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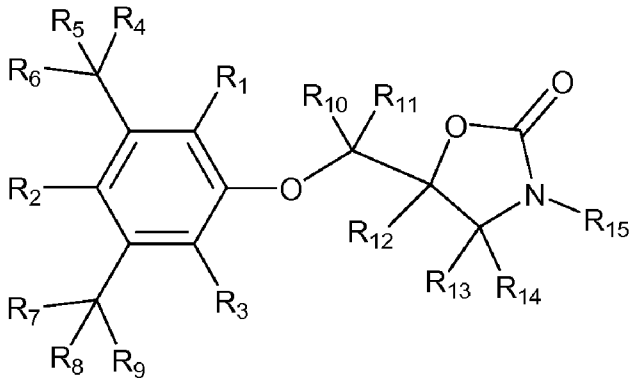
(54) **Title**: SUBSTITUTED OXAZOLIDINONES



Formula I

(57) **Abstract**: The present invention relates to new oxazolidinone modulators of skeletal muscle function and tone, pharmaceutical compositions thereof, and methods of use thereof.

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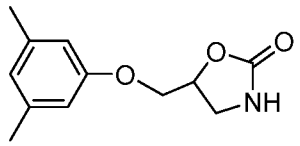
SUBSTITUTED OXAZOLIDINONES

[0001] This application claims the benefit of priority of United States provisional application No. 61/048,028, filed April 25, 2008, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[0002] Disclosed are new oxazolidinone compounds, compositions, and their application as pharmaceuticals for the treatment of disorders. Methods for modulating skeletal muscle function and tone are also provided for the treatment of disorders such as muscle spasms, muscle sprains, dorsalgia, fibromyalgia, myofascial pain syndrome, radiculopathy, diabetic peripheral neuropathy, tension headaches, and/or any disorder which can lessened, alleviated, or prevented by administering a skeletal muscle relaxant.

[0003] Metaxalone (Skelaxin®), 5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone, is an orally administered skeletal muscle relaxant. Metaxalone is commonly prescribed to treat discomforts associated with acute painful muscolosketal disorders such as muscle spasms, (Nicholson, *International Congress and Symposium Series – Royal Society of Medicine,* **2000**, *245(Medical Management of Selected Neurological Disorders: Epilepsy, Spasticity and Pain),* 45-53; dorsalgia (Toth et al., *Clinical Therapeutics,* **2004**, *26(9)*, 1355-1367); radiculopathy (Toth et al., *Clinical Therapeutics,* **2004**, *26(9)*, 1355-1367); myofascial pain syndrome (Alarcon et al., *American Journal of the Medical Sciences. Fibromyalgia*, 315(6), 397-404; diabetic peripheral neuropathy (Pfeifer et al., *Diabetes Care,* **1993**, *16(8)*, 1103-15); fibromyalgia (Alarcon et al., *American Journal of the Medical Sciences. Fibromyalgia*, 315(6), 397-404); and tension headaches (Solomon, *Cleve. Clin. J. Med.,* **2002**, *69*, 167-72). Metaxalone is considered to be a moderately strong muscle relaxant, with relatively low toxicity.

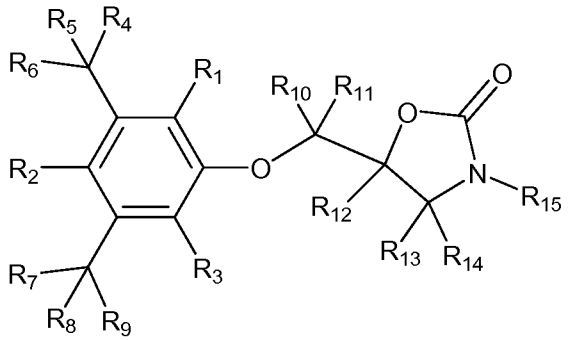


Metaxalone

[0004] Metaxalone is extensively metabolized in the human liver by oxidation. The major metabolite, 5-(3-methyl-5-carboxyphenoxymethyl)-2-oxazolidinone, is formed by oxidation of an aryl methyl group by cytochrome P_{450} enzymes. Other known metabolites are

generated from cleavage at metaxolone's ether group and the glucuronidation of 5-(3-methyl-5-carboxyphenoxymethyl)-2-oxazolidinone carboxylic acid (Bruce et al., *Journal of Medicinal Chemistry* **1966**, *9(3)*, 2868). The conversion of metaxalone to 5-(3-methyl-5-carboxyphenoxymethyl)-2-oxazolidinone and other known transformations occur through polymorphically-expressed enzymes, such as CYP2C19. (U.S. Pat. No. 7,122,566). Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions (Skelaxin® monograph, 2001 Physician's Desk Reference®, Medical Economics Company, Inc; U.S. Pat. No. 6,407,128). Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of metaxolone from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (Cmax) and area under the curve (AUC). Metaxalone metabolism is affected by age, gender, and coadministering with food. The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day. The most frequent side effects to metaxalone include: drowsiness, dizziness, headache, nervousness or irritability, nausea, vomiting, gastrointestinal upset, hypersensitivity reactions, rash with or without pruritus, leukopenia, hemolytic anemia, and jaundice. Though rare, anaphylactoid reactions have been reported with metaxalone.

[0005] In certain embodiments of the present invention, compounds have structural Formula I:



(I)

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

R_1-R_{15} are each independently selected from the group consisting of hydrogen and deuterium; and

at least one of R_1-R_{15} is independently deuterium.

[0006] Also disclosed herein are pharmaceutical compositions comprising at least one of

the compounds disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof; in combination with one or more pharmaceutically acceptable excipients or carriers.

[0007] In a further embodiment are processes for preparing a compound as disclosed herein as a musculoskeletal modulator, or other pharmaceutically acceptable derivatives such as salts, solvates, or prodrugs.

[0008] Also disclosed herein are articles of manufacture and kits containing compounds as disclosed herein. By way of example only a kit or article of manufacture can include a container (such as a bottle) with a desired amount of at least one compound (or pharmaceutical composition of a compound) as disclosed herein. Further, such a kit or article of manufacture can further include instructions for using said compound (or pharmaceutical composition of a compound) disclosed herein. The instructions can be attached to the container, or can be included in a package (such as a box or a plastic or foil bag) holding the container.

[0009] In another embodiment is a method for treating, preventing, or ameliorating one or more symptoms of a musculoskeletal-mediated disorder which comprises administering to a subject a therapeutically effective amount of at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0010] In a further embodiment said method for treating, preventing, or ameliorating one or more of the following musculoskeletal-mediated disorders including, but not limited to, muscle spasms, muscle sprains, dorsalgia, fibromyalgia, myofascial pain syndrome, radiculopathy, diabetic peripheral neuropathy, tension headaches, and/or any disorder which can lessened, alleviated, or prevented by administering a musculoskeletal muscle relaxant which comprises administering to a subject a therapeutically effective amount of at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0011] In certain embodiments said musculoskeletal-mediated disorder is dorsalgia.

[0012] In yet another embodiment said method can be lessened, allievated, or prevented by administering a muscle relaxant.

[0013] In yet further embodiments said method further comprises an additional therapeutic agent.

[0014] In other embodiments said therapeutic agent is selected from the group consisting of: non-steroidal anti-inflammatory agents, antiepileptics, anilide analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), diabetic neuropathy treatments,

norepinephrine reuptake inhibitors (NRIs), dopamine reuptake inhibitors (DARIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitor (NDRIs), serotonin-norepinephrine-dopamine-reuptake-inhibitors (SNDRIs), monoamine oxidase inhibitors, hypothalamic phospholipids, antifugal agents, antibacterials, antimycobacterial agents, opioids, sepsis treatments, steroidal drugs, anticoagulants, thrombolytics, antiplatelet agents, endothelin converting enzyme (ECE) inhibitors, thromboxane enzyme antagonists, potassium channel openers, thrombin inhibitors, growth factor inhibitors, platelet activating factor (PAF) antagonists, Factor VIIa Inhibitors, Factor Xa Inhibitors, renin inhibitors, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, anti-atherosclerotic agents, MTP Inhibitors, calcium channel blockers, potassium channel activators, alpha-PDE5 agents, beta-PDE5 agents, antiarrhythmic agents, diuretics, anti-diabetic agents, PPAR-gamma agonists, mineralocorticoid enzyme antagonists, aP2 inhibitors, protein tyrosine kinase inhibitors, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-disruptor agents, microtubule-stablizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, and platinum coordination complexes.

[0015] In yet further embodiments said therapeutic agent is a non-steroidal anti-inflammatory agent.

[0016] In certain embodiments said 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, faislamine, 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.

[0017] In other embodiments said therapeutic agent is an anilide analgesic.

[0018] In further embodiments said anilide analgesic is selected from the group consisting of acetaminophen and phenacetin.

[0019] In yet other embodiments said anilide analgesic is acetaminophen.

[0020] In certain embodiments said therapeutic agent is an antiepileptic.

[0021] In yet other embodiments said antiepileptic is selected from the group consisting of methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, ethosuximide, phensuximide, mesuximide, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, tiagabine, sultiame, phenacemide, lamotrigine, felbamate, topiramate, gabapentin, pheneturide, levetiracetam, zonisamide, pregabalin, stiripentol, and beclamide.

[0022] In further embodiments said therapeutic agent is a tricyclic antidepressant.

[0023] In certain embodiments said tricyclic antidepressant is selected from the group consisting of amitriptyline, butriptyline, amoxapine, clomipramine, desipramine, dosulepin hydrochloride, doxepin, imipramine, dibenzepin, iprindole, lofepramine, nortriptyline, opipramol, protriptyline, and trimipramine.

[0024] In other embodiments said therapeutic agent is a SSRI.

[0025] In certain embodiments, said SSRI is selected from the group consisting of alaproclate, citalopram, dapoxetine, escitalopram, etoperidone, fluoxetine, fluvoxamine, paroxetine, sertraline, and zimelidine.

[0026] In yet other embodiments said therapeutic agent is a diabetic neuropathy treatment.

[0027] In certain embodiments, said diabetic neuropathy treatment is selected from the group consisting of methylcobalamin, α-lipoic acid, epalrestat, and C-peptide.

[0028] In other 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.

[0029] In yet further embodiments said compound 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.

[0030] 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.

[0031] In other embodiments said cytochrome P_{450} isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0032] 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.

