacy. For all of the foregoing reasons, a medicine with a longer half-life may result in greater efficacy and cost savings. 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, (f) decrease the production of deleterious metabolites in specific tissues, and/or (g) 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 the metabolism via various oxidative mechanisms, attenuate interpatient variability, and prevent the formation of toxic metabolites.

[0074] In one embodiment, disclosed herein is a compound having structural formula I:

![Structural formula](image)

(I)

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

- $R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and deuterium;
- $R_{21}$ and $R_{22}$ are independently selected from the group consisting of $CD_3$, $CD_2H$, $CDH_2$, and $CH_3$; and at least one of $R_i-R_2$ is deuterium or contains deuterium.

[0075] In another embodiment, at least one of $R_i-R_{22}$ independently has deuterium enrichment of no less than about 10%, no less than about 50%, no less than about 90%, or no less than about 98%.

[0076] In yet another embodiment, disclosed herein is a compound having structural formula II
or a pharmaceutically acceptable salt thereof; wherein

$R_1 - R_{20}$ are independently selected from the group consisting of hydrogen and deuterium;

$R_{21}$ and $R_{22}$ are independently selected from the group consisting of CD$_3$, CD$_2$H, CDH$_2$, and CH$_3$; and

at least one of $R_i$ contains deuterium.

[0077] In another embodiment, at least one of $R_{21}$ has deuterium enrichment of no less than about 10%, no less than about 50%, no less than about 90%, or no less than about 98%.

[0078] 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.

[0079] In another embodiment, at least one of the positions indicated as D independently has deuterium enrichment of no less than about 10%, no less than about 50%, no less than about 90%, or no less than about 98%.

[0080] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of a single enantiomer and about 10% or less by weight of the other 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.

[0081] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of a single enantiomer of the compound and about 40% or less by weight of the other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of a single enantiomer of the
compound and about 30% or less by weight of the other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of a single enantiomer of the compound and about 20% or less by weight of the other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of a single enantiomer of the compound and about 10% or less by weight of the other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of a single enantiomer of the compound and about 5% or less by weight of the other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of a single enantiomer of the compound and about 1% or less by weight of the other enantiomer of the compound.

[0082] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of a single diastereomer of the compound and about 40% or less by weight of any other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of a single diastereomer of the compound and about 30% or less by weight of any other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of a single diastereomer of the compound and about 20% or less by weight of any other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of a single diastereomer of the compound and about 10% or less by weight of any other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of a single diastereomer of the compound and about 5% or less by weight of any other enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of a single diastereomer of the compound and about 1% or less by weight of any other enantiomer of the compound.

[0083] The deuterated compound as 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.

[0084] 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$_2$O or about 0.00001% DHO, assuming that all of the C-D bonds in the compound as disclosed herein are metabolized and released as D$_2$O or DHO. This quantity is a small fraction of the naturally occurring background levels of D2O or DHO in circulation. In certain embodiments, the
levels of D₂O shown to cause toxicity in animals is much greater than even the maximum limit of exposure because of the deuterium enriched compound as disclosed herein. Thus, in certain embodiments, the deuterium-enriched compound disclosed herein should not cause any additional toxicity because of the use of deuterium.

[0085] 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 (T½), 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.

[0086] Isotopic hydrogen can be introduced into a compound 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. 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.

[0087] 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 Wu et al., Pyrrolidines IV 1961, 1531-1533; Forrat et al., Tetrahedron: Asymmetry 17 2006, 2054-2058; Ueura et al., J of Organometallic Chemistry 2006, 691, 2821-2826; Stucky et al. Journal of the American Chemical Society 1963, 85, 1002; Chaudhari et al., Sylett 1999, (11), 1763-1765; Rosenau et al., Synthetic Communications 2002, 32(3), 457-465; Moll et al., Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischem Gesellschaft. 1968, 301(1 1), 872-7; Ebnöther et al., Helvctia Chimica Acta 1976, 59(264), 2462-2468; 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.
The following schemes can be used to synthesize compounds disclosed herein. Any position shown as hydrogen may optionally be replaced with deuterium.

Scheme 1

1 → 2 → 3

4 → 5 → 6
[0089] Compound 1 is reacted with isobutyl chloroformate in the presence of an appropriate base, such as N-methylmorpholine, in an appropriate solvent, such as tetrahydrofuran, to give a mixed anhydride intermediate that is then reduced with an appropriate reducing agent, such as sodium borohydride, in an appropriate solvent, such as tetrahydrofuran, to give compound 2. Compound 2 is reacted with an appropriate reagent for conversion of an alcohol to a leaving group, such as tosyl chloride, in the presence of an appropriate base, such as triethylamine, in the presence of an appropriate catalyst, such as A-dimethylaminopyridine, in an appropriate solvent, such as dichloromethane, at an elevated temperature to give compound 3. Compound 3 is reacted with sodium cyanide in an appropriate solvent, such as dimethylsulfoxide, at an elevated temperature to afford compound 4. Compound 4 is treated with an appropriate acid, such as a mixture of hydrochloric acid and glacial acetic acid, at an elevated temperature to give compound 5. Compound 5 is reacted with di-tert-butyl dicarbonate in the presence of an appropriate base,
such as sodium hydroxide, in an appropriate solvent, such as a mixture of water and acetone, to afford compound 6. Compound 6 is reacted with an appropriate reducing reagent, such as lithium aluminum hydride, in an appropriate solvent, such as 1,4-dioxane, at an elevated temperature to give compound 7. Compound 7 is reacted with an appropriate chlorinating reagent, such as thionyl chloride, in an appropriate solvent, such as chloroform, at an elevated temperature to afford compound 8. Compound 9 is reacted with compound 10 in an appropriate solvent, such as tetrahydrofuran, to give compound 11. Compound 11 is reacted with compound 8 in the presence of an appropriate base, such as sodium amide, in an appropriate solvent, such as toluene, to afford compound 12, which is then resolved with an appropriate chiral preparatory HPLC column, such as Chiralpak IA, to give compound 13 of Formula 1.

[0090] 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 of R1-R7, compound 1 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R8-R9, sodium borodeuteride can be used. To introduce deuterium at one or more positions of R0-R1, sodium borodeuteride can be used. To introduce deuterium at one or more positions of R8-R9, sodium borodeuteride can be used. To introduce deuterium at one or more positions of R12-R15 and R22, compound 9 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R6-R9, compound 10 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.
Scheme 2

[0091] Compound 14 reacts with ethylmagnesium bromide in an appropriate solvent, such as tetrahydrofuran, to give compound 15, which then reacts with compound 16 to form
compound 17. Compound 17 reacts with an appropriate reducing agent, such as a combination of hydrogen and an appropriate catalyst, such as platinum dioxide, in an appropriate solvent, such as ethanol, to give compound 18. Compound 18 reacts with an appropriate alkylating agent, such as a mixture of paraformaldehyde and oxalic acid dihydrate, to yield compound 19, which reacts with an appropriate chlorinating reagent, such as thionyl chloride, in an appropriate solvent, such as dichloromethane, to form compound 20. Compound 21 reacts with magnesium in an appropriate solvent, such as tetrahydrofuran, to give compound 22, which reacts with compound 23, in an appropriate solvent, such as tetrahydrofuran, to yield compound 24. Compound 24 reacts with compound 20 in the presence of an appropriate base, such as sodium amide, in an appropriate solvent, such as cyclohexane, to yield compound 25, which is reacted with an appropriate resolving reagent, such as di-benzoyl-tartaric acid, in an appropriate solvent, such as ethanol, to afford compound 26 of Formula 1.

[0092] 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 of R₁, R₃ and R₅, compound 14 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R₁i, paraformaldehyde and/or oxalic acid dihydrate with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R₂, R₄, R₆, and R₇, deuterium gas and d₆-ethanol can be used. To introduce deuterium at one or more positions of R₁₂, R₁₃, R₁₄, R₁₅, and R₂₂, compound 23 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R₈, R₉, R₁₀, and Rₙ, compound 16 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R₁₆, R₁₇, R₁₈, R₁₉, and R₂₀, compound 21 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.

[0093] 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.
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 of Formula I.

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 as disclosed herein may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound as 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.

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.

When the compound as 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).
Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acetylated 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, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, laureic 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.

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, hydramamine, IH-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, pipеразине, 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.

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

**Pharmaceutical Composition**

[00101] Disclosed herein are pharmaceutical compositions comprising a compound as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; in combination with one or more pharmaceutically acceptable excipients or carriers.

[00102] 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.

[00103] 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.

[00104] 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 enteric coated dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[00105] 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.

[00106] 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.

[00107] Disclosed herein are pharmaceutical compositions that comprise about 0.1 to about 5000 mcg/5mL, about 1 to about 500 mcg/5mL, about 2 to about 100 mcg/5mL, about 1 mcg/5mL, about 2 mcg/5mL, about 3 mcg/5mL, about 5 mcg/5mL, about 10 mcg/5mL, about 20 mcg/5mL, about 30 mcg/5mL, about 40 mcg/5mL, about 50 mcg/5mL, about 100 mcg/5mL, about 500 mcg/5mL, about 1000 mcg/5mL, about 5000 mcg/5mL, of one or more compounds as disclosed herein in the form of a syrup for oral administration. The pharmaceutical compositions further comprise ethyl alcohol (5.5%), flavoring agents, maleic
acid, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sodium hydroxide, and sorbitol.

[00108] Disclosed herein are pharmaceutical compositions that comprise about 0.1 to about 5000 meg, about 1 to about 500 meg, about 2 to about 100 meg, about 1 meg, about 2 meg, about 3 meg about 5 meg, about 10 meg, about 20 meg, about 30 meg, about 40 meg, about 50 meg, about 100 meg, about 500 meg, about 1000 meg, about 5000 meg of one or more compounds as disclosed herein in the form of extended release tablets for oral administration. The pharmaceutical compositions further comprise colloidal silicon dioxide, dibasic calcium phosphate, lactose, magnesium stearate, methylcellulose, polyethylene glycol, Sodium Free povidone, starch, synthetic polymers, titanium dioxide and Yellow 10.

[00109] Disclosed herein are pharmaceutical compositions that comprise about 0.1 to about 1000 meg, about 1 to about 500 meg, about 2 to about 100 meg, about 1 meg, about 2 meg, about 3 meg about 5 meg, about 10 meg, about 20 meg, about 30 meg, about 40 meg, about 50 meg, about 100 meg, about 500 meg, about 1000 meg, of one or more compounds as disclosed herein in the form of tablets for oral administration. The pharmaceutical compositions further comprise lactose, povidone, starch, stearic acid, and talc.

[00110] 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 ampoules, 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.

[00111] 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).

[00112] 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.

[00113] 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.

[00114] 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").

[00115] 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 disorder is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

A. Oral Administration

[00116] The pharmaceutical compositions disclosed herein may be disclosed 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.

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, pregelatinized 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.

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.

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 pregelatinized 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.

[00120] 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.

[00121] 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 carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaureate, 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.

[00122] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00123] The pharmaceutical compositions disclosed herein may be disclosed 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, phenylalicylate, 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.

[00124] 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.

[00125] The pharmaceutical compositions disclosed herein may be disclosed 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 propylparabens, 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.

[00126] The pharmaceutical compositions disclosed herein may be disclosed 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.

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 polyalkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetruglyme, 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.

The pharmaceutical compositions disclosed herein for oral administration may be also disclosed 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.