[0033] In certain embodiments said cytochrome P_{450} or monoamine oxidase isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19,

CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAO_A, and MAO_B.

[0034] In 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.

[0035] In yet further embodiments said diagnostic hepatobiliary function endpoint is selected from the group consisting of alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGTP," "γ-GTP," "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein.

[0036] In a futher embodiment is the use of at least one compound as disclosed herein as a medicament.

[0037] In another embodiment is the use of at least one compound as disclosed herein in the manufacture of a medicament for treating a disorder in an animal in which modulating musculoskeletal function and tone contributes to the pathology and/or symptomology of the disorder.

INCORPORATION BY REFERENCE

[0038] 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.

DETAILED DESCRIPTION

[0039] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood in the art to which

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

[0040] The singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0041] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0042] When ranges of values are disclosed, and the notation "from n_1 ... to n_2" or "n_1-n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values.

[0043] 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.

[0044] The term "is/are deuterium," when used to describe a given position in a molecule such as R_1-R_{15} 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 one embodiment deuterium enrichment is no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

[0045] 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.

[0046] 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.

[0047] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as D-isomers and L-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0048] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0049] The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms.

[0050] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder or one or more of the symptoms associated with a disorder; or alleviating or eradicating the cause(s) of the disorder itself. As used herein, reference to "treatment"of a disorder is intended to include prevention. 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.

[0051] 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.

[0052] 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.

[0053] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the disorders described herein.

[0054] The term “musculoskeletal” refers to the muscles, tendons, ligaments, bones, joints, and associated tissues that move the body and maintain its form.

[0055] The term “muscle relaxant” refers to a compound which affects skeletal muscle function and decreases muscle tone. It may be used to alleviate symptoms such as muscle spasm and pain, and hyperreflexia. The term "muscle relaxant" as used herein, refers to two major therapeutic groups: neuromuscular blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no central nervous system activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis. Spasmolytics, also known as "centrally-acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions.

[0056] The term “musculoskeletal-mediated disorder,” refers to a disorder characterized by abnormal skeletal muscle tone and fuction, that when the skeletal muscle tone and fuction is modified leads to the amelioration of other abnormal biological processes. A musculoskeletal-mediated disorder may be completely or partially mediated by modulating the function and tone of skeletal muscles. In particular, a musculoskeletal-mediated disorder is one in which modulation of skeletal muscle tone and function results in some effect on the underlying disorder e.g., administering a musculoskeletal modulator results in some improvement in at least some of the patients being treated.

[0057] The term “halogen”, “halide” or “halo” includes fluorine, chlorine, bromine, and iodine.

Deuterium Kinetic Isotope Effect

[0058] In an attempt to eliminate foreign substances, such as therapeutic agents, from its circulation system, the animal body expresses various enzymes, such as the cytochrome P_{450} enzymes or CYPs, esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C-H) bond to either a carbon-oxygen (C-O) or a 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.

[0059] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, $k = Ae^{-Eact/RT}$, where E_{act} is the activation energy, T is temperature, R is the molar gas constant, k is the rate constant for the reaction, and A (the frequency factor) is a constant specific to each reaction that depends on the probability that the molecules will collide with the correct orientation. The Arrhenius equation states that the fraction of molecules that have enough energy to overcome an energy barrier, that is, those with energy at least equal to the activation energy, depends exponentially on the ratio of the activation energy to thermal energy (RT), the average amount of thermal energy that molecules possess at a certain temperature.

[0060] The transition state in a reaction is a short lived state (on the order of 10^{-14} sec) along the reaction pathway during which the original bonds have stretched to their limit. By definition, the activation energy E_{act} for a reaction is the energy required to reach the transition state of that reaction. Reactions that involve multiple steps will necessarily have a number of transition states, and in these instances, the activation energy for the reaction is equal to the energy difference between the reactants and the most unstable transition state. Once the transition state is reached, the molecules can either revert, thus reforming the original reactants, or 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.

[0061] 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.

[0062] 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 H_2O, and have been widely used for isotopic studies. If a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), then substituting a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE). 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.

[0063] 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 (D_2O or "heavy water") is formed. D_2O looks and tastes like H_2O, but has different physical properties. It boils at 101.41 °C and freezes at 3.79 °C. Its heat capacity, heat of fusion, heat of vaporization, and entropy are all higher than H_2O. It is more viscous and has different solubilizng properties than H_2O.

[0064] When pure D_2O is given to rodents, it is readily absorbed and reaches an equilibrium level that is usually about eighty percent of the concentration of what was consumed. The quantity of deuterium required to induce toxicity is extremely high. When 0% to as much as 15% of the body water has been replaced by D_2O, animals are healthy but are unable to gain

weight as fast as the control (untreated) group. When about 15% to about 20% of the body water has been replaced with D_2O, the animals become excitable. When about 20% to about 25% of the body water has been replaced with D_2O, the animals are so excitable that they go into frequent convulsions when stimulated. Skin lesions, ulcers on the paws and muzzles, and necrosis of the tails appear. The animals also become very aggressive; males becoming almost unmanageable. When about 30%, of the body water has been replaced with D_2O, the animals refuse to eat and become comatose. Their body weight drops sharply and their metabolic rates drop far below normal, with death occurring at about 30 to about 35% replacement with D_2O. The effects are reversible unless more than thirty percent of the previous body weight has been lost due to D_2O. Studies have also shown that the use of D_2O can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

[0065] Tritium (T) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Mixing tritium with a phosphor provides a continuous light source, a technique that is commonly used in wristwatches, compasses, rifle sights and exit signs. It was discovered by Rutherford, Oliphant and Harteck in 1934, and is produced naturally in the upper atmosphere when cosmic rays react with H_2 molecules. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O, a colorless and odorless liquid. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level.

[0066] 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. This method, however, 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 *a priori* for any drug class.

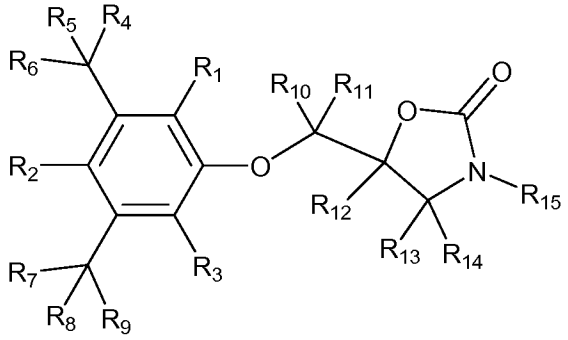
Deuterated Substituted Oxazolidinone Derivatives

[0067] Metaxalone is a substituted oxazolidinone-based skeletal muscle relaxant. The carbon-hydrogen bonds of metaxalone 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 musculoskeletal modulators in comparison with compounds having naturally occurring levels of deuterium.

[0068] Based on discoveries made in our laboratory, as well as considering the KIE literature, metaxalone is likely oxidized in humans at one of the aryl methyl groups. The current approach has the potential to prevent oxidation at these sites. Other sites on the molecule may also undergo transformations leading to metabolites with as-yet-unknown pharmacology/toxicology. Limiting the production of these metabolites has the potential to decrease the danger of the administration of such drugs and may even allow increased dosage and concomitant increased efficacy. All of these transformations can and do occur through polymorphically-expressed enzymes, such as cytochrome P_{450} isoenzyme CYP2C19, thus exacerbating interpatient variability. Further, disorders, such as diabetic neuropathy, are best treated when the subject is medicated around the clock for an extended period of time. For all of foregoing reasons, there is a strong likelihood that a longer half-life medicine will diminish these problems with 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, and/or f) decrease the production of deleterious metabolites in specific tissues and/or create a

more effective drug and/or a safer drug for polypharmacy, whether the polypharmacy be intentional or not. The deuteration approach has strong potential to slow the metabolism via various oxidative mechanisms and attenuate interpatient variability.

[0069] In certain embodiments of the present invention, compounds have structural Formula I:



(I)

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

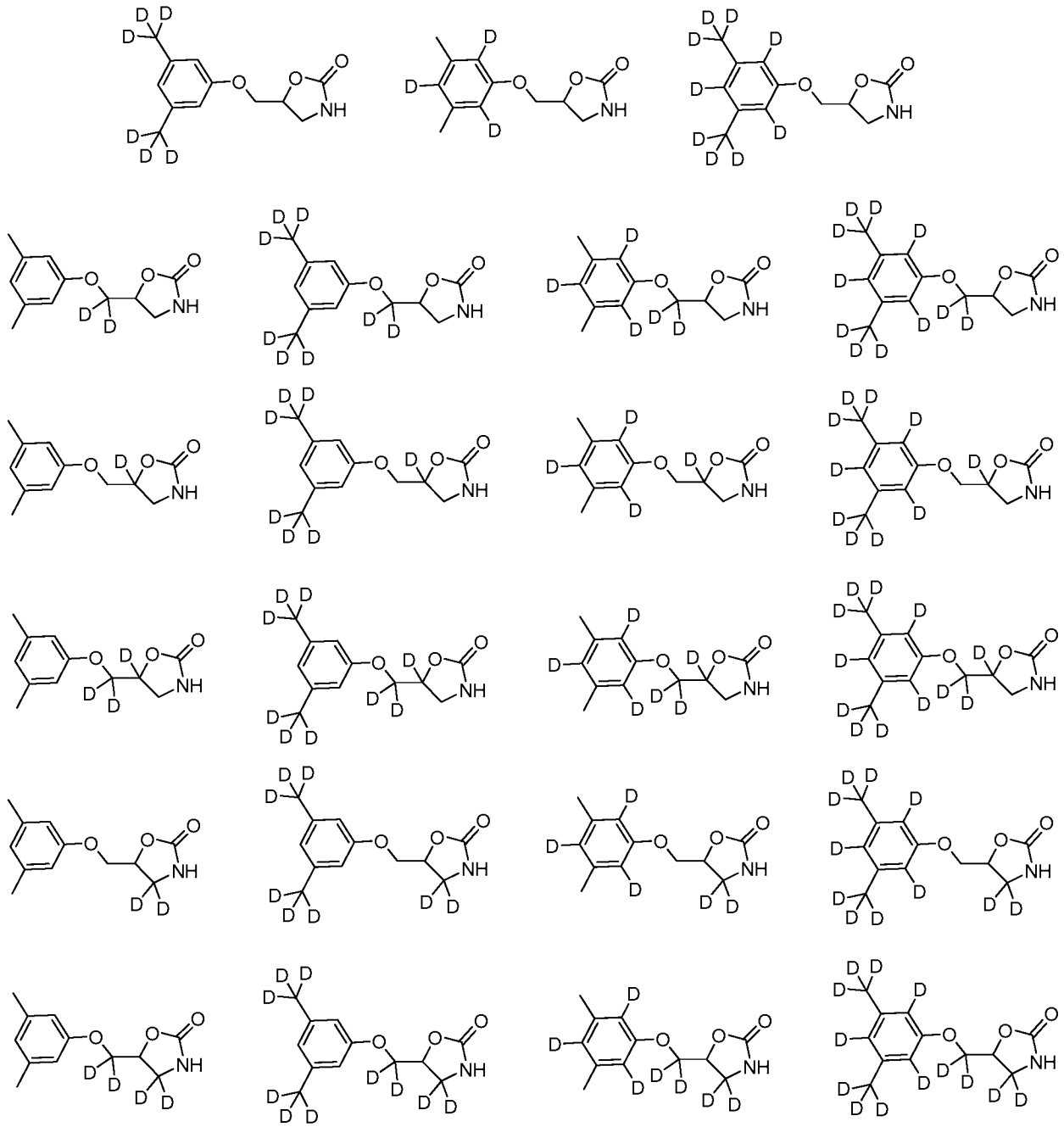
R_1-R_{15} are each independently selected from the group consisting of hydrogen and deuterium; and

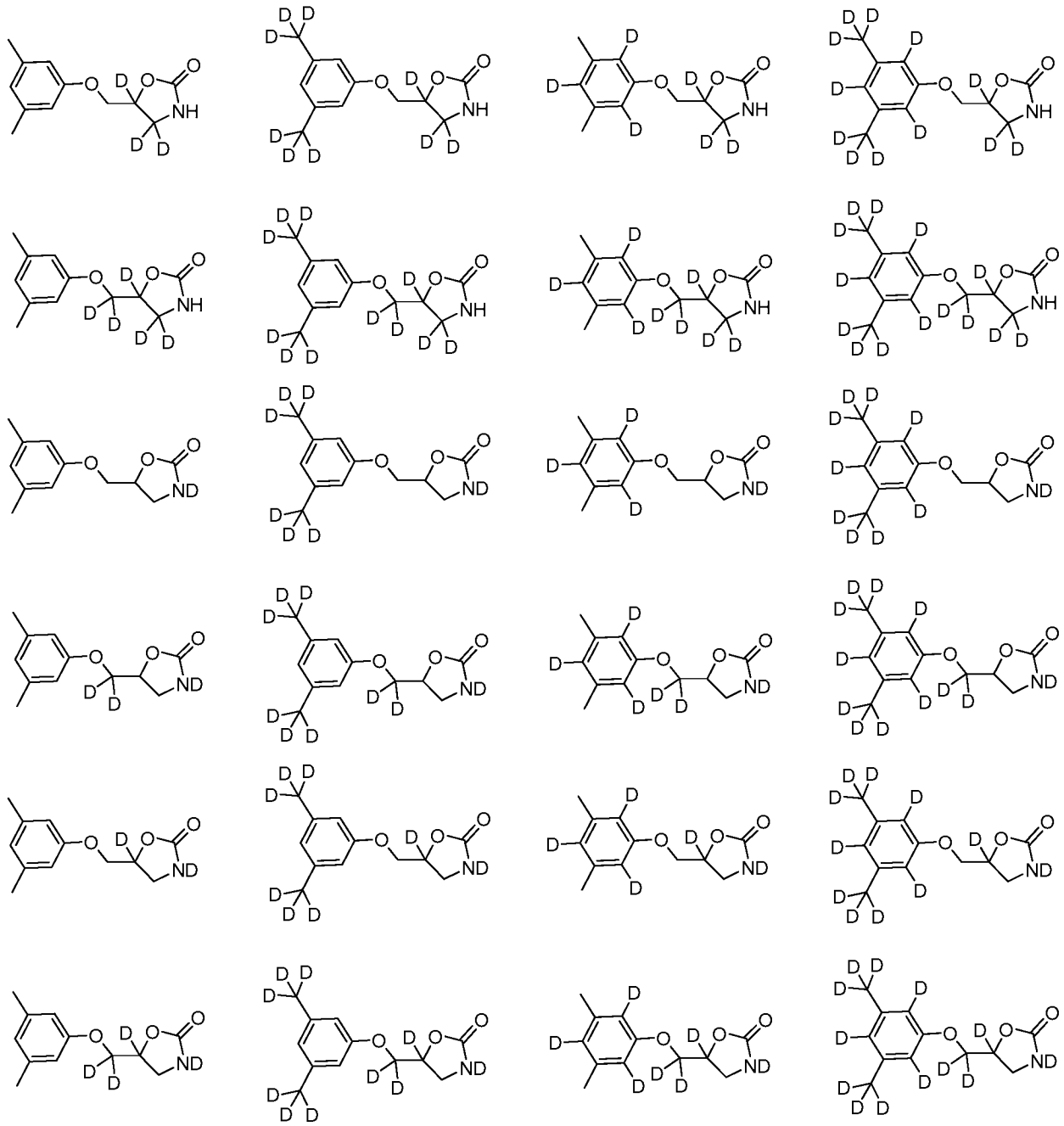
at least one of R_1-R_{15} is deuterium.

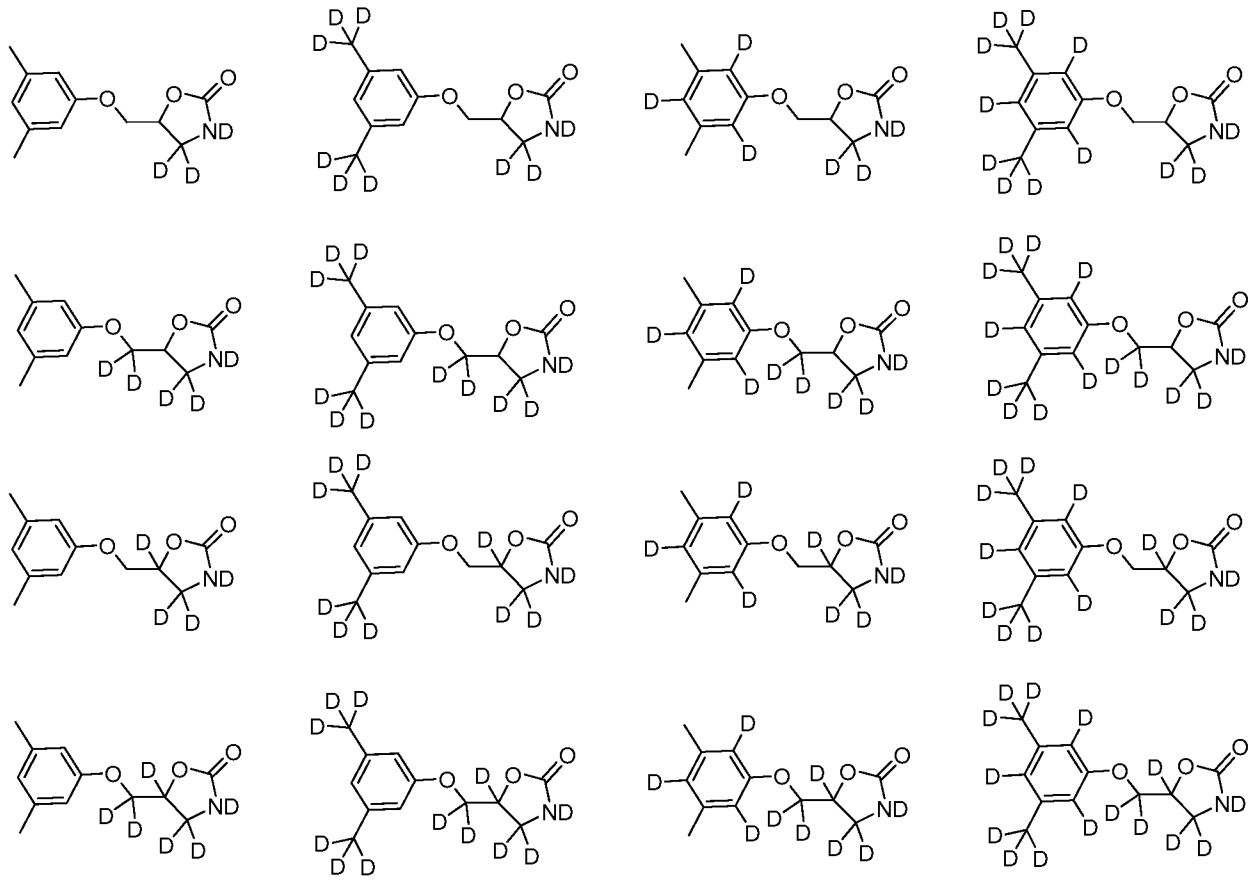
[0070] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[0071] In another embodiment, at least one of R_1-R_{15} independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[0072] In yet another embodiment, the compound as disclosed herein is selected from the group consisting of:

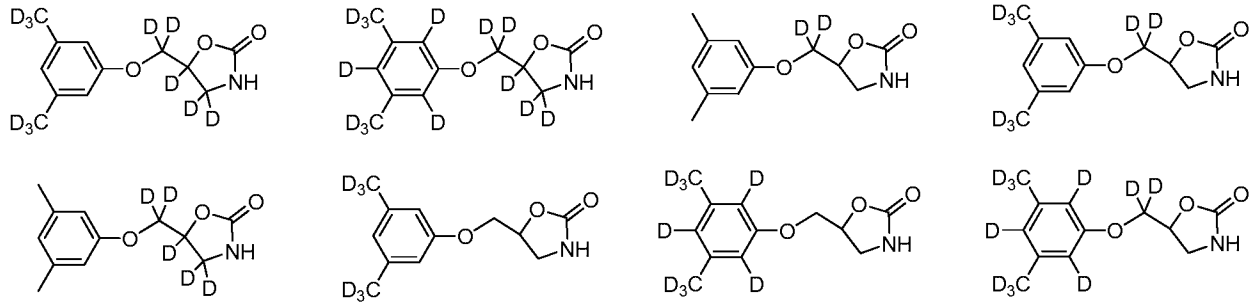






or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0073] In further embodiment, the compound as disclosed herein is selected from the group consisting of:



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

[0074] In another embodiment, at least one of the positions represented as D independently has deuterium enrichment of no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[0075] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[0076] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (-)-enantiomer of the compound and about 40% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (-)-enantiomer of the compound and about 30% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (-)-enantiomer of the compound and about 20% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (-)-enantiomer of the compound and about 10% or less by weight of the (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of the (-)-enantiomer of the compound and about 5% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of the (-)-enantiomer of the compound and about 1% or less by weight of (+)-enantiomer of the compound.