The pharmaceutical compositions disclosed herein may be disclosed 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.

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

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.

[00132] 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

[00133] 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.

[00134] 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).

[00135] 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.

[00136] 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,
caster 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.

[00137] 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 propylparabens, 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 carboxymethylcellulose, 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).

[00138] 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.

[00139] In one embodiment, the pharmaceutical compositions are disclosed as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are disclosed 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 disclosed as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are disclosed as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are disclosed as ready-to-use sterile emulsions.
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.

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.

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.

Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, 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/vinylxyethanol copolymer.

C. Topical Administration

The pharmaceutical compositions disclosed herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, include (intradermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

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, nonsystems, and mixtures thereof.

[00146] 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, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00147] 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).

[00148] The pharmaceutical compositions disclosed herein may be disclosed 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 (OAV) 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.

[00149] 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.

[00150] 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 trituratum, mechanical mixing, and/or stirring.

[00151] 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.

[00152] 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. Pharmacologically 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.

[00153] 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.

[00154] The pharmaceutical compositions disclosed herein may be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions may be disclosed 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 disclosed 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.

[00155] 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 an surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00156] 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.

[00157] 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.

[00158] 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

[00159] 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 polymorphism of the active ingredient(s).

[00160] 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**


[00162] In one embodiment, the pharmaceutical compositions disclosed herein in a modified release dosage form is formulated using an erodible matrix device, which is waterswellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00163] 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.

[00164] 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/vinylxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene-terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, and 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.

[00165] 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.

[00166] 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**

[00167] 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).

[00168] 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 crosscarmellose, 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.

[00169] 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-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00170] 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.

[00171] 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.

[00172] 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 dimethylaminooacetate, 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.

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.


[00178] 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.

[00179] 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

[00180] 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.
[00181] 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**

[00182] 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; 6,071,495; 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.

[00183] Disclosed are methods for treating, preventing, or ameliorating one or more symptoms of a histamine receptor-mediated disorder, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00184] Histamine receptor-mediated disorders include, but are not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or or any disorder ameliorated by modulation of histamine receptors.

[00185] Also disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder associated with histamine receptors, by administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00186] Further disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder responsive to modulation of histamine receptors, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.
Furthermore, disclosed herein are methods of modulating the activity of histamine receptors, comprising contacting the receptors with at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the histamine receptor is expressed by a cell.

Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder, involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors, or for preventing such disease, disorder, or condition, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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 disorder as compared to the corresponding non-isotopically enriched compound.

In certain embodiments, the inter-individual variation in plasma levels of the compounds of Formula I, 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.

Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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.

In certain embodiments, the average plasma levels of the compound as 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.

[00192] In certain embodiments, the average plasma levels of a metabolite of the compound as 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.

[00193] Plasma levels of a compound disclosed herein, or metabolites thereof, may be measured using the methods described by Li et al. (Rapid Communications in Mass Spectrometry 2005, 19, 1943-1950), and Horvath et al., (J of Chromatography B 2005, 816, 153-159).

[00194] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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<sub>4</sub>50 or monoamine oxidase isoform in the subject during the treatment of the disease as compared to the corresponding non-isotopically enriched compound.

[00195] Examples of cytochrome P<sub>4</sub>50 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, CYP4F13, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYPI1A1, CYPI1B1, CYPI1B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[00196] Examples of monoamine oxidase isoforms in a mammalian subject include, but are not limited to, MAO<sub>A</sub>, and MAO<sub>B</sub>.

[00197] In certain embodiments, the decrease in inhibition of the cytochrome P<sub>4</sub>50 or monoamine oxidase isoform by a compound as disclosed herein is greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%,
40%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

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).

Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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.

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

In certain embodiments, the decrease in metabolism of the compound as 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.

The metabolic activities of liver microsomes and the cytochrome P$_{450}$ isoforms are measured by the methods described in Examples 8 and 9. The metabolic activities of the monoamine oxidase isoforms are measured by the methods described in Examples 10 and 11.

Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation.
of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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.

[00204] Examples of improved disorder-control and/or disorder-eradication endpoints include, but are not limited to, statistically-significant improvement in persistent cough, headache, pruritis, rhinorrhea, tearing eyes, wheezing, stridor, angioedema, sneezing, nasal congestion, pharyngitis, conjunctivitis, tachypnea, rhonchi, paradoxic pulse, anosmia, myalgia, arterial pressure, abdominal pain, anemia, chest pain, dyspnea, fatigue, muscle weakness, pericarditis, peripheral neuropathy, peritonitis, pleural effusion, pleurisy, pneumothorax, and/or diminution of toxicity including but not limited to, hepatotoxicity or other toxicity, or a decrease in aberrant liver enzyme levels as measured by standard laboratory protocols, as compared to the corresponding non-isotopically enriched compound when given under the same dosing protocol including the same number of doses per day and the same quantity of drug per dose.

[00205] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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.

[00206] Examples of an improved clinical effect include, but are not limited to, statistically-significant improvement in persistent cough, headache, pruritis, rhinorrhea, tearing eyes, wheezing, stridor, angioedema, sneezing, nasal congestion, pharyngitis, conjunctivitis, tachypnea, rhonchi, paradoxic pulse, anosmia, myalgia, arterial pressure, abdominal pain, anemia, chest pain, dyspnea, fatigue, muscle weakness, pericarditis, peripheral neuropathy, peritonitis, pleural effusion, pleurisy, pneumothorax, and/or diminution of toxicity including but not limited to, hepatotoxicity or other toxicity, or a
decrease in aberrant liver enzyme levels as measured by standard laboratory protocols, as compared to the corresponding non-isotopically enriched compound.

[00207] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as 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.

[00208] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or or any disorder ameliorated by modulation of histamine receptors, or for preventing such disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof; so as to allow the treatment of allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or or any disorder ameliorated by modulation of histamine receptors while reducing or eliminating deleterious changes in any diagnostic hepatobiliary function endpoints as compared to the corresponding non-isotopically enriched compound.

[00209] 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," "γ-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.

[00210] Depending on the disorder to be treated and the subject's condition, the compound as 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.

[00211] 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 microgram, from about 0.1 to about 500 micrograms, or from 0.5 about to about 100 microgram active ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of alternative, be administered as a continuous infusion.

[00212] In certain embodiments, an appropriate dosage level is about 0.01 to about 100 microgram per kg patient body weight per day (mcg/kg per day), about 0.01 to about 50 microgram/kg per day, about 0.01 to about 25 microgram/kg per day, or about 0.05 to about 10 microgram/kg per day, which may be administered in single or multiple doses. A suitable dosage level may be about 0.01 to about 100 microgram/kg per day, about 0.05 to about 50 microgram/kg per day, or about 0.1 to about 10 microgram/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 microgram/kg per day.

Combination Therapy

[00213] 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, but not limited to, allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, sneezing, and/or any disorder ameliorated, prevented or lessened by bronchodilation, and/or any disorder ameliorated by modulation of histamine receptors. 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.

[00214] 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 as disclosed herein. When a compound as 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.

[00215] In certain embodiments, the compounds disclosed herein can be combined with one or more therapeutic agents, including, but not limited to, decongestant treatments, antitussive treatments, mucolytic treatments, expectorant treatments, antiallergic non-steroidal treatments, steroidal drugs, antihistamine treatments, leukotriene receptor antagonists, phosphodiesterase inhibitors, CYP3A inhibitors, CYP3A inducers, protease inhibitors, antifungal agents, antibacterials, antimycobacterial agents, sepsis treatments, steroidal drugs, anticoagulants, thrombolytics, non-steroidal anti-inflammatory agents, antiplatelet 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 Vila 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-stabilizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, and platinum coordination complexes.

[00216] In certain embodiments, the compounds disclosed herein can be combined with one or more antitussive treatments known in the art, including, but not limited to, dextromethorphan, ethylmorphine, hydrocodone, codeine, normetahdone, noscapine, pholcodine, thebacon, dimemorfan, actylidihydrocodeine, benzonatate, benproperine,
clobutinol, isoaminile, pentoxyverine, oxolamine, oxeladin, clofedanol, pipazetate, bibenzonium bromide, butamirate, fedrilate, zipeprol, dibunate, droxypropine, prenoxidiazine, dropropizine, cloperastine, meprotixol, piperidine, tipepidine, morclofone, nepinalone, levodropropizine, and dimethoxanate.

[00217] In certain embodiments, the compounds disclosed herein can be combined with one or more mucolytic treatments known in the art, including, but not limited to, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, dornase alfa, neltenezone, and erdosteine.

[00218] In certain embodiments, the compounds disclosed herein can be combined with one or more expectorant treatments known in the art, including, but not limited to, tyloxapol, potassium iodide, guaifenesin, ipecacuanha, althea root, senega, antimony pentasulfide, creosote, guaiacolsulfonate, and levoverbenone.

[00219] In certain embodiments, the compounds disclosed herein can be combined with one or more antiallergic non-steroidal treatments known in the art, including, but not limited to, cromoglicic acid, levocabastine, azelastine, antazoline, spaglumic acid, thonzylamine, nedarcomil, and olopatadine.

[00220] In certain embodiments, the compounds disclosed herein can be combined with one or more steroidal drugs known in the art, including, but not limited to, aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone acetate, hydrocortisone (Cortisol), prednisolone, prednisone, methylprenisolone, dexamethasone, and triamcinolone, flunisolide, flucticasone, mometasone furoate, tixocortol, and budesonide.

[00221] In certain embodiments, the compounds disclosed herein can be combined with one or more antihistamine treatments known in the art, including, but not limited to, mepyramine, antazoline, diphenhydramine, carbinoxamine, doxylamine, dimenhydrinate, pheneramine, chlorphenamine, brompheniramine, tripolidine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, promethazine, alimemazine, cyproheptadine, azatadine, and ketotifen.

[00222] In yet other embodiments, the compounds disclosed herein can be combined with one or more leukotriene receptor antagonists known in the art, including, but not limited to, montelukast, pranlukast, and zafirlukast.

[00223] In certain embodiments, the compounds disclosed herein can be combined with one or more non-steroidal anti-inflammatory agents known in the art, including, but not limited to, aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac,
etoracoxib, failslamine, fenbuten, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mfenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, sulfinprazone, suprofen, tenoxicam, tiaprofenic acid, and tolmetin.

[00224] In certain embodiments, the compounds disclosed herein can be combined with one or more decongestant treatments known in the art, including, but not limited to, phenylpropanolamine hydrochloride, pseudoephedrine, phenylephrine, ephedrine, tuaminoheptane, xylometazoline, tetryzoline, naphazoline, cyclopentamine, tramazoline, metizoline, fenoxazoline, tymazoline, and oxymetazoline.

[00225] In certain embodiments, the compounds disclosed herein can be combined with phenylpropanolamine hydrochloride.

[00226] 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, ticlodipine and CS-747), and aspirin; anticoagulants, such as warfarin; low molecular weight heparins, such as enoxaparin; Factor Vila Inhibitors and Factor Xa Inhibitors; renin inhibitors; neutral endopeptidase (NEP) inhibitors; vasoepsidase 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; fribrates; 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-histamine H1 agents; beta-histamine H1 agents, such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzothiazide, ethacrynic acid, tricrynafan, 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), thiazolidinediones (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 pyridine 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., cortisol), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; microtubule-disruptor agents, such as eceatinascidins; 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**

[00227] 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.

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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.

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.