[0077] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (+)-enantiomer of the compound and about 40% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (+)-enantiomer of the compound and about 30% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (+)-enantiomer of the compound and about 20% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (+)-enantiomer of the compound and about 10% or less by weight of the (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of the (+)-enantiomer of the compound and about 5% or less by weight of (-)-enantiomer of the

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

[0078] 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.

[0079] In certain embodiments, without being bound by any theory, the compound disclosed herein may expose a patient to a maximum of about 0.000005% D_2O or about 0.00001% DHO, assuming that all of the C-D bonds in the compound as disclosed herein are metabolized and released as D_2O or DHO. This quantity is a small fraction of the naturally occurring background levels of D_2O or DHO in circulation. In certain embodiments, the levels of D_2O shown to cause toxicity in animals is much greater than even the maximum limit of exposure because of the deuterium enriched compound 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.

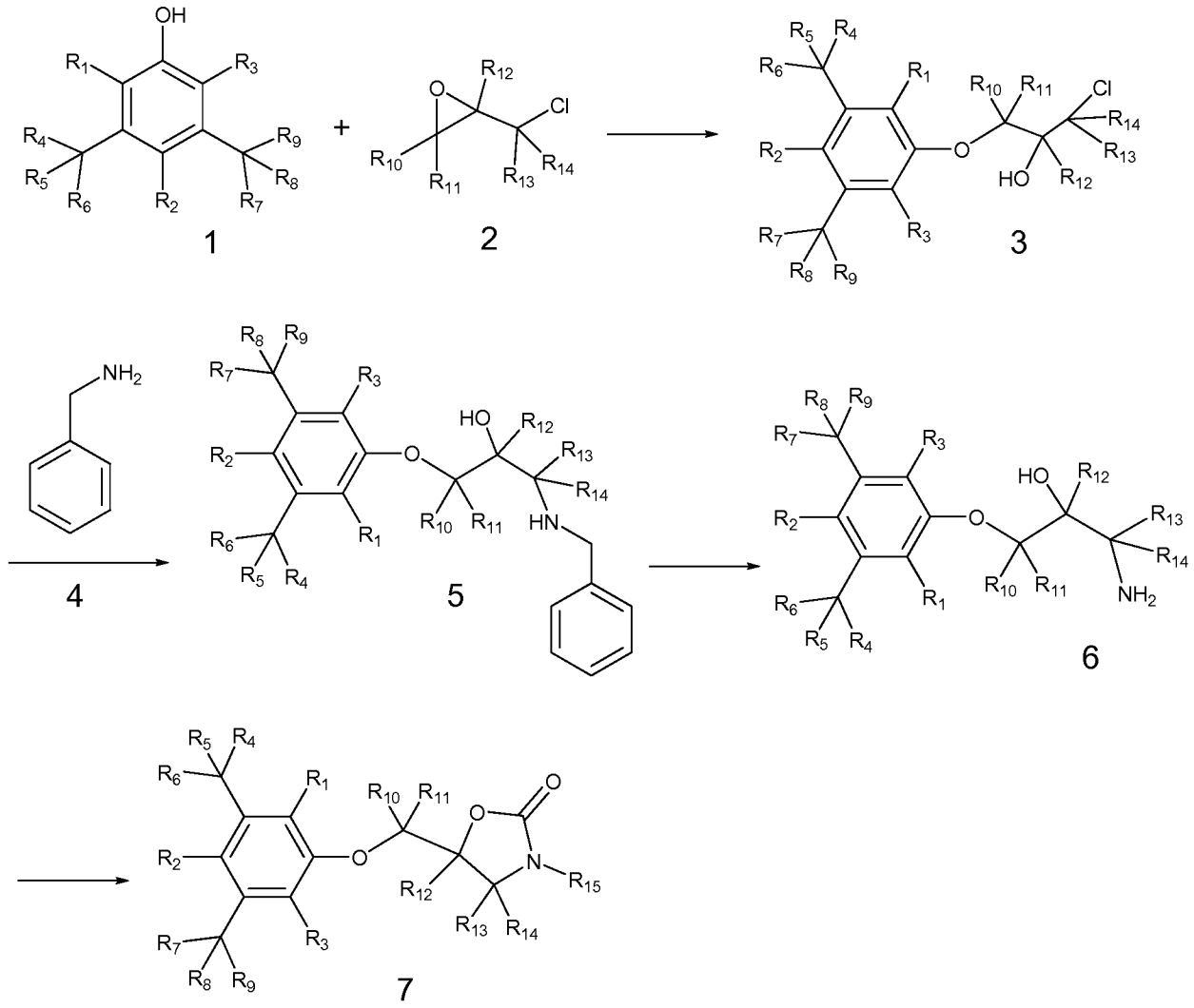
[0080] In one embodiment, the deuterated compounds disclosed herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

[0081] 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.

[0082] 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 US 6,538,142 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.

[0083] The following schemes can be used to practice the present invention. Any position shown as hydrogen may optionally be replaced with deuterium.

Scheme 1

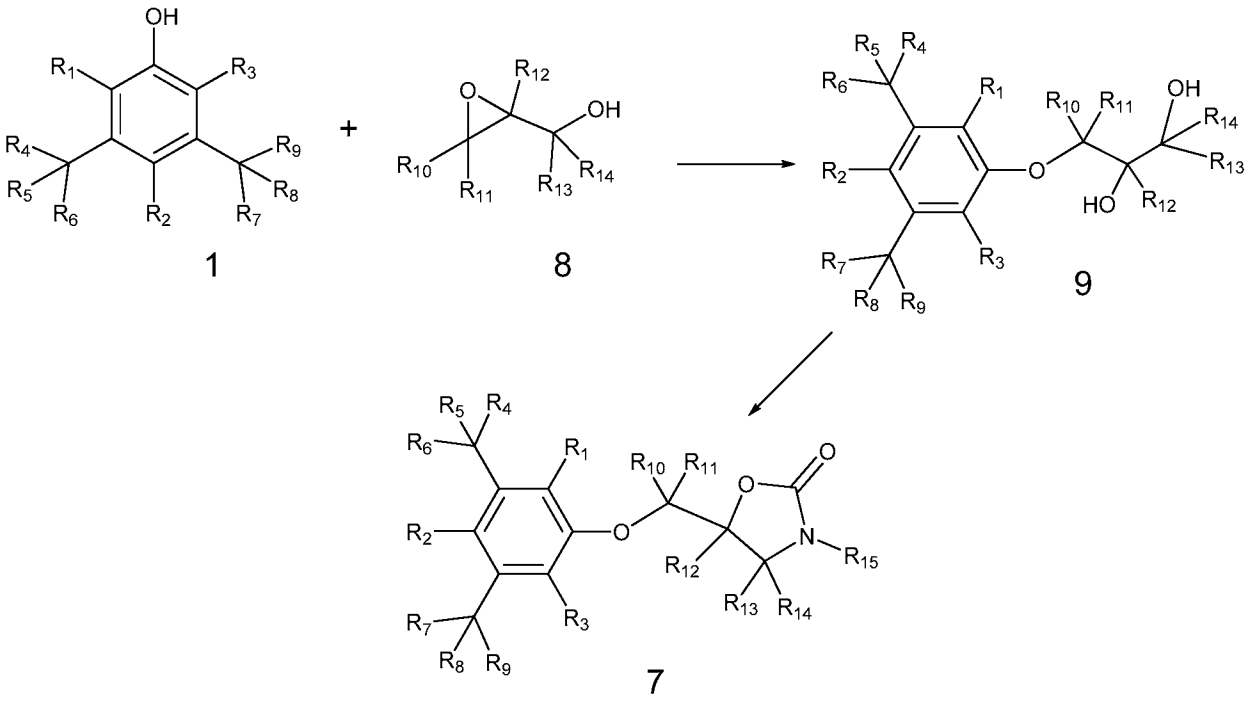


[0084] Compound **1** is reacted with compound **2** in the presence of an appropriate phase transfer catalyst, such as tetrabutylammonium bromide, at an elevated temperature to give

compound **3.** Compound **3** is reacted with compound **4** at an elevated temperature to form compound **5**. Compound **5** is treated with an appropriate base, such as ammonia, and an appropriate reducing agent, such as a combination of hydrogen gas and palladium on carbon, in an appropriate solvent, such as methanol, at an elevated temperature, to yield compound **6**. Compound **6** reacts with carbonic acid dimethylester in the presence of an appropriate base, such as sodium methoxide, in an appropriate solvent, such as methanol, at an elevated temperature to afford compound 7of Formula (I).

[0085] 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 R_1-R_9, compound **1** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{10}-R_{14}, compound **2** 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.