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) or as otherwise determined by one of ordinary skill in the art.
The disclosure is further illustrated by the following examples.

**EXAMPLE 1**

(\(\tau\))-2-[(\(\tau\))-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine fumarate

![Chemical structure](image)

**Step 1**

\[\begin{array}{c}
\text{C}_{\text{Boc}}\text{O}_{\text{H}} \\
\text{CO}_{\text{H}}
\end{array} \rightarrow \begin{array}{c}
\text{C}_{\text{Boc}} \\
\text{OH}
\end{array} \]

\([00232]\) (\(R\))-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: At about 0 °C, N-methylmorpholine (6.14 mL, 55.85 mmol) was added dropwise to a mixture of pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (10.0 g, 46.46 mmol), isobutyl chloroformate (7.24 mL, 55.82 mmol) and tetrahydrofuran (100 mL). After stirring for about 10 minutes at about 0 °C, the mixture was filtered over Celite. The filtrate was then added to a suspension of sodium borohydride (2.12 g, 56.04 mmol) in tetrahydrofuran (100 mL). The suspension was stirred at about 0 °C for about 30 minutes and then stirred at ambient temperature for an additional 5 hours. Following standard extractive workup with ethyl acetate, the crude residue was purified by silica gel column chromatography (15% ethyl acetate in petroleum ether) to yield the title product as an oil (5.80 g, 62%). \([\sigma]_{D}^{20} +47.9^\circ (c 1.0, \text{chloroform})\); \(^1\)H NMR (400 MHz, DMSO-\(d_{6}\)) \(\delta\) 1.39 (s, 9H), 1.66-1.92 (m, 4H), 3.16-3.26 (m, 3H), 3.42-3.50 (m, IH), 3.60-3.72 (m, IH), 4.65 (t, \(J = 5.6\) Hz, IH, exchangeable with deuterium oxide); IR (film) \(\nu\) 3428, 2971, 2880, 2376, 1683, 1407 cm\(^{-1}\); MS 202 (M + 1).
(R)-2-(Toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: A mixture of (R)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5.60 g, 27.82 mmol), tosyl chloride (7.97 g, 41.80 mmol), triethylamine (9.7 mL, 69.59 mmol), A-dimethylaminopyridine (1.12 g, 9.17 mmol) and dichloromethane (56 mL) was heated at reflux for about 7 hours. Following standard extractive workup with dichloromethane, the crude residue was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to yield the title product as an oil (7.30 g, 74%). [α]D20 +8.3° (c 1.1, chloroform); 1H NMR (400 MHz, DMSO-d6) δ 1.29, 1.35 (2s, 9H), 1.63-1.80 (m, 3H), 1.83-1.97 (m, 1H), 2.42 (s, 3H), 3.09-3.23 (m, 2H), 3.79-3.87 (m, IH), 3.91-4.02 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.77 (d, J = 7.9 Hz, 2H); IR (film) ν 2973, 2934, 2884, 1694, 1459, 1392, 1177 cm⁻¹; MS 356 (M + 1).

(R)-2-Cyanomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: A solution of (R)-2-(toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (11.50 g, 32.39 mmol) and sodium cyanide (4.76 g, 97.18 mmol) in dimethylsulfoxide (115 mL) was stirred at about 90 °C for about 7 hours. Following standard extractive workup with ethyl acetate, the crude residue was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to yield the title product as an oil (5.70 g, 84%). [α]D20 +87.2° (c 0.9, chloroform); 1H NMR (400 MHz, DMSO-d6) δ 1.41 (s, 9H), 1.70-1.84 (m, 2H), 1.86-2.00 (m, IH), 2.03-2.14 (m, IH), 2.71-2.90 (m, 2H), 3.20-3.32 (m, 2H), 3.85-3.95 (m, IH); IR (film) ν 2975, 2885, 2248, 1693, 1462, 1397, 1254 cm⁻¹; MS 211 (M + 1).
Step 4

\[
\text{Step 4) -2-(Pyrrolidin-2-yl)acetic acid hydrochloride: A mixture of (R)-2-cyanomethyl-pyrrolidine-1-carboxylic acid tert-butyldimethyl ester (5.70 g, 27.14 mmol), cone. hydrochloric acid (85 mL) and glacial acetic acid (57 mL) was heated at reflux for about 6 hours. After the mixture was cooled to ambient temperature, standard extractive workup with ethyl acetate yielded the title product as an off-white solid which was used in the next step without further purification (3.70 g, 83%).}
\]

\[\left[\alpha\right]_{D}^{29} -21.9^\circ (c 1.1, 2\text{ N HCl})\]

1H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 1.50-1.63 (m, 1H), 1.76-1.99 (m, 2H), 2.04-2.16 (m, 1H), 2.68-2.92 (m, 2H), 3.06-3.20 (m, 2H), 3.61-3.73 (m, 1H), 9.38, 9.52 (br, 2H, exchangeable with deuterium oxide), 12.65 (br, 1H, exchangeable with deuterium oxide); IR (KBr) \(\nu\) 3009, 2494, 1732, 1594, 1410 \(\text{cm}^{-1}\); MS 130 (M + 1).

Step 5

\[
\text{Step 5) -2-Carboxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: At about 0 } {\text{°}}\text{C, a 5% sodium hydroxide solution was added dropwise to a solution of (R)-2-(pyrrolidin-2-yl)acetic acid hydrochloride (3.00 g, 18.18 mmol) in water (30 mL). After diluting the solution with acetone (30 mL), di-tert-butyl dicarbonate (5.94 g, 27.27 mmol) was added dropwise. The resulting mixture was stirred at ambient temperature for about 6 hours and the acetone was removed in vacuo. The pH was adjusted to 3 by adding 3M hydrochloric acid dropwise, at about 0 } {\text{°}}\text{C. Following standard extractive workup with ethyl acetate, the crude residue was purified by silica gel column chromatography (10% ethyl acetate in chloroform) to yield the title product as an off-white solid (2.70 g, 65%).} \]

\[\left[\alpha\right]_{D}^{29} +33.8^\circ (c 2.0, \text{DMF})\]

1H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 1.37 (s, 3H), 1.60-1.85 (m, 3H), 1.90-2.00 (m, 1H), 2.14-2.27 (m, 1H); 2.54-2.93 (m, 2H), 3.15-3.24 (m, 2H), 3.87-3.95 (m, 1H), 12.13 (s, 1H, exchangeable with deuterium oxide); IR (KBr) \(\nu\) 3184, 2976, 2882, 1732, 1594, 1410 \(\text{cm}^{-1}\); MS 228 (M - I).
Step 6

\[(R)-2-((1\text{-Methylpyrrolidin}-2\text{-yl})\text{ethanol} : \text{At about } 0^\circ\text{C, a solution of } (R)-2\text{-carboxymethyl-}

\text{pyrrolidine-1-carboxylic acid tert-butyl ester (1.30 g, 5.68 mmol) in dry 1,4-

dioxane (10 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.08 g, 28.46 mmol) in dry 1,4-dioxane (10 mL). With slow temperature ramping, the mixture was first heated at about 50^\circ\text{C for about 1 hour, then heated at about 70^\circ\text{C for about 1 hour, and finally heated at reflux for about 5 hours. After cooling the mixture to about 0^\circ\text{C, cold water was added dropwise until a white granular precipitate was obtained. The precipitate was collected by filtration, washed with ethyl acetate, and the washes were combined with the filtrate. The combined filtrate was concentrated } in \text{vacuo} \text{ to yield the title compound as a brown oil which was used in the next step without further purification (0.600 g, 82\%).}^{1}\text{H NMR (400 MHz, DMSO-\text{d}_6) } \delta \text{ 1.46-1.56 (m, IH), 1.72-1.84 (m, 3H), 1.87-2.05 (m, 2H), 2.12-2.20 (m, IH), 2.36 (s, 3H), 2.56-2.63 (m, IH), 3.03-3.09 (m, IH), 3.65-3.72 (m, IH), 3.96-4.03 (m, IH); IR (KBr) } \nu \text{ 3379, 2955, 2789, 1655, 1458 cm}^{-1}; \text{MS 130 (M + 1).}^{1}\text{H NMR (400 MHz, DMSO-\text{d}_6) } \delta \text{ 1.46-1.56 (m, IH), 1.72-1.84 (m, 3H), 1.87-2.05 (m, 2H), 2.12-2.20 (m, IH), 2.36 (s, 3H), 2.56-2.63 (m, IH), 3.03-3.09 (m, IH), 3.65-3.72 (m, IH), 3.96-4.03 (m, IH); IR (KBr) } \nu \text{ 3379, 2955, 2789, 1655, 1458 cm}^{-1}; \text{MS 130 (M + 1).}]

Step 7

\[(R)-2-(2\text{-Chloroethyl)-1-methyl-pyrrolidine hydrochloride : For about 30 minutes, dry hydrochloric gas was bubbled into a solution of (R)-2-(1-methylpyrrolidin-2-y1)\text{ethanol (0.500 g, 3.87 mmol) in chloroform (10 mL). Thionyl chloride (1.38 g, 11.62 mmol) was added and the resulting mixture was heated at reflux for about 2 hours. The solvent and thionyl chloride were removed in \text{vacuo}, and the resulting residue was triturated with pentane to yield the title compound as a brown solid which was used in the next step without further purification (0.540 g, 77\%).}^{1}\text{H NMR (400 MHz, DMSO-\text{d}_6) } \delta \text{ 1.83-2.20 (m, 2H), 2.08-2.26 (m, 2H), 2.30-2.40 (m, IH), 2.75 (d, } J = \text{ 5.0 Hz, 3H), 2.95-3.05 (m, IH), 3.27-3.39 (m, IH), 3.45-3.54 (m, IH), 3.62-3.70 (m, IH), 3.78-3.85 (m, IH), 11.05 (s, IH, exchangeable with deuterium oxide); IR (film) } \nu \text{ 3451, 2962, 2676, 2580, 1637, 1459 cm}^{-1}; \text{MS 148, 150 (M + 1, M + 3).}^{1}\text{H NMR (400 MHz, DMSO-\text{d}_6) } \delta \text{ 1.83-2.20 (m, 2H), 2.08-2.26 (m, 2H), 2.30-2.40 (m, IH), 2.75 (d, } J = \text{ 5.0 Hz, 3H), 2.95-3.05 (m, IH), 3.27-3.39 (m, IH), 3.45-3.54 (m, IH), 3.62-3.70 (m, IH), 3.78-3.85 (m, IH), 11.05 (s, IH, exchangeable with deuterium oxide); IR (film) } \nu \text{ 3451, 2962, 2676, 2580, 1637, 1459 cm}^{-1}; \text{MS 148, 150 (M + 1, M + 3).}]

Step 8

[00239] 1-(4-Chlorophenyl)-1-phenylethanol: Under nitrogen, a solution of bromobenzene (20.31 g, 129.35 mmol) in dry tetrahydrofuran (50 mL) was added dropwise to a mixture of magnesium turnings (3.88 g, 159.61 mmol), dry tetrahydrofuran (50 mL) and a crystal of iodine. After heating at reflux for about 2 hours, the resulting solution was cooled to about 0°C and then added dropwise to a solution of 1-(4-chloro-phenyl)-ethanone (10.0 g, 64.69 mmol) in tetrahydrofuran (100 mL). The mixture was stirred for about 18 hours at ambient temperature, cooled to about 0°C, and then quenched by slowly adding a saturated ammonium chloride solution. Following standard extractive workup with ethyl acetate, the resulting crude residue was purified by silica gel column chromatography (5% ethyl acetate in petroleum ether) to yield the title product as an oil (3.80 g, 25%). 1H NMR (400 MHz, CDCl₃) δ 1.94 (s, 3H), 2.17 (s, IH, exchangeable with deuterium oxide), 7.23-7.42 (m, 9H); IR (film) ν 3414, 3061, 2978, 2927, 2859, 1597, 1489, 1449, 1394 cm⁻¹; MS 215, 217 [(M + I) - H₂O, (M + 3) - H₂O].