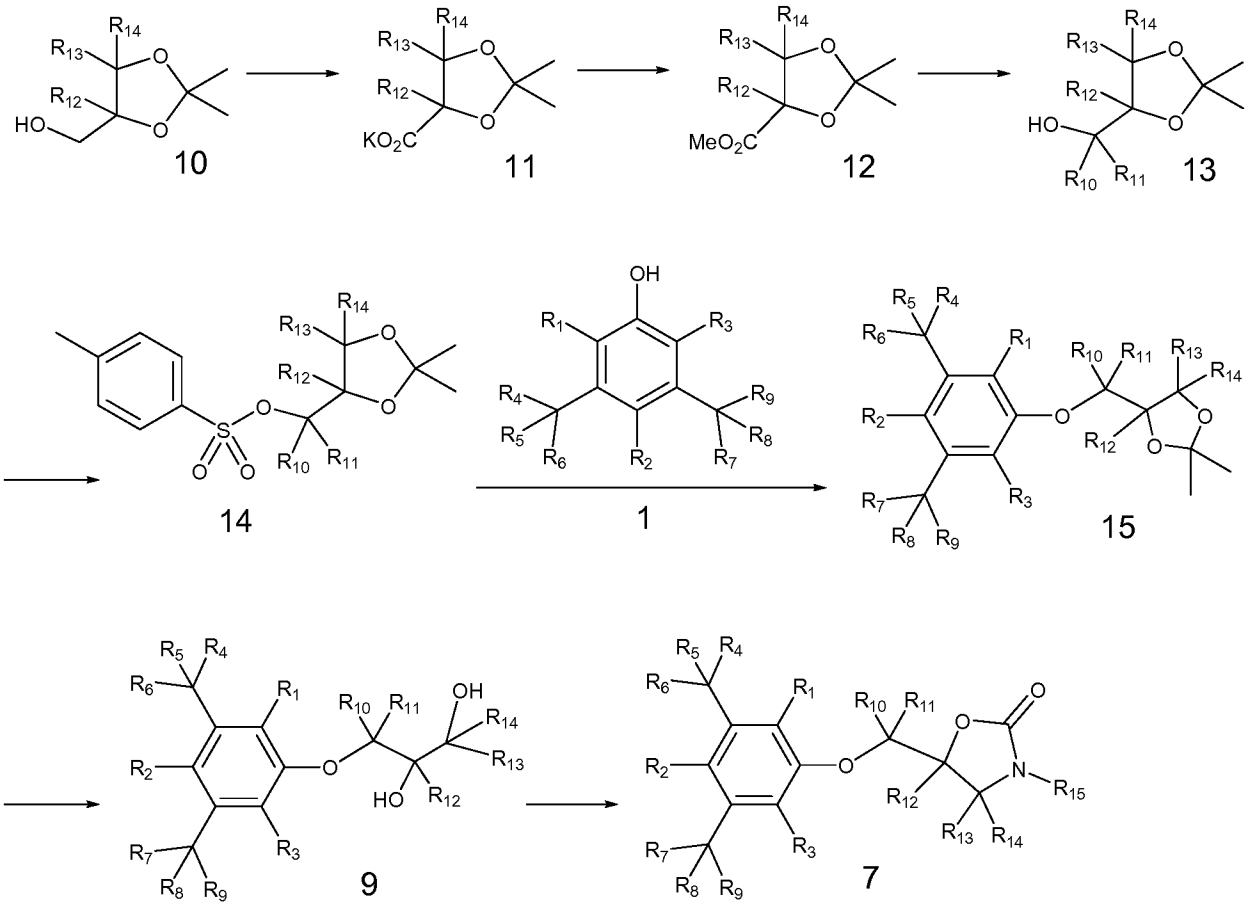
Scheme 2



[0086] Compound **1** is reacted with compound **8** in the presence of an appropriate base, such as triethylamine, in an appropriate solvent, such as ethanol, at an elevated temperature to give compound **9.** Compound **9** is reacted with urea at an elevated temperature to form compound **7** of Formula (I).

[0087] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 2, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions of R_1-R_9, compound **1** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{10}-R_{14}, compound **8** 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.

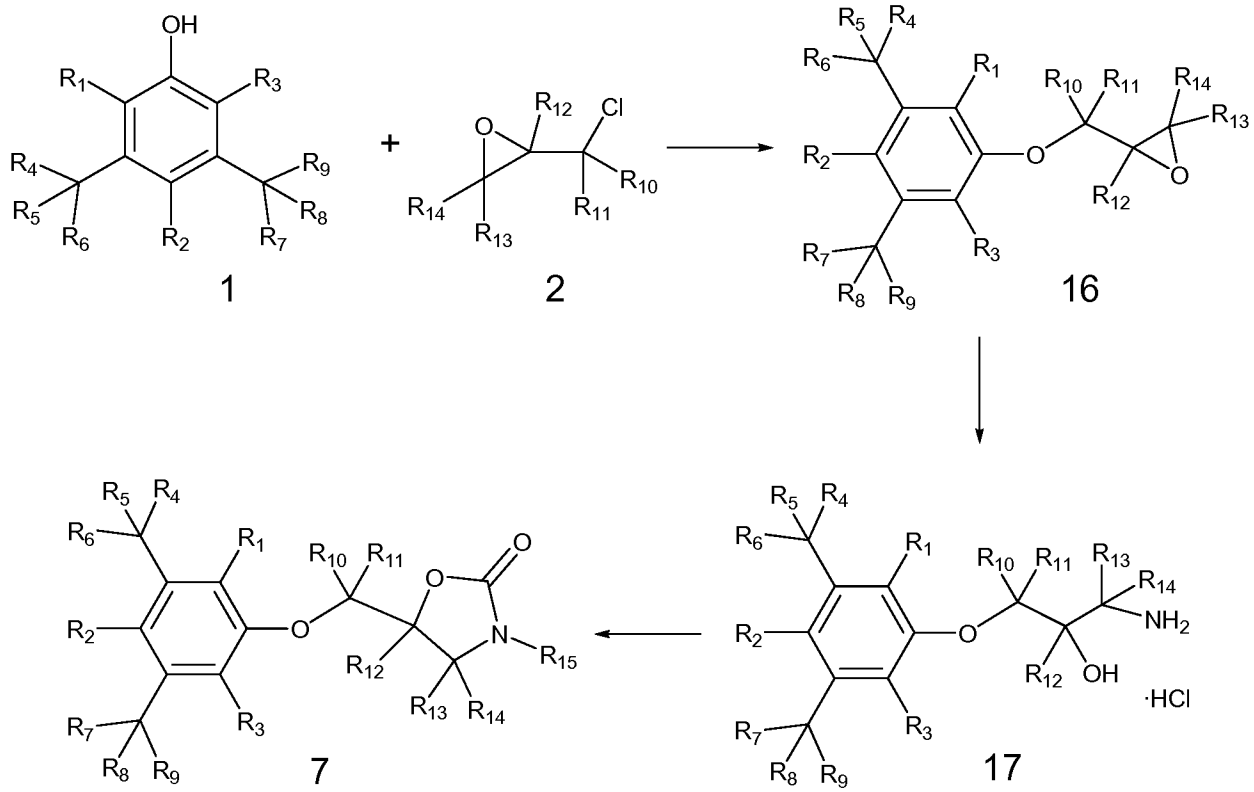
Scheme 3



[0088] Compound **10** is treated with an appropriate base, such as potassium hydroxide, and an appropriate oxidizing agent, such as potassium permanganate, in an appropriate solvent, such as water, to afford compound **11**. Compound **11** is treated with an appropriate base, such as *N,N,N',N'*-tetramethylethylenediamine, and reacted with an appropriate methylating reagent, such as iodomethane, in an appropriate solvent, such as acetonitrile, at an elevated temperature to give compound **12**. Compound **12** is reacted with an appropriate reducing reagent, such as lithium aluminum hydride, in an appropriate solvent, such as tetrahydrofuran, to afford compound **13**. Compound **13** is treated with an appropriate base, such triethylamine, and reacted with an appropriate activating reagent, such as para-toluenesulfonyl chloride, in an appropriate solvent, such as dichloromethane, to give compound **14**. Compound **14** is reacted with compound **1** in the presence of an appropriate base, such as cesium carbonate, in an appropriate solvent, such as acetonitrile, at an elevated temperature to afford compound **15**. Compound **15** is treated with an appropriate acid, such as hydrochloric acid, in an appropriate solvent, such as acetone, at elevated temperature to give compound **9**. Compound **9** is reacted with urea at an elevated temperature to give Compound **7** of Formula (I).

[0089] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 3, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions of R_1-R_9, compound **1** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{10}-R_{11}, lithium aluminum deuteride can be used. To introduce deuterium at one or more positions of R_{12}-R_{14}, 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 4



[0090] Compound **1** is reacted compound **2** in the presence of an appropriate base, such as potassium hydroxide, to afford compound **16**. Compound **16** is reacted with ammonia in an appropriate solvent, such as 2-propanol, at an elevated temperature to give Compound **17**. Compound **17** is reacted with ethyl chloroformate in the presence of an appropriate base, such as anhydrous potassium carbonate, in an appropriate solvent, such as toluene, at an elevated temperature to afford compound **7** of Formula (I).

[0091] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 4, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions of R_1-R_9, compound **1** with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{10}-R_{14}, compound **2** 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.

[0092] Deuterium can also be incorporated to various positions having an exchangeable proton, such as the amine N-H, via proton-deuterium equilibrium exchange. To introduce deuterium at R_{15}, this proton may be replaced with deuterium selectively or non-selectively through a proton-deuterium exchange method known in the art.

[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.

[0094] 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 as disclosed herein.

[0095] Where a compound as disclosed herein contains an alkenyl or alkenylene group, the compound may exist as one or mixture of geometric *cis/trans* (or Z/E) isomers. Where structural isomers are interconvertible *via* a low energy barrier, the compound disclosed herein may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound disclosed herein that contains for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[0096] 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.

[0097] When the compound disclosed herein contains an acidic or basic moiety, it may also disclosed as a pharmaceutically acceptable salt (*See*, Berge et al., *J. Pharm. Sci.* **1977**, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

[0098] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[0099] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine,

dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00100] The compound as disclosed herein may also be designed as a prodrug, which is a functional derivative of the compound as disclosed herein and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich et al. in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang et al., *Curr. Pharm. Design* 1999, *5*, 265-287; Pauletti et al., *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen et al., *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault et al., *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon et al., Ed., Marcell Dekker, 185-218, 2000; Balant et al., *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.***1992**, *8*, 1-38; Fleisher et al., *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher et al., *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar et al., *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman et al., *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar et al., *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella et al., *Drugs* **1985**, *29*, 455-73; Tan et al., *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and

Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; Waller et al., *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507.

Pharmaceutical Composition

[00101] Disclosed herein are pharmaceutical compositions comprising a compound as disclosed herein 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 of Formula I, 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 1000 mg, about 1 to about 800 mg, about 2 to about 400 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 400 mg, about 800 mg of one or more compounds as disclosed herein in the form of tablets for oral adminstration. The pharmaceutical compositions further comprise alginic acid, ammonium calcium alginate, B-Rose Liquid, corn starch and magnesium stearate.

[00108] 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.

[00109] 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).

[00110] 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.

[00111] 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, disorder or condition.

[00112] 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").

[00113] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

A. Oral Administration

[00114] The pharmaceutical compositions disclosed herein may be formulated in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration

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

[00115] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions disclosed herein.

[00116] 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.

[00117] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-

exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions disclosed herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions disclosed herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00118] 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.