Step 9

[00240] (R)-2-[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine: A mixture of (R)-2-(2-chloroethyl)-1-methyl-pyrrolidine hydrochloride (0.530 g, 2.91 mmol), 1-(4-chlorophenyl)-1-phenylethanol (1.01 g, 4.39 mmol), sodium amide (0.567 g, 14.53 mmol) and toluene (10 mL) was heated at reflux for about 8 hours, cooled to ambient temperature, and filtered. The filtrate was concentrated and the resulting residue was purified by Preparative HPLC on a Kromasil C18 (30 x 250 mm, 10 µm) column, by eluting with acetonitrile / 0.01 M ammonium acetate (3:1) at a flow rate of 42 mL/min. The racemic title compound eluted at 1.57 min. Standard extractive workup with ethyl acetate afforded the racemic title product as an oil (0.360 g, 36%).

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Step 10

(R)-2-[2-[2-[(R)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine: (R)-2-[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine enantiomers were separated by preparative HPLC on a Chiralpak IA (19 x 250 mm, 10 µm) column, by eluting with hexane / ethanol / diethylamine (95:5:0.1) at a flow rate of 10 mL/min. The title product fraction eluted at 4.18 minutes, and was concentrated to give the title product a viscous oil (0.180 g). [α]D20 +38.7° (c 2.0, ethanol); 1H NMR (400 MHz, CDCl3) δ 1.36-1.53 (m, 2H), 1.61-1.80 (m, 2H), 1.83 (s, 3H), 1.85-1.94 (m, 1H), 1.99-2.07 (m, 1H), 2.08-2.21 (m, 2H), 2.32 (s, 3H), 3.02-3.08 (m, 1H), 3.18-3.35 (m, 2H), 7.20-7.35 (m, 9H); IR (film) ν 2948, 2874, 2778, 1597, 1487, 1450 cm⁻¹; MS 344, 346 [(M + 1), (M + 3)].

Step 11

(R)-2-[2-[2-[(R)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine fumarate: A solution of (R)-2-[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine (0.150 g, 0.43 mmol) in ethanol (2 mL) was added dropwise to a solution of fumaric acid (0.045 g, 0.39 mmol) in ethanol (2 mL). The mixture was heated at reflux for about 30 minutes, the solvent was removed in vacuo, and the resulting residue was triturated with diisopropyl ether to yield the title compound as a white solid (0.110 g, 55%). m.p. 155-159 °C; [α]D20 +22.0° (c 2.0, methanol); 1H NMR (400 MHz, CD3OD) δ 1.67-1.82 (m, 2H), 1.88 (s, 3H), 1.97-2.14 (m, 2H), 2.22-2.33 (m, 2H), 2.92 (s, 3H), 3.11-3.21 (m, 1H), 3.23-3.38 (m, 1H), 3.39-3.53 (m 2H), 3.58-3.68 (m, 1H), 6.69 (s, 2H), 7.21-7.37 (m, 9H); IR (KBr) ν 3439, 2935, 1696, 1618, 1388, 1288, 1240 cm⁻¹; MS 344, 346 [(M + 1) - fumaric acid, (M + 3) - fumaric acid].
EXAMPLE 2

(+/?)-2-[(+/?)-(4-Chlorophenyl)-1-phenylethoxy]ethyl-2,2-\(\alpha\)-l-methylpyrrolidine fumarate

Step 1

\[\text{(R)}-2-(1-Methyl-pyrrolidin-2-yl)acetic acid hydrochloride : A mixture of (R)-2-(pyrrolidin-2-yl)acetic acid hydrochloride (1.0 g, 6.04 mmol), a 37% formaldehyde solution (3.0 mL), 10% palladium on carbon (0.300 g) and dry methanol (20 mL) was hydrogenated at 60 psi pressure for about 16 hours, and then filtered through a pad of Celite. The filtrate was concentrated \textit{in vacuo} and the crude residue was diluted with dichloromethane-methanol (9:1). The mixture was re-filtered and the filtrate was concentrated to dryness \textit{in vacuo} to yield the title compound as an off-white solid which was used in the next step without further purification (0.700 g, 65%).}^{1}H NMR (400 MHz, DMSO\(\text{d}_6\)) \(\delta\) 1.61-1.72 (m, 1H), 1.83-2.02 (m, 2H), 2.21-2.31 (m, 1H), 2.66-2.75 (m, 1H), 2.76 (s, 3H), 2.99-3.09 (m, 1H), 3.22-3.60 (3H), 11.50 (br, 2H); IR (KBr) \(\nu\) 2991, 2258, 1727, 1591, 1392 O\(\text{n}^{-1}\); MS 144 (M + 1).

Step 2

\[\text{(R)-(1-Methyl-pyrrolidin-2-yl)-acetic acid methyl ester: Thionyl chloride (1.40 mL, 19.19 mmol) was added dropwise to a solution of (R)-2-(1-methyl-pyrrolidin-2-yl)acetic acid hydrochloride (0.700 g, 3.90 mmol) in methanol (10 mL). The resulting solution was heated at reflux for about 6 hours and the volatiles were removed \textit{in vacuo}. At about 0 °C, the resulting residue was diluted with water (10 mL), basified to pH 8 by adding solid sodium carbonate, and extracted with dichloromethane-methanol (9:1). The organic layer was concentrated \textit{in vacuo} to yield the title compound as an oil (0.320 g, 52%).}^{1}H
NMR (400 MHz, CDCl$_3$) δ 1.50-1.60 (m, IH), 1.65-1.85 (m, 2H), 2.00-2.11 (m, IH), 2.18-2.32 (m, 2H), 2.33 (s, 3H), 2.49-2.57 (m, IH), 2.67 (dd, $J = 14.8$, 4.3 Hz, IH), 3.02-3.09 (m, IH), 3.68 (s, 3H); MS 158 (M + 1).

Step 3

\[
\begin{array}{c}
\text{C} \\
\text{CO} \text{-CH} \text{D} \\
\downarrow \\
\text{O} \\
\text{D} \text{D} \\
\end{array}
\]

[(R)-2-((1-Methyl-pyrrolidin-2-yl)ethanol-1,1-dy. At about -40 °C, a solution of (R)-(1-methyl-pyrrolidin-2-yl)-acetic acid methyl ester (0.300 g, 1.91 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a stirred suspension of lithium aluminum deuteride (0.120 g, 2.86 mmol) in dry tetrahydrofuran (5 mL). The reaction mixture was maintained at about -40 °C for about 2 hours and then cold deuterium oxide (0.3 mL) was added dropwise. The resulting precipitate was collected by filtration and washed several times with dry tetrahydrofuran. The washes were combined with filtrate and concentrated in vacuo to yield the title compound as a brown oil which was used without further purification (0.210 g, 84%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.47 (dd, $J = 14.6$, 3.3 Hz, IH), 1.72-2.07 (m, 5H), 2.12-2.20 (m, IH), 2.36 (s, 3H), 2.55-2.62 (m, IH), 3.03-3.09 (m, IH); IR (KBr) $\nu$ 3440, 2954, 2793, 2193, 2092, 1654, 1457, 1367 cm$^{-1}$; MS 132 (M + 1).

Step 4

\[
\begin{array}{c}
\text{N} \\
\text{D} \text{D} \text{OH} \\
\downarrow \\
\text{N} \\
\text{HCl} \text{Cl} \\
\end{array}
\]

[(R)-2-(2-Chloroethyl-2,2-t/ u)-l-methylpyrrolidine hydrochloride: A mixture of (R)-2-(l-methyl-pyrrolidin-2-yl)ethanol-1,1-d$_2$ (0.200 g, 1.52 mmol), thionyl chloride (0.45 mL, 6.17 mmol) and chloroform (4 mL) was heated at reflux for about 3 hours. The solvent and thionyl chloride were removed in vacuo, and the resulting residue was triturated with pentane to yield the title compound as a yellow solid which was used in the next step without further purification (0.260 g, 92%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 1.63-1.74 (m, IH), 1.83-2.03 (m, 2H), 2.20-2.11 (m, IH), 2.18-2.28 (m, IH), 2.35 (dd, $J = 13.9$, 4.1 Hz, IH), 2.78 (d, $J = 4.9$ Hz, 3H), 2.98-3.08 (m, IH), 3.29-3.40 (m, IH), 3.48-3.57 (m, IH), 10.68 (br, IH); IR (film) $\nu$ 3417, 2962, 1636, 1461 cm$^{-1}$; MS 150, 152 (M + 1, M + 3).
Step 5

\[ (R)-2\text{-ri-(4-Chlorophenyl)-1-phenylethoxylethyl-2.2-Al-l-} \] methylpyrrolidine: The procedure of Example 1, Step 9 was followed but substituting \((R)-2\text{-}(2\text{-chloroethyl-2,2-}d\text{-})\text{-}1\text{-methyl-pyrrolidine hydrochloride for } (R)-2\text{-}(2\text{-chloroethyl})\text{-}l\text{-methyl-pyrrolidine hydrochloride.}\]

Step 6

\[ (R)-2\text{-}d\text{-}(R)-1-(4\text{-Chlorophenyl}-l\text{-phenylethoxy})\text{-}ethyl-2.2\text{-Al-l-} \] methylpyrrolidine: The procedure of Example 1, Step 10 was followed but substituting \((R)-2\text{-}[2\text{-}[1\text{-}(4\text{-Chlorophenyl})-l\text{-phenylethoxy}]\text{-}ethyl\text{-}]\text{-}1\text{-methylpyrrolidine for } (R)-2\text{-}[2\text{-}[1\text{-}(4\text{-Chlorophenyl})-l\text{-phenylethoxy}] \text{ethyl}\text{-}]\text{-}1\text{-methylpyrrolidine. The title product was isolated as a viscous oil (0.080 g).} \]
\[\left[\alpha\right]_D^{20} +39.3^\circ \text{ (c 1.65, ethanol); } ^1\text{H NMR (400 MHz, CDCl}_3) \delta 1.34-1.52 \text{ (m, 2H), 1.61-1.80 \text{ (m, 2H), 1.83 \text{ (s, 3H), 1.84-1.94 \text{ (m, IH), 2.01 \text{ (dd, J = 13.3, 3.1 Hz, IH), 2.09-2.20 \text{ (m, 2H); 2.32 \text{ (s, 3H), 3.02-3.09 \text{ (m, IH), 7.18-7.37 \text{ (m, 9H); MS 346, 348 [(M + 1), (M + 3).}}}ight] \]

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Step 7

[00249] (R)-2\2\2\(R)-1-(4-Chlorophenyl)-1-phenylethoxylethyl^Al^-1-methyl-
pyrroldine fumarate: The procedure of Example 1, Step 11 was followed but substituting
(R)-2-[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl-2,2-d_2]-1-methyl-pyrroldine for (R)-2-
[2-[1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methyl-pyrroldine. The Title compound
was isolated as a white solid (0.110 g, 55%). m.p. 155-159 °C; [\alpha]_D^{20} +22.0° (c 2.0,
methanol); \^H NMR (400 MHz, CD_3OD) \^H 1.67-1.82 (m, 2H), 1.88 (s, 3H), 1.97-2.14 (m,
2H), 2.22-2.33 (m, 2H), 2.92 (s, 3H), 3.11-3.21 (m, IH), 3.23-3.38 (m, IH), 3.39-3.53 (m
2H), 3.58-3.68 (m, IH), 6.69 (s, 2H), 7.21-7.37 (m, 9H); IR (KBr) \^H 3439, 2935, 1696,
1618, 1388, 1288, 1240 cm\(^{-1}\); MS 344, 346 [(M + 1) - fumaric acid, (M + 3) - fumaric acid].

EXAMPLE 3
(R)-2-[2-[(\beta)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl-2,2-\4]-1-methyl-pyrroldine
fumarate

Step 1

[00250] (R\text{\textendash}hydroxymethyl\textendash tfe\textendash pyrroldine\textendash l\textendash carboxylic \_acid \_tert\textendash butyl\_ ester: The procedure of Example 1, Step 1 was followed, but substituting lithium aluminum deuteride
for sodium borohydride, and deuterium oxide for water. The title product was isolated as an
oil (3.20 g, 68%). \^H NMR (400 MHz, DMSO-d_6) \^H 1.39 (s, 9H), 1.66-1.93 (m, 4H), 3.13-
3.26 (m, 2H), 3.58-3.69 (m, IH), 4.61 (s, IH, exchangeable with deuterium oxide); IR (film)
\^H 3418, 2977, 2877, 2206, 2096, 1678, 1405 cm\(^{-1}\); MS 204 (M + 1).
Step 2

The procedure of Example 1, Step 2 was followed but substituting (R)-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester for (R)-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester. The title product was isolated as an oil (3.73 g, 71%). 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.28, 1.35 (2s, 9H), 1.62-1.82 (m, 3H), 1.83-1.98 (m, 1H), 2.42 (s, 3H), 3.08-3.23 (m, 2H), 3.76-3.87 (m, 1H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.78 (d, $J = 7.9$ Hz, 2H); IR (film) $\nu$ 2974, 2932, 2882, 1694, 1394, 1366, 1180 cm$^{-1}$; MS 358 (M + 1).

Step 3

The procedure of Example 1, Step 3 was followed but substituting (R)-2-(toluene-4-sulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester for (R)-2-(toluene-4-sulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester. The title product was isolated as an oil (0.36 g, 61%). 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.41 (s, 9H), 1.69-1.83 (m, 2H), 1.86-2.00 (m, IH), 2.03-2.14 (m, IH), 3.21-3.34 (m, 2H), 3.86-3.94 (m, IH); IR (film) $\nu$ 2974, 2932, 2882, 1694, 1394, 1366, 1180 cm$^{-1}$; MS 213 (M + 1).

Step 4

A mixture of (R)-tert-butyl 2-(cyanomethyl-$^{1,2}$)-pyrrolidine-l-carboxylate (0.700 g, 3.30 mmol), a 20% deuterochloric acid solution (14 mL), and acetic acid-OD (7 mL) was heated at reflux for about 6 hours. The reaction mixture was allowed to cool to ambient temperature and extracted with ethyl acetate. The deuterium oxide layer was concentrated to dryness in vacuo. The resulting residue (0.500 g, 89%) was dissolved in deuterium oxide (10 mL) and
anhydrous potassium carbonate (1.65 g, 11.94 mmol) was added. The mixture was heated in a sealed tube at about 100 °C for about 2 hours, cooled to ambient temperature, and used in the next step without work up. ¹H NMR (400 MHz, deuterium oxide) δ 1.67-1.83 (m, 1H), 1.86-2.16 (m, 2H), 2.24-2.36 (m, 1H), 3.37-3.45 (m, 2H), 3.83-3.98 (m, 1H); IR (KBr) ν 2995, 2262, 1728, 1387 cm⁻¹; MS 132 (M + 1).

Step 5

![Diagram](image)

(R)-2-(l-Methyl-pyrrolidin-2-yl)acetic acid-2,2-d₂ hydrochloride: The procedure of Example 2, Step 1 was followed but substituting (R)-2-(pyrrolidin-2-yl)acetic acid-d₃ deuterohloride for (R)-2-(pyrrolidin-2-yl)acetic acid-hydrochloride. The title product was isolated as an off-white solid which was used in the next step without further purification (0.660 g, crude). ¹H NMR (400 MHz, DMSO-d₆) δ 1.56-1.69 (m, 1H), 1.80-1.89 (m, 2H), 2.16-2.25 (m, 1H), 2.66-2.74 (m, 2H), 2.91 (s, 3H), 3.38-3.43 (m, 1H); MS 146 (M + 1).

Step 6

![Diagram](image)

(R)-(l-Methyl-prorolidin-2-yl)-acetic acid-2,2-d₂ methyl-d₂ ester: The procedure of Example 2, Step 2 was followed but substituting (R)-2-(pyrrolidin-2-yl)-acetic acid-d₃ deuterohloride for (R)-2-(pyrrolidin-2-yl)-acetic acid-hydrochloride, deuterium oxide for water, and methanol⁻ for methanol. The title compound was isolated as an oil (0.150 g). ¹H NMR (400 MHz, CDCl₃) δ 1.50-1.60 (m, 1H), 1.65-1.84 (m, 2H), 2.00-2.10 (m, 1H), 2.16-2.24 (m, 1H), 2.32 (s, 3H), 2.47-2.53 (m, 1H), 3.02-3.08 (m, 1H); MS 163 (M + 1).

Step 7

![Diagram](image)

(R)-2-(l-Methylpyrolidin-2-yl)ethanol-2,2-d₂: The procedure of Example 2, Step 3 was followed but substituting (R)-(l-methyl-prorolidin-2-yl)-acetic acid-2,2-d₂
methyl-\(^{\text{ester}}\) for \((R)-(\text{I}-\text{methyl-\text{prrolidin-2-yl})-\text{acetic acid-methyl-ester.}\) The title product was isolated as an oil (0.150 g). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.50-1.60 (m, 1H), 1.65-1.84 (m, 2H), 2.00-2.10 (m, IH), 2.16-2.24 (m, IH), 2.32 (s, 3H), 2.47-2.53 (m, IH), 3.02-3.08 (m, IH); MS 163 (M + 1).

Step 8

\[
\begin{align*}
\text{(R)-2-(2-Chloroethyl-1,1,2,2-Cl}_4\text{)-1-methylpyrrolidine hydrochloride:}  \\
\text{The procedure of Example 2, Step 4 was followed but substituting \((R)-2-(1-methylpyrrolidin-2-yl)\text{ethanol-1,1,2,2-t/4 for \((R)-2-(1-methylpyrrolidin-2-yl)\text{ethanol-2,2-d2. The title product was isolated as a brown solid, which was used in the next step without further purification} (0.100 g, 71%).} \end{align*}
\]

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 1.63-1.74 (m, 1H), 1.83-2.06 (m, 2H), 2.18-2.26 (m, IH), 2.78 (d, \(J = 4.9\) Hz, 3H), 2.97-3.08 (m, IH), 3.28-3.37 (m, IH), 3.46-3.59 (m, IH), 10.70 (br, IH); IR (film) \(\nu\) 3421, 2964, 2706, 1640, 1461 cm\(^{-1}\); MS 152, 154 (M + 1, M + 3).

Step 9

\[
\begin{align*}
\text{(R)-2-(4-Chlorophenyl)-1-phenylethoxy\text{ethyl-1,1,2,2-A1-l-methylpyrrolidine: The procedure of Example 2, Step 5 was followed but substituting \((R)-2-(2-chloroethy l-1,1,2,2-d_4\)-1-methylpyrrolidine hydrochloride for \((R)-2-(2-chloroethyl-2,2-d_2)-1-methylpyrrolidine hydrochloride.}
\end{align*}
\]

Step 10

\[
\begin{align*}
\text{(R)-2-(4-Chlorophenyl)-1-phenylethoxy\text{ethyl-1,1,2,2-A1-l-methylpyrrolidine: The procedure of Example 1, Step 10 was followed, but substituting \((R)-2-[2-[\text{1-(4-chlorophenyl)-1-phenylethoxy}]\text{ethyl-1,1,2,2-dN}-1-methyl-pyrrolidine for \((R)-2-[2-[\text{(R)-1-}
\end{align*}
\]
The title product was isolated as a viscous oil (0.080 g). ¹H NMR (400 MHz, CDCl₃) δ 1.38-1.53 (m, 1H), 1.62-1.80 (m, 2H), 1.83 (s, 3H), 1.84-1.94 (m, 1H), 2.10-2.20 (m, 2H), 2.32 (s, 3H), 3.03-3.10 (m, 1H), 7.20-7.35 (m, 9H); IR (film) ν 2948, 2874, 2778, 1597, 1487, 1450 cm⁻¹; MS 344, 346 [(M + 1), (M + 3)].

**Step 11**

![Chemical structure of the title compound](image)

(R)-2-(2-[(R)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl)-l-methyl-pyrrolidine fumarate: The procedure of Example 1, Step 11 was followed, but substituting (R)-2-[(2-[(4-chlorophenyl)-1-phenylethoxy]ethyl]-l-methyl-pyrrolidine for (R)-2-[(2-[(4-chlorophenyl)-1-phenylethoxy]ethyl]-l-methyl-pyrrolidine. Title compound was isolated as a white solid (0.060 g, 64%). m.p. 142-145 °C; [α]D²⁰ +18.8° (c 2.0, methanol); ¹H NMR (400 MHz, CD₃OD) δ 1.65-1.81 (m, 1H), 1.87 (s, 3H), 1.95-2.14 (m, 2H), 2.15-2.33 (m, 1H), 2.91 (s, 3H), 3.10-3.30 (m, 1H), 3.42-3.50 (m, 1H), 3.59-3.72 (m, 1H), 6.69 (s, 2H), 7.21-7.39 (m, 9H); IR (KBr) ν 3439, 2935, 1696, 1618, 1388, 1288, 1240 cm⁻¹; MS 344, 346 [(M + 1) - fumaric acid, (M + 3) - fumaric acid].

**EXAMPLE 4**

\((^\wedge-\text{[l-[C^\wedge{l-\text{Chlorophenyl}}}}-{\text{[l-phenylethoxy]ethyl}}]-\text{l-methyl}}-{\text{l-pyrrolidine}}\) fumarate

**Step 1**

![Chemical structure of the title compound](image)

(R)-2-(2-Hydroxy-ethyl)-pyrrolidine-l-carboxylic acid tert-butyl ester: At about 0 °C, N-methylmorpholine (1.16 mL, 10.55 mmol) was added dropwise to a mixture of
(R)-2-[l-(tert-butoxycarbonyl)pyrrolidin-2-yl]acetic acid (2.0 g, 8.72 mmol), isobutyl chloroformate (1.36 mL, 10.49 mmol) and tetrahydrofuran (30 mL). After stirring for about 10 min at about 0 °C, the mixture was filtered through a pad of Celite. The filtrate was then added to a suspension of sodium borohydride (0.40 g, 10.57 mmol) in tetrahydrofuran (30 mL). The reaction mixture was stirred at about 0 °C for 30 minutes and then at ambient temperature for about 16 hours. Following standard extractive workup with ethyl acetate, the crude residue was purified by silica gel column chromatography (7% ethyl acetate in chloroform) to yield the title compound as an oil (1.35 g, 72%). 1H NMR (400 MHz, DMSO-d 6 ) δ 1.39 (s, 9H), 1.61-2.06 (m, 6H), 3.12-3.28 (m, 2H), 3.35-3.44 (m, 2H), 3.67-3.79 (m, 1H), 4.37 (t, J = 5.2 Hz, 1H, exchangeable with deuterium oxide); IR (KBr) ν 3425, 2969, 2880, 1681, 1404 cm⁻¹; MS 216 (M + 1).