[00119] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add,

sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00120] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00121] The pharmaceutical compositions disclosed herein may be formulated as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00122] 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.

[00123] The pharmaceutical compositions disclosed herein may be formulated as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule

(SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms disclosed herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00124] The pharmaceutical compositions disclosed herein may be formulated in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00125] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) disclosed herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate,

vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00126] The pharmaceutical compositions disclosed herein for oral administration may be also formulated in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00127] The pharmaceutical compositions disclosed herein may be formulated as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00128] Coloring and flavoring agents can be used in all of the above dosage forms.

[00129] 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.

[00130] 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

[00131] 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.

[00132] 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).

[00133] 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.

[00134] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

[00135] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to

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

[00136] 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.

[00137] In one embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are formulated as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are formulated as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are formulated as ready-to-use sterile emulsions.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[00142] The pharmaceutical compositions disclosed herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, include (intra)dermal, conjuctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, uretheral, respiratory, and rectal administration.

[00143] The pharmaceutical compositions disclosed herein may be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches. The topical formulation of the pharmaceutical compositions disclosed herein may also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00144] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations disclosed herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryopretectants, lyoprotectants, thickening agents, and inert gases.

[00145] 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).

[00146] The pharmaceutical compositions disclosed herein may be formulated in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including such as lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00147] 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.

[00148] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, Carbopol®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00149] 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.

[00150] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions disclosed herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00151] 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.

[00152] The pharmaceutical compositions disclosed herein may be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions may be formulated in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions may also be formulated as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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

[00157] The pharmaceutical compositions disclosed herein may be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres,

liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00158] 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

[00159] The pharmaceutical compositions disclosed herein in a modified release dosage form may be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999).

[00160] In one embodiment, the pharmaceutical compositions disclosed herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00161] 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.

[00162] In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00163] 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.

[00164] 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

[00165] 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).

[00166] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00167] The other class of osmotic agents are osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00168] 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.

[00169] 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.

[00170] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxlated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00176] 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.

[00177] 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

[00178] 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.

[00179] 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

[00180] The pharmaceutical compositions disclosed herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

Methods of Use

[00181] Disclosed are methods for treating, preventing, or ameliorating one or more symptoms of a musculoskeletal-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.

[00182] Musculoskeletal-mediated disorders, include, but are not limited to, muscle spasms, muscle sprains, dorsalgia, fibromyalgia, myofascial pain syndrome, radiculopathy,

diabetic peripheral neuropathy, tension headaches, and/or any disorder which can lessened, alleviated, or prevented by administering a skeletal muscle relaxant.

[00183] Also disclosed herein are methods of treating, preventing, or ameliorating one or more symptoms of a disorder associated with musculoskeletal muscle function and tone 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.

[00184] Further disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder responsive to modulation of skeletal muscle tone and function, 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.

[00185] Furthermore, disclosed herein are methods of modulating skeletal muscle tone and function, comprising administering at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the skeletal muscles are found in the body of a subject.

[00186] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound of 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.

[00187] In certain embodiments, the inter-individual variation in plasma levels of the compounds as disclosed herein, or metabolites thereof, is decreased by greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or by greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[00188] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective

amount of a compound 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.

[00189] 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.

[00190] 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.

[00191] Plasma levels of the compound as 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 Nirogi et al., *J Anal Toxicol* **2006**, *30*(4), 245-51.

[00192] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound 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_{450} or monoamine oxidase isoform in the subject during the treatment of the disorder as compared to the corresponding non-isotopically enriched compound.

[00193] Examples of cytochrome P_{450} isoforms in a mammalian subject include, but are not limited to, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[00194] Examples of monoamine oxidase isoforms in a mammalian subject include, but are not limited to, MAO_A, and MAO_B.

[00195] In certain embodiments, the decrease in inhibition of the cytochrome P_{450} 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%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

[00196] 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).

[00197] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound 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 disorder as compared to the corresponding non-isotopically enriched compound.

[00198] Examples of polymorphically-expressed cytochrome P_{450} isoforms in a mammalian subject include, but are not limited to, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[00199] 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.

[00200] 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.

[00201] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound 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.

[00202] Examples of improved disorder-control and/or disorder-eradication endpoints include, but are not limited to, significant improvement on pain scores, the ability to sleep through the night, and quality of life based on patient surveys; a reduction in swelling; a reduction of inflammation; a reduction in pain; normalization of muscle function and tone; normalization of ligament function and integrity; normalization of tendon function and integrity; normalization of joint function; 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.

[00203] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound 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. Examples of improved clinical effect include, but are not limited to, significant improvement on pain scores, the ability to sleep through the night, and quality of life based on patient surveys; a reduction in swelling; a reduction of inflammation; a reduction in pain; normalization of muscle function and tone; normalization of ligament function and integrity; normalization of tendon function and integrity; normalization of joint function; 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.

[00204] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound 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.

[00205] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a musculoskeletal-mediated disorder, or for preventing such a disorder, in a subject prone to the disorder; comprising administering to the subject a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof; so as to allow the treatment of the musculoskeletal-mediated disorder while reducing or eliminating deleterious changes in any diagnostic hepatobiliary function endpoints as compared to the corresponding non-isotopically enriched compound.

[00206] 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.

[00207] 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.

[00208] The dose may be in the form of one, two, three, four, five, six, or more sub-doses that are administered at appropriate intervals per day. The dose or sub-doses can be administered in the form of dosage units containing from about 0.1 to about 1000 milligram, from about 0.1 to about 500 milligrams, or from 0.5 about to about 100 milligram active ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of alternative, be administered as a continuous infusion. In one embodiment the dose(s) must be taken with food.

In another embodiment, the dose(s) must be taken under a fasting condition. In yet a further embodiment, the dose(s) can be taken under a fasting condition or with food.

[00209] In certain embodiments, an appropriate dosage level is about 0.01 to about 100 mg per kg patient body weight per day (mg/kg per day), about 0.01 to about 50 mg/kg per day, about 0.01 to about 25 mg/kg per day, or about 0.05 to about 10 mg/kg per day, which may be administered in single or multiple doses. A suitable dosage level may be about 0.01 to about 100 mg/kg per day, about 0.05 to about 50 mg/kg per day, or about 0.1 to about 10 mg/kg per day. Within this range the dosage may be about 0.01 to about 0.1, about 0.1 to about 1.0, about 1.0 to about 10, or about 10 to about 50 mg/kg per day.

Combination Therapy

[00210] 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 a musculoskeletal-mediated disorder. 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).

[00211] 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. In one embodiment, a compound disclosed herein may be used as an adjuvant to one or more of the following, heat therapy, physical therapy (including stretching and strengthening with specific focus on the muscles which support the spine), massage therapy, body awareness therapy, manipulation, acupuncture, acupressure, and rest.

[00212] 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 the group including aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoracoxib, faislamine, 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.

[00213] In certain embodiments, the compounds disclosed herein can be combined with one or more anilide analgesics known in the art, including, but not limited to the group including acetaminophen, and phenacetin.

[00214] In certain embodiments, the compounds disclosed herein can be combined with one or more antiepileptics known in the art, including, but not limited to methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, ethosuximide, phensuximide, mesuximide, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, tiagabine, sultiame, phenacemide, lamotrigine, felbamate, topiramate, gabapentin, pheneturide, levetiracetam, zonisamide, pregabalin, stiripentol, and beclamide.

[00215] In certain embodiments, the compounds disclosed herein can be combined with one or more tricyclic antidepressants known in the art, including, but not limited to amitriptyline, butriptyline, amoxapine, clomipramine, desipramine, dosulepin hydrochloride, doxepin, imipramine, dibenzepin, iprindole, lofepramine, nortriptyline, opipramol, protriptyline, and trimipramine.

[00216] In certain embodiments, the compounds disclosed herein can be combined with one or more selective serotonin reuptake inhibitors (SSRIs) known in the art, including, but not limited to alaproclate, citalopram, dapoxetine, escitalopram, etoperidone, fluoxetine, fluvoxamine, paroxetine, sertraline, and zimelidine.

[00217] In certain embodiments, the compounds disclosed herein can be combined with one or more diabetic neuropathy treatments known in the art, including, but not limited to methylcobalamin, α-lipoic acid, Epalrestat, and C-peptide.

[00218] In certain embodiments, the compounds disclosed herein can be combined with one or more sepsis treatments known in the art, including, but not limited to drotrecogin-α or a biosimilar of activated protein C.

[00219] 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.

[00220] In certain embodiments, the compounds disclosed herein can be combined with one or more antibacterial agents known in the art, including, but not limited to the group including amikacin, amoxicillin, ampicillin, arsphenamine, azithromycin, aztreonam, azlocillin, bacitracin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cephalexin, cefdinir, cefditorin, cefepime, cefixime, cefoperazone, cefotaxime, cefoxitin, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, cilastin, ciprofloxacin, clarithromycin, clindamycin, cloxacillin, colistin, dalfopristan, demeclocycline, dicloxacillin, dirithromycin, doxycycline, erythromycin, enafloxacin, ertepenem, ethambutol, flucloxacillin, fosfomycin, furazolidone, gatifloxacin, geldanamycin, gentamicin, herbimicin, imipenem, isoniazide, kanamicin, levofloxacin, linezolid, lomefloxacin, loracarbef, mafenide, moxifloxacin, meropenem, metronidazole, mezlocillin, minocycline, mupirozin, nafcillin, neomycin, netilmicin, nitrofurantoin, norfloxacin, ofloxacin, oxytetracycline, penicillin, piperacillin, platensimycin, polymixin B, prontocil, pyrazinamide, quinupristine, rifampin, roxithromycin, spectinomycin, streptomycin, sulfacetamide, sulfamethizole, sulfamethoxazole, teicoplanin, telithromycin, tetracycline, ticarcillin, tobramycin, trimethoprim, troleandomycin, trovafloxacin, and vancomycin.

[00221] In certain embodiments, the compounds disclosed herein can be combined with one or more antifungal agents known in the art, including, but not limited to the group including amorolfine, amphotericin B, anidulafungin, bifonazole, butenafine, butoconazole, caspofungin, ciclopirox, clotrimazole, econazole, fenticonazole, filipin, fluconazole, isoconazole, itraconazole, ketoconazole, micafungin, miconazole, naftifine, natamycin, nystatin, oxyconazole, ravuconazole, posaconazole, rimocidin, sertaconazole, sulconazole, terbinafine, terconazole, tioconazole, and voriconazole.