Step 2

[00262] (R)-2-[1-Methyl-^pyrrolidin-2-yl]ethanol: The procedure of Example 1, Step 6 was followed, but with the following changes: substituting (R)-2-(2-hydroxy-ethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester for (R)-2-[l-(tert-butoxycarbonyl)pyrrolidin-2-yl]acetic acid, substituting lithium aluminum deuteride for lithium aluminum hydride, and deuterium oxide for water. The title product was isolated as a brown oil which was used in the next step without further purification (0.650 g, 76%). 1H NMR (400 MHz, DMSO-d 6 ) δ 1.29-1.43 (m, 2H), 1.55-1.64 (m, 2H), 1.70-1.79 (m, IH), 1.79-1.91 (m, IH), 1.96-2.11 (m, 2H), 2.47-2.56 (m, IH), 3.38-3.53 (m, 2H), 4.54 (br, IH, exchangeable with deuterium oxide); IR (KBr) ν 3369, 2951, 2800, 2188, 2043, 1655, 1459 cm⁻¹; MS 133 (M + 1).

Step 3

[00263] (R)-2-(2-Chloroethyl)-1-methyl-^pyrrolidine hydrochloride: The procedure of Example 1, Step 7 was followed, but substituting (R)-2-(1-methyl-1H-pyrrolidin-2-yl)ethanol for (R)-2-(1-methyl-pyrrolidin-2-yl)ethanol. The title product was isolated as a brown solid which was used in the next step without further purification (0.450 g, 81%). 1H NMR (400 MHz, DMSO-d 6 ) δ 1.63-1.78 (m, IH), 1.78-2.06 (m, 2H), 2.06-2.29 (m, 3H),
2.29-2.44 (m, IH), 2.93-3.12 (m, IH), 3.47-3.58 (m, IH), 3.58-3.74 (m, IH), 3.78-3.90 (m, IH), 11.00 (br, IH, exchangeable with deuterium oxide); IR (film) ν 3444, 2937, 2689, 2655, 1631, 1450 cm⁻¹; MS 151, 153 (M + 1, M + 3).

Step 4

\[
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{Cl} + \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{Cl} \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\]

(R)-2\-2\-(1-(4-Chlorophenyl)-1-phenylethoxy)ethyl\1-1-methyl-cp-pyrrolidine:
The procedure of Example 1, Step 9 was followed, but substituting (i?)-2-(2-chloroethyl)-l-methyl-cp-pyrrolidine hydrochloride for (i?)-2-(2-chloroethyl)-l-methyl-pyrrolidine hydrochloride.

Step 5

\[
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{O} - \text{Cl} + \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{O} - \text{Cl} \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\]

(R)-2\-r2-r(R)-l-(4-Chlorophenyl)-l-phenylethoxy1ethyl]-l-methyl-^-pyrrolidine: The procedure of Example 1, Step 10 was followed, but substituting (R)-2\-[2-[l-(4-chlorophenyl)-l-phenylethoxy]ethyl]-l-methyl-^-pyrrolidine for (i?)-2-[2-[l-(4-chlorophenyl)-l-phenylethoxy]ethyl]-l-methyl-pyrrolidine. The title product was isolated as a viscous oil (0.150 g). [α]D²⁰ +46.2° (c 2.0, ethanol); \(^1\)H NMR (400 MHz, CDCl₃) δ 1.34-1.52 (m, 2H), 1.61-1.79 (m, 2H), 1.83 (s, 3H), 1.84-1.93 (m, IH), 1.98-2.07 (m, IH), 2.08-2.20 (m, 2H), 3.01-3.07 (m, IH), 3.18-3.33 (m, 2H), 7.20-7.34 (m, 9H); IR (film) ν 2949, 2875, 2785, 2178, 2032, 1488, 1448, 1391, 1371 cm⁻¹; MS 347, 349 [(M + 1), (M + 3)].

Step 6

\[
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{O} - \text{Cl} + \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{CD}_3 - \text{C} - \text{O} - \text{Cl} \text{PhCH(OH)CH}_2 \text{Cl} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HO}_2 \text{C} - \text{CO}_2 \text{H} \\
\end{array}
\]

79
The procedure of Example 1, Step 11 was followed, but substituting (R)-2-[(R)-1-(4-chlorophenyl)-1-phenylethoxy]ethyl-1-methylpyrrolidine for (R)-2-[(R)-1-(4-chlorophenyl)-1-phenylethoxy]ethyl-1-methyl-pyrrolidine. The title compound was isolated as a white solid (0.100 g, 75%). m.p. 148-152°C; [α]D20 +22.7° (c 2.0, methanol); 1H NMR (400 MHz, CD3OD) δ 1.66-1.82 (m, 2H), 1.88 (s, 3H), 1.96-2.14 (m, 2H), 2.21-2.33 (m, 2H), 3.10-3.22 (m, 1H), 3.23-3.39 (m, 1H), 3.40-3.51 (m 2H), 3.57-3.63 (m, 1H), 6.68 (s, 2H), 7.20-7.37 (m, 9H); IR (KBr) υ 3438, 2927, 1700, 1618, 1386, 1286, 1241 cm⁻¹; MS 347, 349 [(M + 1) - fumaric acid, (M + 3) - fumaric acid].

EXAMPLE 5

(R)-2-[(/?)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl-2,2/-2-1-methyl</pyrrolidine fumarate

Step 1

The procedure of Example 1, Step 6 was followed, but substituting lithium aluminum deuteride for lithium aluminum hydride, and deuterium oxide for water. The title product was isolated as a brown oil which was used without further purification (0.120 g, 76%). 1H NMR (400 MHz, CDCl3) δ 1.47 (dd, J = 14.6 Hz, 3.1 Hz, IH), 1.70-1.92 (m, 4H), 1.97 (dd, J = 14.6 Hz, 3.5 Hz, IH), 2.11-2.19 (m, IH), 2.54-2.62 (m, IH), 3.02-3.09 (m, IH), 3.70 (s, IH); IR (KBr) υ 3402, 2952, 2800, 2189, 2100, 2042, 1658, 1457, 1366 cm⁻¹; MS 135 (M + 1).
Step 2

\[
\text{(R)-2-(2-Chloro-ethyl-2,2-A)-l-methyl-^-pyrrolidine hydrochloride:} \text{ The procedure of Example 1, Step 7 was followed, but substituting (R)-2-(l-methyl-<i _3>-pyrrolidin-2-yl)ethanol-1,1-l<sup>i2</sup> for (R)-2-(l-methyl-pyrrolidin-2-yl)ethanol. The title product was isolated as a brown solid which was used in the next step without further purification (0.160 g, 76%).} \text{ } \]

\[
1\text{H NMR (400 MHz, DMSO-{d}_6) } \delta 1.62-1.74 (m, 1H), 1.84-2.13 (m, 3H), 2.18-2.28 (m, 1H), 2.35 (dd, } J = 13.7 \text{ Hz, } 4.1 \text{ Hz, } 1H), 2.1 1-2.19 (m, } 1H), 2.97-3.08 (m, 1H), 3.47-3.57 (m, 1H), 10.42 (br, 1H); \text{ IR (film) } \nu 3428, 2949, 2676, 2599, 1638, 1444 \text{ cm}^{-1}; \text{ MS 153, 155 (M + 1, M + 3).}
\]

Step 3

\[
\text{(R)-2-r2-π -(4-Chlorophenyl-l-phenylethoxy1ethyl-2.2-A-l-methyl-^-pyrrolidine:} \text{ The procedure of Example 1, Step 9 was followed, but substituting (R)-2-(2-chloroethyl-2,2-<i _3>-l-methyl-<i _3>-pyrrolidine hydrochloride for (R)-2-(2-chloroethyl-l-}
\]

\[
\text{methyl-pyrrolidine hydrochloride.}
\]

Step 4

\[
\text{(R)-2-r2-r(R)-l-(4-Chlorophenyl-l-phenylethoxy1ethyl-2.2-A1-l-methyl-A-}
\]

\[
\text{pyrrolidine:} \text{ The procedure of Example 1, Step 10 was followed, but substituting (R)-2-[2-[1-(4-chlorophenyl)-l-phenylethoxy1ethyl-2,2-<i _d2>-l-methyl-^-pyrrolidine for (R)-2-[2-[1-(4-}
\]

\[
\text{chlorophenyl)-l-phenylethoxy1ethyl]-1-methyl-pyrrolidine. } \text{ The title product was isolated as a viscous oil (0.070 g).} \text{ } \]

\[
1\text{H NMR (400 MHz, CDCl}_3) \delta 1.39-1.51 (m, 2H), 1.62-1.80 (m, 2H), 1.83 (s, 3H), 1.85-1.99 (m, 1H), 2.02 (dd, } J = 13.5 \text{ Hz, } 3.3 \text{ Hz, } 1H), 2.11-2.25 (m, 2H), 3.05-3.12 (m, 1H), 7.20-7.35 (m, 9H); \text{ MS 349, 351 [(M + 1, (M + 3)].}
\]
Step 5

[0027] \((R)-2-\text{r}2-\text{r}(R)-1-(4\text{-Chlorophenyl})-\text{phenylethoxy}1\text{ethyl}-2.2-\text{A1}-1\text{-methyl}\text{-pyrrolidine} \) fumarate: The procedure of Example 1, Step 11 was followed, but substituting \((R)-2-[2-[\text{-(R)}-1-(4\text{-Chlorophenyl})-1\text{-phenylethoxy}1\text{ethyl]-2,2-}\text{-fim}\text{-1-methyl}\text{-pyrrolidine} \) for \((R)-2-[2-[\text{-(R)}-1-(4\text{-chlorophenyl})-1\text{-phenylethoxy}1\text{ethyl}]1\text{-methyl-pyrrolidine} \). The title compound was isolated as a white solid (0.055 g, 63%). m.p. 141-145 °C; \([\alpha]_\text{D}^{20}+20.6^\circ \) (c 2.0, methanol); \(^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CD}_2\text{OD}) \delta 1.66-1.81 \text{ (m, 2H)}, 1.87 \text{ (s, 3H)}, 1.96-2.14 \text{ (m, 2H)}, 2.21-2.32 \text{ (m, IH)}, 3.09-3.20 \text{ (m, IH)}, 3.21-3.31 \text{ (m, IH)}, 3.39-3.47 \text{ (m, IH)}, 3.58-3.68 \text{ (m, IH)}, 6.68 \text{ (s, 2H)}, 7.20-7.37 \text{ (m, 9H)}; \text{IR (KBr)} \nu 2930, 2654, 1687, 1615, 1489, 1393 \text{ cm }^{-1}; \text{MS 349, 351 }[(\text{M}+1) \text{- fumaric acid}, (\text{M}+3) \text{- fumaric acid}].

**EXAMPLE 6**

\((R)-2-[2-[\text{-(R)}-1-(4\text{-Chlorophenyl})-1\text{-phenylethoxy}1\text{ethyl]-1,1,2,2-\text{-cld1-methyl}} \text{-pyrrolidine} \) fumarate

[00272]

**Step 1**

[00272] \((R)-2\text{-Carboxymethyl-}\text{-pyrrolidine-1-carboxylic acid tert-butyl ester} \): At about 0 °C, a 5% solution of sodium hydroxide-\text{-ii} in deuterium oxide was added dropwise to \((R)-2-(\text{pyrrolidin}-1\text{-yl})\text{acetic acid-}\text{deuterochloride} \) until the pH was adjusted to 10. The solution was diluted with acetone (15 mL) and di-tert-butyl dicarbonate (0.990 g, 4.54 mmol) was added dropwise, at about 0 °C. The mixture was stirred at ambient temperature for about 16 hours. Acetone was evaporated \text{in vacuo} \) and the pH was adjusted to 3 by adding a 3 M
deuterochloric acid solution dropwise, at about 0°C. Following standard extractive workup with ethyl acetate, the crude product was purified by silica gel column chromatography (3% methanol in chloroform) to yield the title product as an off-white solid (0.450 g, 59%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.39 (s, 9H), 1.61-1.89 (m, 3H), 1.91-2.04 (m, IH), 3.21 (t, $J$ = 6.7 Hz, 2H), 3.93 (dd, $J$ = 7.5, 2.6 Hz, IH), 12.14 (s, IH); IR (KBr) $\nu$ 3196, 2975, 2884, 1723, 1694, 1414 cm$^{-1}$; MS 231 (M + 1).

Step 2

[00273] (R)-2-(1-Methyl-A-pyrrolidin-2-vmethanol-1,1,2,2-d$_4$: The procedure of Example 1, Step 6 was followed, but substituting (R)-2-carboxymethyl-d$_5$-pyrrolidine-1-carboxylic acid tert-butyl ester for (i?)-2-carboxymethyl-pyrrolidine-l-carboxylic acid tert-butyl ester, lithium aluminum deuteride for lithium aluminum hydride, and deuterium oxide for water. The title product was isolated as a brown oil which was used in the next step without further purification (0.170 g, 64%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.32-1.43 (m, IH), 1.53-1.65 (m, 2H), 1.79-1.89 (m, IH), 1.95-2.08 (m, IH), 2.87-2.93 (m, IH), 4.38 (s, IH); IR (KBr) $\nu$ 3400, 2949, 2801, 2188, 2093, 2044, 1661, 1454, 1368 cm$^{-1}$; MS 136 (M + 1).

Step 3

[00274] (R)-2-(2-Chloroethyl-1,1,2,2-Cd$_4$: 1-methyl-d$_4$-pyrrolidine hydrochloride: The procedure of Example 1, Step 7 was followed, but substituting (R)-2-(1-methyl-<i>l</i>-pyrrolidin-2-yl)ethanol-1,1,2,2-d$_4$ for (i?)-2-(1-methyl-pyrrolidin-2-yl)ethanol. The title product was isolated as a brown solid which was used in the next step without further purification (0.190 g, 80%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 1.64-1.75 (m, IH), 1.84-2.04 (m, 2H), 2.17-2.27 (m, IH), 2.96-3.07 (m, IH), 3.29-3.38 (m, IH), 3.47-3.56 (m, IH), 10.89 (br, IH, exchangeable with deuterium oxide); IR (film) $\nu$ 3419, 2936, 1724, 1648, 1392 cm$^{-1}$; MS 155, 157 (M + 1, M + 3).
Step 4

(R)-2\(-2-(1-(4-Chlorophenyl)-1-phenylethoxy)ethy\-1.1.2.2-\(d\)\-1-methyl-A-pyrrolidine: The procedure of Example 1, Step 9 was followed, but substituting (R)-2-(2-chloroethyl-1,1,2,2-A)-1-methyl-A-pyrrolidine hydrochloride for (R)-2-(2-chloroethyl-1)-1-methyl-pyrrolidine hydrochloride.

Step 5

(R)-2\(-2\)-(R)-1-(4-Chlorophenyl)-1-phenylethoxy)ethyl-1.1.2.2-(LiI-1-methyl-d3-pyrrolidine: The procedure of Example 1, Step 10 was followed, but substituting (R)-2-[2-[1-(4-chlorophenyl)-1-phenylethoxy)ethyl]-1,1,2,2-A]-1-methyl-A-pyrrolidine for (R)-2-[2-[1-(4-chlorophenyl)-1-phenylethoxy)ethyl]-1-methyl-pyrrolidine. The title compound was isolated as a viscous oil (0.120 g). 1H NMR (400 MHz, CDCl3) δ 1.35-1.47 (m, 1H), 1.62-1.79 (m, 2H), 1.83 (s, 3H), 1.84-1.93 (m, 1H), 2.09-2.19 (m, 2H), 3.02-3.09 (m, 1H), 7.19-7.34 (m, 9H); MS 351, 353 [(M + 1), (M + 3)].

Step 6

(R)-2\(-2\)-(R)-1-(4-Chlorophenyl)-1-phenylethoxy)ethyl-1.1.2.2-AI-1-methyl-A-pyrrolidine fumarate: The procedure of Example 1, Step 11 was followed, but substituting (R)-2-[2-[1-(4-chlorophenyl)-1-phenylethoxy)ethyl]-1,1,2,2-d4]-1-methyl-d3-pyrrolidine for (R)-2-[2-[1-(4-chlorophenyl)-1-phenylethoxy)ethyl]-1-methyl-pyrrolidine. The title compound was isolated as a white solid (0.090 g, 68%). m.p. 142-146 °C; [\(\epsilon\)]\(D\)^20 +22.7° (c 1.9, methanol); 1H NMR (400 MHz, CD3OD) δ 1.63-1.82 (m, 2H), 1.87 (s, 3H), 1.95-2.14
EXAMPLE 7

(R)-2-[2-[(/?)-l-(4-Chlorophenyl)-l-phenylethoxy]ethyl]-l-methyl-pyrrolidine-

Step 1

\[ N\text{-pyrryl-}(\text{4-magnesium bromide)}: \]

The procedure of Step 1 is carried out using the methods described by Wu et al., *Pyrrolidines. IV. 1961*, 1531-1533, but substituting 4-pyrrylmagnesium bromide for pyrrylmagnesium bromide, and 4-oxirane for oxirane.

Step 2

\[ 2-(1\text{-Pyrryl-}(4-2yl)-ethanol-}\text{i4} : \]

The procedure of Step 2 is carried out using the methods described by Moll et al., *Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischem Gesellschaft. 1968*, 301(11), 872-7, but substituting \text{d}_{4}\text{-pyrrylmagnesium bromide for pyrrylmagnesium bromide, and }\text{i4-oxirane for oxirane.}
Step 3

2-Pyrrolidin-d7-2yl-ethanol-d4: The procedure of Step 3 is carried out using the methods described by Wu et al., *Pyrrolidines. IV. 1961*, 1531-1533, but substituting 2-(1H-pyrrol-d3-2yl)-ethanol-d4 for 2-(1H-pyrrol-2yl)-ethanol and ethanol-d6 for ethanol.

Step 4

2-(1-Methyl-d3-pyrrolidin-d7-2yl)-ethanol-d4: The procedure of Step 4 is carried out using the methods described by Rosenau et al., *Synthetic Communications 2002*, 32(3), 457-46, but substituting d6-oxalic acid dihydrate for oxalic acid dehydrate, perdeuterated paraformaldehyde for paraformaldehyde, deuterium oxide for water, and 2-pyrrolidin-d7-2yl-ethanol-d4 for 2-Pyrrolidin-2yl-ethanol. d6-Oxalic acid dehydrate can be prepared using the methods described by Delaplane et al., *Acta Cryst. 1969, B25*, 2423.

Step 5

2-(2-Chloro-ethyl-d4)-1-methyl-d4-pyrrolidine-d: The procedure of Step 5 is carried out using the methods described by Chaudhari et al., *Synlett, 1999, (11)*, 1763-1765, but substituting 2-(1-Methyl-d3-pyrrolidin-d7-2yl)-ethanol-d4 for 2-(1-Methyl-pyrrolidin-2yl)-ethanol.
Phenyl-A-magnesium bromide: The procedure of Step 6 is carried out using the methods described by Stucky et al. *Journal of the American Chemical Society* 1963, 85, 1002, but substituting bromobenzene-ds for bromobenzene.

**Step 7**

1-(4-Chloro-phenyl-<4>-ethanone-<4: 1-(4-Chloro-phenyl-<i>-ethanone

(available commercially from Sigma-Aldrich Co. St. Louis MO) is added to a solution of potassium carbonate and methanol-<^>. The mixture is heated at reflux for about 1 hour, allowed to cool to ambient temperature, and poured into deuterium oxide. Following standard extractive workup with ethyl acetate, the crude residue is purified by column chromatography to afford the title product.

1-(4-Chloro-phenyl-<4V l-phenyl-<i>-ethanol-<i>: The procedure of Example 1, Step 8 is followed but substituting phenyl-ds-magnesium bromide for phenylmagnesium bromide, and L^-Chloro-phenyl-fi^-ethanol-fi^ for 1-(4-Chloro-phenyl)-ethanone.
Step 8

[00286] \(2\text{-}T2\) r1-M-chlorophenyl-ck)- l-phenyl-^\text{\textendash}ethoxy-^\text{\textendash}ethyl-^\text{\textendash}l- 1-methyl-cb- pyrrolidine-t/ : The procedure of Step 8 is carried out using the methods described in Ebnöther et al., *Helvetica Chimica Acta* **1976**, 59(264), 2462-2468, but substituting 1-(4-Chloro-phenyl-<i>\textendash</i>)l-phenyl-<i>\textendash</i>5-ethanol-<i>\textendash</i>3 for 1-(4-Chloro-phenyl)-l-phenyl-ethanol, and 2-(2-Chloro-ethyl-<i>\textendash</i>)l-1-methyl-\text<i>\textendash</i>d<sub>3</sub>-pyrrolidine-\text<i>\textendash</i>d<sub>3</sub> for 2-(2-Chloro-ethyl)- 1-methyl-pyrrolidine.

Step 9

[00287] \((R)\text{-}2\text{-}r2\text{-}((R)\text{-}l\text{-}(4\text{-}chlorophenyl-\textendash A)-l-phenyl-\textendash ethoxy-\textendash Aethyl-\textendash 1-l- methyl-\textendash d<sub>3</sub>-pyrrolidine-\textendash d<sub>3</sub>\): The procedure of Step 9 is carried out using the methods described in Ebnöther et al., *Helvetica Chimica Acta* **1976**, 59(264), 2462-2468, but substituting 2-[2l-(4-chlorophenyl-<i>\textendash</i>)l-phenyl-<i>\textendash</i>ds-ethoxy-fiyethyl-fiy- 1-methyl-^\text{\textendash}pyrrolidine-^\text{\textendash} for 2-[2 [1-(4-chlorophenyl)-l-phenyl-ethoxy] ethyl]- 1-methyl-pyrrolidine.