[00222] In certain embodiments, the compounds disclosed herein can be combined with one or more anticoagulants known in the art, including, but not limited to the group including acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximalagatran.

[00223] In certain embodiments, the compounds disclosed herein can be combined with one or more thrombolytics known in the art, including, but not limited to the group including anistreplase, reteplase, t-PA (alteplase activase), streptokinase, tenecteplase, and urokinase.

[00224] In certain embodiments, the compounds disclosed herein can be combined with one or more antiplatelet agents known in the art, including, but not limited to the group including abciximab, cilostazol, clopidogrel, dipyridamole, ticlopidine, and tirofibin.

[00225] The compounds disclosed herein can also be administered in combination with other classes of compounds, including, but not limited to, norepinephrine reuptake inhibitors (NRIs) such as atomoxetine; dopamine reuptake inhibitors (DARIs), such as methylphenidate; serotonin-norepinephrine reuptake inhibitors (SNRIs), such as milnacipran; norepinephrine-dopamine reuptake inhibitor (NDRIs), such as bupropion; serotonin-norepinephrine-dopamine-reuptake-inhibitors (SNDRIs), such as venlafaxine; monoamine oxidase inhibitors, such as selegiline; hypothalamic phospholipids; endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; opioids, such as tramadol; thromboxane receptor antagonists, such as ifetroban; potassium channel openers; thrombin inhibitors, such as hirudin; hypothalamic phospholipids; growth factor inhibitors, such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents, such as GPIIb/IIIa blockers (e.g., abdximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants, such as warfarin; low molecular weight heparins, such as enoxaparin; Factor VIIa Inhibitors and Factor Xa Inhibitors; renin inhibitors; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants, such as questran; niacin; anti-atherosclerotic agents, such as ACAT inhibitors; MTP Inhibitors; calcium channel blockers, such as amlodipine besylate; potassium channel activators; alpha-adrenergic agents; beta-adrenergic agents, such as carvedilol and metoprolol;

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

Kits/Articles of Manufacture

[00226] 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.

[00227] 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.

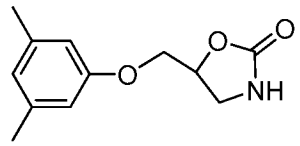
[00228] A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such 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.

[00229] 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.

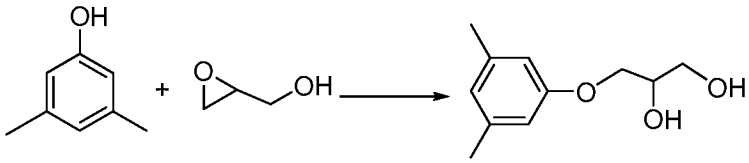
[00230] The invention is further illustrated by the following examples.

EXAMPLE 1

5-[(3,5-dimethylphenoxy)methyl]oxazolidin-2-one

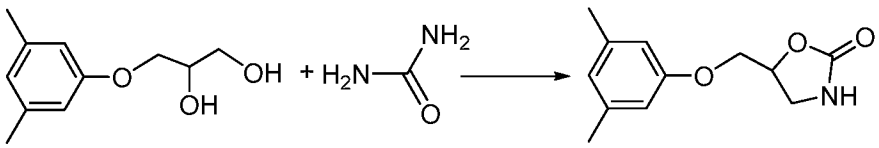


Step 1



[00231] 3-(3,5-Dimethylphenoxy)propane-1,2-diol: A mixture of 3,5-dimethylphenol (5.00 g, 40.93 mmol), (±)-glycidol (2.72 mL, 41.01 mmol), triethylamine (0.29 mL, 2.08 mmol) and ethanol (25 mL) was heated at reflux for about 7 hours. After ethanol was removed *in vacuo*, the resulting residue was purified by silica gel column chromatography (25% ethyl acetate in petroleum ether) to give the title product as a white solid (6.00 g, 75%). m.p. 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 3.68-3.87 (m, 2H), 3.94-4.04 (m, 2H), 4.04-4.12 (m, 1H), 6.55 (s, 2H), 6.62 (s, 1H); IR (film) υ 3383, 2923, 2875, 1600, 1462, 1324 cm^{-1}; MS 197 (M + 1).

Step 2

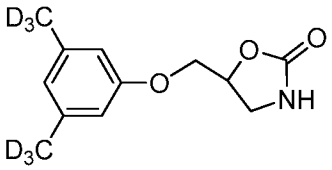


[00232] 5-[(3,5-Dimethylphenoxy)methyl]oxazolidin-2-one: A mixture of 3-(3,5-dimethylphenoxy)propane-1,2-diol (1.00 g, 5.10 mmol) and urea (0.618 g, 10.29 mmol) was heated at 185-195 °C for about 6 hours. The resulting brown viscous material was cooled to ambient temperature and partitioned between water and chloroform. The organic layer was concentrated *in vacuo* to provide a crude residue that was purified by Preparative HPLC on a Zodiacsil C18 (250 × 33 mm, 10 μ) column (eluting with acetonitrile / 0.1% formic acid (55:45)

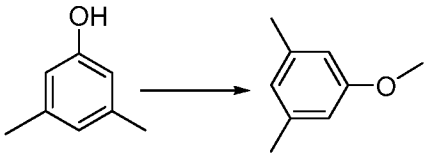
at a flow rate of 48 mL/min). The title compound eluted at 5.74 min. Following standard extractive workup with ethyl acetate, the solvent was removed *in vacuo* to yield the title compound as a white solid (0.180 g, 16%). m.p. 121-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.57-3.63 (m, 1H), 3.72-3.79 (m, 1H), 4.07-4.16 (m, 2H), 4.90-4.98 (m, 1H), 5.02 (br, exchangeable with D_2O, 1H), 6.54 (s, 2H), 6.64 (s, 1H); IR (KBr) υ 3283, 1734, 1600, 1321, 1236 cm^{-1}; MS 222 (M + 1).

EXAMPLE 2

5-[(3,5-dimethyl-d_6-phenoxy)methyl]oxazolidin-2-one

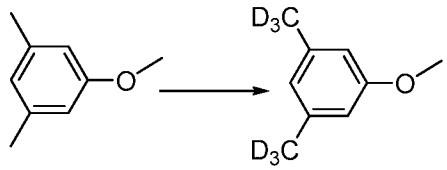


Step 1



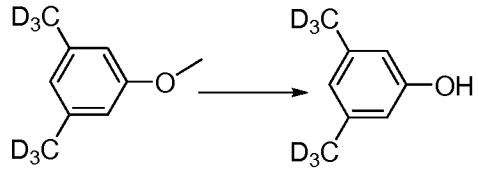
1-Methoxy-3,5-dimethyl-benzene: At about 0 °C, a solution of 3,5-dimethylphenol (20.0 g, 163.7 mmol) in tetrahydrofuran (50 mL) was added dropwise to a suspension of sodium hydride in mineral oil (60% in mineral oil, 9.83 g, 245.8 mmol). The mixture was stirred at about 0 °C for about 1 hour and then iodomethane (15.3 mL, 245.8 mmol) was added dropwise. The mixture was stirred at ambient temperature for about 24 hours, cooled to about 0 °C, and ice-water was added dropwise. Standard extractive work up provided a crude residue which was purified by silica gel column chromatography (2% ethyl acetate in petroleum ether) to give the title product as a yellow liquid (15.2 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (s, 6H), 3.68 (s, 3H), 6.52 (s, 2H), 6.54 (s, 1H); IR (film) υ 2926, 2846, 1601, 1465, 1319 cm^{-1}; MS 137 (M + 1).

Step 2



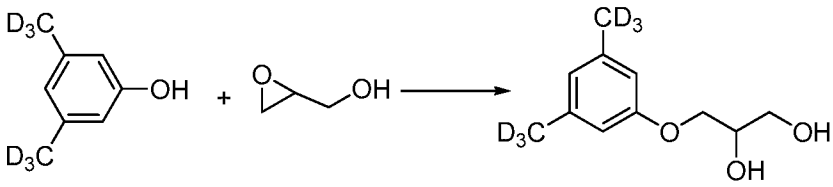
[00233] 1-Methoxy-3,5-dimethyl-d_6-benzene: A mixture of 1-methoxy-3,5-dimethyl-benzene (5.00 g, 36.71 mmol), potassium *tert*-butoxide (17.90 g, 159.52 mmol) and dimethyl sulfoxide-d_6 (30 mL) was heated under argon in a sealed tube at about 100 °C for about 3 hours. The reaction mixture was cooled to ambient temperature, poured into deuterium oxide (50 mL), and extracted with ether. The organic layer was concentrated *in vacuo* and the resulting residue (4.50 g, 33.04 mmol, deuteration 90%) was heated with potassium *tert*-butoxide (8.07 g, 71.92 mmol) and d_6-dimethyl sulfoxide (20 mL) in a sealed tube under argon at about 100 °C for about 2 hours. The reaction mixture was cooled to ambient temperature, poured into deuterium oxide (30 mL) and extracted with ether. The organic layer was concentrated *in vacuo* to give the title compound as a yellow liquid (3.60 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 3H), 6.52 (s, 0.3H), 6.54 (s, 0.15H); IR (film) υ 2944, 2837, 1595, 1453, 1325 cm^{-1}; MS 143 (M + 1).

Step 3



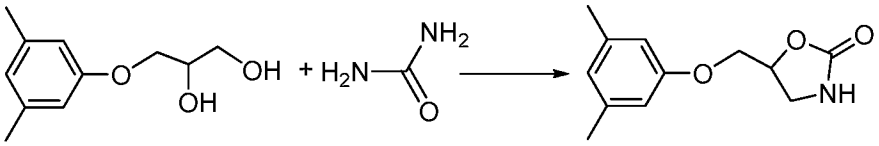
[00234] 3,5-Dimethyl-d_6-phenol: At about 0 °C, a solution of boron tribromide (2.60 mL, 27.50 mmol) in dichloromethane (10 mL) was added dropwise to a solution of 1-methoxy-3,5-dimethyl-d_6-benzene (2.00 g, 14.06 mmol) in dichloromethane (50 mL). The mixture was stirred at ambient temperature for about 2 hours, cooled to about 0 °C, and cold deuterium oxide (15 mL) was then added dropwise. Standard extractive work up provided a crude residue which was purified by silica gel column chromatography (5% ethyl acetate in petroleum ether) to give the title product as a white solid (0.950 g, 53%). m.p. 57-60 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.36 (s, 0.34H), 6.39 (s, 0.16H), 9.04 (br, exchangeable with D_2O, 1H); IR (KBr) υ 3395, 3305, 1578, 1465, 1392, 1314 cm^{-1}.