[00288] 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.
Changes in the metabolic properties of the compound of Examples 2-7 as compared to its non-isotopically enriched analog 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 8

In vitro Liver Microsomal Stability Assay

Liver microsomal stability assays were conducted at 1 mg per mL liver microsome protein with an NADPH-generating system in 2% NaHC\textsubscript{3} (2.2 mM NADPH, 25.6 mM glucose 6-phosphate, 6 units per mL glucose 6-phosphate dehydrogenase and 3.3 mM MgC\textsuperscript{2+}). Test compounds were prepared as solutions in 20% acetonitrile-water and added to the assay mixture (final assay concentration 1 \textmu M) and incubated at about 37 °C. Final concentration of acetonitrile in the assay should be <1%. Aliquots (50 \mu L) were taken out at times 0, 0.25, 0.30, and 1 hours, and diluted with ice cold acetonitrile (200 \mu L) to stop the reactions. Samples were centrifuged at 12,000 RPM for about 10 min to precipitate proteins. Supernatants were transferred to micro centrifuge tubes and stored for LC/MS/MS analysis of the degradation half-life of the test compounds. It has thus been found that the compounds disclosed herein that have been tested in this assay, showed improved degradation half-life as compared to the non-isotopically enriched drug. Some of the compounds showed a decrease of degradation half-life, as compared to the non-isotopically enriched drug. Additionally, some of the compounds showed at least 5% increase of degradation half-life, as compared to the non-isotopically enriched drug. Further, some of the compounds showed greater than 10% increase of degradation half-life, as compared to the non-isotopically enriched drug.

Results of in vitro human liver microsomal (HLM) stability assay - Percent change in degradation half-life

<table>
<thead>
<tr>
<th>Example</th>
<th>-25% - 0%</th>
<th>0% - 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 2</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Example 3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Example 4</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Example 5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Example 6</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.
EXAMPLE 9

In vitro metabolism using human cytochrome P$_{450}$ enzymes

[00291] 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.

<table>
<thead>
<tr>
<th>Cytochrome P$_{450}$</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>$[^{13}]$C-(S)-mephenytoin</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Dielofenac</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>$[^{13}]$C-(S)-mephenytoin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(+/-)-Bufuralol</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorzoxazone</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Testosterone</td>
</tr>
<tr>
<td>CYP4A</td>
<td>$[^{13}]$C-Lauric acid</td>
</tr>
</tbody>
</table>

EXAMPLE 10

Monoamine Oxidase A Inhibition and Oxidative Turnover

[00292] The procedure is carried out using the methods described by Weyler, Journal of Biological Chemistry 1985, 260, 13199-13207, which is hereby incorporated by reference in its entirety. 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$_1$ 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 11**

**Monoamine Oxidase B Inhibition and Oxidative Turnover**

[00293] The procedure is carried out as described in Uebelhack, *Pharmacopsychiatry* 1998, 37(5), 187-192, which is hereby incorporated by reference in its entirety.

**EXAMPLE 12**

**In Vivo detection of Clemastine in Human Plasma**

[00294] The procedure is carried out using the methods described by Horvath et al., *J of Chromatography B* 2005, 816, 153-159, which is hereby incorporated by reference in its entirety.

**EXAMPLE 13**

**In Vivo Radioimmunoassay for Clemastine**

[00295] The procedure is carried out using the methods described by Schran et al., *Clin Pharmacol* 1996, 36, 911, which is hereby incorporated by reference in its entirety.

* * * * *

[00296] 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 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. However, with respect to any similar or identical terms found in both the incorporated publications, references, patent or patent applicationsand those explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.
What is claimed is:

1. A compound having structural formula I

![Structural formula I](image)

or a pharmaceutically acceptable salt thereof; wherein

R1-R20 are independently selected from the group consisting of hydrogen and deuterium;

R21 and R22 are independently selected from the group consisting of CD3, CD2H, CDH2, and CH3; and

at least one of R1-R20 is deuterium or contains deuterium.

2. The compound as recited in Claim 1, wherein said compound has structural formula II

![Structural formula II](image)

or a pharmaceutically acceptable salt thereof; wherein

R1-R2O are independently selected from the group consisting of hydrogen and deuterium;

R21 and R22 are independently selected from the group consisting of CD3, CD2H, CDH2, and CH3; and
at least one of $R_1$-$R_{22}$ is deuterium or contains deuterium.

3. The compound as recited in Claim 1, wherein at least one of $R_1$-$R_{22}$ has deuterium enrichment of no less than about 10%.

4. The compound as recited in Claim 1, wherein at least one of $R_1$-$R_{22}$ has deuterium enrichment of no less than about 50%.

5. The compound as recited in Claim 1, wherein at least one of $R_1$-$R_{22}$ has deuterium enrichment of no less than about 90%.

6. The compound as recited in Claim 1, wherein at least one of $R_1$-$R_{22}$ has deuterium enrichment of no less than about 98%.

7. The compound as recited in Claim 1, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

8. The compound as recited in Claim 7, wherein each of said positions represented as D have deuterium enrichment of at least 10%.

9. The compound as recited in Claim 7, wherein each of said positions represented as D have deuterium enrichment of at least 50%.

10. The compound as recited in Claim 7, wherein each of said positions represented as D have deuterium enrichment of at least 90%.

11. The compound as recited in Claim 7, wherein each of said positions represented as D have deuterium enrichment of at least 98%.

12. The compound as recited in Claim 1, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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

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

14. A pharmaceutical composition comprising the compound as recited in Claim 1 and one or more pharmaceutically acceptable carriers.

15. The pharmaceutical composition as recited in Claim 14, further comprising one or more release-controlling carriers.
16. The pharmaceutical composition as recited in Claim 14, further comprising one or more non-release controlling carriers.

17. The pharmaceutical composition as recited in Claims 14, wherein the composition is suitable for oral, parenteral, or intravenous infusion administration.

18. The pharmaceutical composition as recited in Claim 17, wherein the oral dosage form is a tablet, capsule or syrup.

19. The pharmaceutical composition as recited in Claim 17, wherein the compound is administered in a dose of about 0.5 micrograms to about 1,000 micrograms.

20. The pharmaceutical composition as recited in Claim 14, further comprising another therapeutic agent.

21. The pharmaceutical composition as recited in Claim 14, wherein the therapeutic agent is selected from the group consisting of: decongestant treatments, antitussive treatments, mucolytic treatments, expectorant treatments, antiallergic non-steroidal treatments, steroidal drugs, antihistamine treatments, leukotriene receptor antagonists, phosphodiesterase inhibitors, CYP3A inhibitors, CYP3A inducers, protease inhibitors, antifungal agents, antibacterials, antitubercular agents, sepsis treatments, steroidal drugs, anticoagulants, thrombolytics, non-steroidal anti-inflammatory agents, antiplatelet 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 Vila 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-stabilizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, and platinum coordination complexes.

22. The pharmaceutical composition as recited in Claim 21, wherein the therapeutic agent is an antitussive treatment.

23. The method as recited in Claim 22, wherein the antitussive treatment is selected from the group consisting of dextromethorphan, ethylmorphine, hydrocodone, codeine,
normetadone, noscapine, pholcodine, thebacon, dimemorfan, actyldihydrocodeine, benzonatate, benproperine, clobutinol, isoaminile, pentoxyverine, oxolamine, oxeladin, clofedanol, pipazetate, bibenzonium bromide, butamirate, fedrilate, zipeprol, dibunate, droxypropine, prenoxdiazine, dropopizine, cloperastine, meprotixol, piperidione, tipepidine, morclofone, nepinalone, levodropropizine, and dimethoxanate.

24. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is a mucolytic treatment.

25. The pharmaceutical composition as recited in Claim 24, wherein the mucolytic treatment is selected from the group consisting of acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, dornase alfa, neltenezine, and erdosteine.

26. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is an expectorant treatment.

27. The pharmaceutical composition as recited in Claim 26, wherein the expectorant treatment is selected from the group consisting of tyloxapol, potassium iodide, guaifenesin, ipecacuanha, althea root, senega, antimony pentasulfide, creosote, guaiacolsulfonate, and levoverbenone.

28. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is an antihistamine treatment.

29. The pharmaceutical composition as recited in Claim 28, wherein the antihistamine treatment is selected from the group consisting of mepyramine, antazoline, diphenhydramine, carboxamine, doxylamine, dimenhydrinate, pheniramine, chlorphenamine, brompheniramine, tripolidine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, promethazine, alimemazine, cyproheptadine, azatadine, and ketotifen.

30. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is an antiallergic non-steroidal treatment.

31. The pharmaceutical composition as recited in Claim 30, wherein the antiallergic non-steroidal treatment is selected from the group consisting of cromoglicic acid, levocabastine, azelastine, antazoline, spaglumic acid, thonzylamine, nedocromil, and olopatadine.
32. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is a non-steroidal anti-inflammatory agent.

33. The pharmaceutical composition as recited in Claim 32, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoracoxib, fairoxamine, fenbuten, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, sulfinprazone, suprofen, tenoxicam, tiaprofenic acid, and tolmetin.

34. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is a steroidal drug.

35. The pharmaceutical composition as recited in Claim 34, wherein the steroidal drug is selected from the group consisting of aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone acetate, hydrocortisone (Cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone, flunisolide, fluticasone, mometasone furoate, tixocortol, and budesonide.

36. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is a leukotriene receptor antagonist.

37. The pharmaceutical composition as recited in Claim 36, wherein the leukotriene receptor antagonist is selected from the group consisting of montelukast, pranlukast, and zafirlukast.

38. The pharmaceutical composition as recited in Claim 21, wherein said therapeutic agent is a decongestant treatment.

39. The pharmaceutical composition as recited in Claim 38, wherein the decongestant treatment is selected from the group consisting of phenylpropanolamine hydrochloride, pseudoephedrine, phenylephrine, ephedrine, tuaminoheptane, xylometazoline, tetryzoline, naphazoline, cyclopentamine, tramazoline, metizoline, fenoxazoline, tymazoline, and oxymetazoline.

40. The pharmaceutical composition as recited in Claim 28, wherein said decongestant treatment is phenylpropanolamine hydrochloride.
41. A method for the treatment, prevention, or amelioration of one or more symptoms of a histamine receptor-mediated disorder, comprising administering to a subject a therapeutically effective amount of the compound as recited in Claim 1.

42. The method as recited in Claim 41, wherein the disorder is selected from the group consisting of allergic rhinitis, angioedema, exercise induced asthma, childhood asthma, pruritis, coronary artery bypass surgery, atopic dermatitis, chronic idiopathic urticaria, rhinorrhea, and sneezing.

43. The method as recited in Claim 41, wherein said disorder can be ameliorated by administering a bronchodilator.

44. The method as recited in Claim 41, wherein said disorder can be ameliorated by modulation of histamine receptors.

45. The method as recited in Claim 41, 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.

46. The method as recited in Claim 41, 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.

47. The method as recited in Claim 41, wherein said compound has a decreased metabolism by at least one polymorphically-expressed cytochrome P450 isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

48. The method as recited in Claim 47, wherein said cytochrome P450 isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

49. The method as recited in Claim 41, wherein said compound is characterized by decreased inhibition of at least one cytochrome P450 or monoamine oxidase isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

50. The method as recited in Claim 49, wherein said cytochrome P450 or monoamine oxidase isoform is selected from the group consisting of CYPIA1, CYPIA2, CYPIB1, 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, CYPIA1, CYPIB1, CYP1B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAOA, and MAOB.

51. The method as recited in Claim 41, wherein the 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.

52. The method as recited in Claim 51, 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.