Step 4



[00235] 3-(3,5-Dimethyl-d_6-phenoxy)propane-1,2-diol: The procedure of Example 1, Step 1 was followed, but substituting 3,5-dimethyl-d_6-phenol for 3,5-dimethylphenol. The title product was isolated as a white solid (1.00 g, 63%). m.p. 59-63 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.36-3.48 (m, 2H), 3.71-3.84 (m, 2H), 3.87-3.97 (m, 1H), 4.61 (t, J = 5.7 Hz, exchangeable with D_2O, 1H), 4.86 (d, J = 4.9 Hz, exchangeable with D_2O, 1H), 6.53 (s, 0.32H), 6.55 (s, 0.18H); IR (KBr) υ 3383, 2923, 2875, 1600, 1462, 1324 cm^{-1}; MS 203 (M + 1).

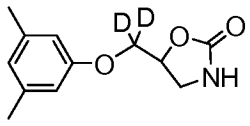
Step 5



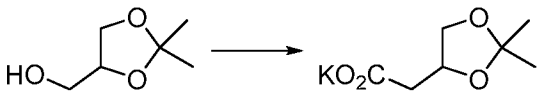
[00236] 5-[(3,5-Dimethyl-d_6-phenoxy)methyl]oxazolidin-2-one: The procedure of Example 1 Step 2 was followed, but substituting 3-(3,5-dimethyl-d_6-phenoxy)propane-1,2-diol for 3-(3,5-dimethyl-phenoxy)propane-1,2-diol. The title product was isolated as a white solid (0.100 g, 10%). m.p. 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56-3.63 (m, 1H), 3.72-3.79 (m, 1H), 4.07-4.16 (m, 2H), 4.90-4.98 (m, 1H), 5.14 (br, exchangeable with D_2O, 1H), 6.54 (s, 0.33H), 6.64 (s, 0.19H); IR (KBr) υ 3285, 1734, 1580, 1391, 1323, 1236 cm^{-1}; MS 228 (M + 1).

EXAMPLE 3

5-[(3,5-dimethyl- phenoxy)methyl-d_2]oxazolidin-2-one

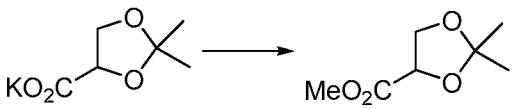


Step 1



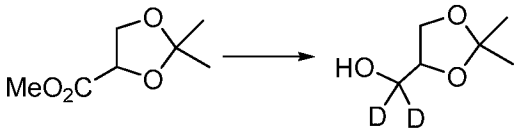
[00237] 1-Methoxy-3,5-dimethyl-benzene: At about 0 °C, a solution of potassium permanganate (17.95 g, 113.59 mmol) in water (100 mL) was added dropwise to solution containing solketal (5.00 g, 37.83 mmol) and potassium hydroxide (2.55 g, 45.45 mmol) in water (50 mL). The mixture was then stirred for about 18 hours at ambient temperature. The resulting precipitate was filtered, washed with water, and the washes were combined with the filtrate. The combined filtrate was evaporated to dryness *in vacuo* to afford the title compound as a very hygroscopic white solid (6.50 g, 93%). ^{1}H NMR (400 MHz, D_2O) δ 1.43 (s, 3H), 1.48 (s, 3H), 3.92-3.98 (m, 1H), 4.27-4.33 (m, 1H), 4.51-4.57 (m, 1H); MS 145 (M – K).

Step 2



[00238] Methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate: A mixture of potassium 2,2-dimethyl-1,3-dioxolane-4-carboxylate (6.50 g, 35.28 mmol), iodomethane (5.50 mL, 88.35 mmol), *N,N,N',N'*-tetramethylethylenediamine (0.53 mL, 3.53 mmol) and acetonitrile (100 mL) was heated at about 60 °C for about 6 hours. The mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ether and filtered. The filtrate was concentrated *in vacuo* to give the title product as a pale yellow liquid (3.10 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.51 (s, 3H), 3.78 (s, 3H), 4.07-4.13 (m, 1H), 4.21-4.26 (m, 1H), 4.56-4.62 (m, 1H); IR (film) υ 2992, 2950, 2890, 1757, 1446, 1377 cm^{-1}; MS 161 (M + 1).

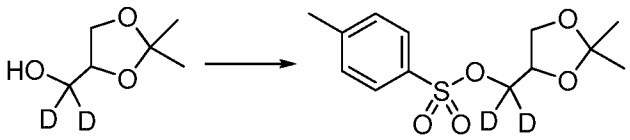
Step 3



[00239] 2,2-Dimethyl-1,3-dioxolan-4-yl)methanol-d_2: At about 0 °C, a solution of methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (3.10 g, 19.35 mmol) in dry tetrahydrofuran (20 mL) was added dropwise to a stirred suspension of lithium aluminum deuteride (0.489 g, 11.65 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred for about 3 hours at ambient temperature, cooled to about 0 °C, and then cold deuterium oxide (3 mL) was added slowly. The resulting precipitate was filtered and washed with ethyl acetate. The filtrate and washings were

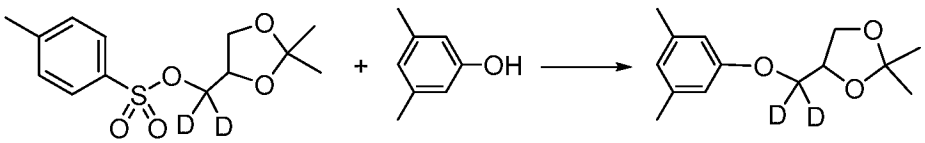
combined and concentrated *in vacuo* to give the title product as an oil (2.30 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.45 (s, 3H), 3.75-3.82 (m, 1H), 4.00-4.06 (m, 1H), 4.20-4.25 (m, 1H); IR (film) υ 3438, 2989, 2937, 2884, 2207, 2094, 1735, 1649, 1377 cm^{-1}; MS 135 (M + 1).

Step 4



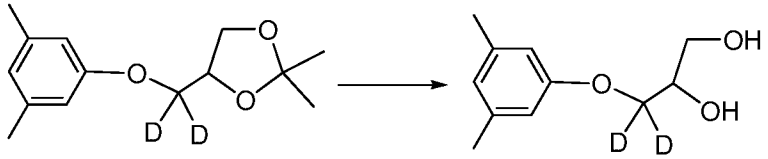
[00240] (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl-d_2 *p*-toluenesulfonate: At about 0 °C, *p*-toluenesulfonyl chloride (3.93 g, 20.61 mmol) was added portionwise to a mixture of 2,2-dimethyl-1,3-dioxolan-4-yl)methanol-d_2 (2.30 g, 17.14 mmol), triethylamine (5.0 mL, 35.87 mmol) and dichloromethane (40 mL). The mixture was stirred at ambient temperature for about 18 hours. Standard extractive work up yielded the title compound as a yellow liquid. (3.80 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.34 (s, 3H), 2.46 (s, 3H), 3.77 (dd, J = 8.7, 6.4 Hz, 1H), 4.04 (dd, J = 8.5, 6.4 Hz, 1H), 4.23-4.29 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H); IR (film) υ 3445, 2934, 2886, 1642, 1601, 1452, 1358 cm^{-1}; MS 289 (M + 1).

Step 5



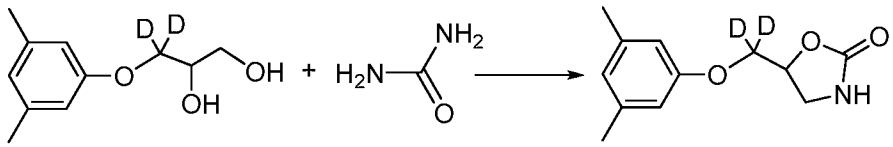
[00241] 4-[(3,5-Dimethylphenoxy)methyl-d_2]-2,2-dimethyl-1,3-dioxolane: A mixture of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl-d_2 *p*-toluenesulfonate (4.00 g, 13.87 mmol), 3,5-dimethylphenol (1.70 g, 13.92 mmol), cesium carbonate (9.10 g, 27.93 mmol) and acetonitrile (80 mL) was heated in a sealed tube at about 60 °C for about 24 hours. The mixture was filtered and the filtrate was concentrated to provide a crude residue that was purified by silica gel column chromatography (3% ethyl acetate in petroleum ether) to give the title compound as a pale yellow liquid (2.40 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 2.28 (s, 6H), 3.89 (dd, J = 8.2, 6.1 Hz, 1H), 4.11-4.17 (m, 1H), 4.21-4.26 (m, 1H), 6.54 (s, 2H), 6.61 (s, 1H); IR (film) υ 2987, 2924, 2866, 2203, 2095, 1599, 1468, 1375, 1320 cm^{-1}; MS 239 (M + 1).

Step 6



[00242] 3-(3,5-Dimethylphenoxy)propane-3,3-d_2-1,2-diol: A mixture of 4-[(3,5-dimethylphenoxy)methyl-d_2]-2,2-dimethyl-1,3-dioxolane (1.30 g, 5.45 mmol), a 20% d_1-hydrogen chloride solution in deuterium oxide (0.5 mL), deuterium oxide (3.0 mL) and dry acetone (10 mL) was heated at reflux for about 4 hours. Acetone was removed *in vacuo* and the resulting residue was diluted with deuterium oxide (7 mL). Following standard extractive workup with dichloromethane, the crude residue which was purified by silica gel column chromatography (20% ethyl acetate in chloroform) to give the title product as a low-melting solid (0.620 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.69-3.86 (m, 2H), 4.05-4.11 (m, 1H), 6.55 (s, 2H), 6.63 (s, 1H); IR (KBr) υ 3418, 3331, 2926, 1597, 1445, 1316 cm^{-1}; MS 199 (M + 1).

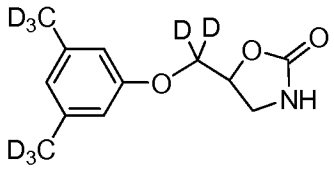
Step 7



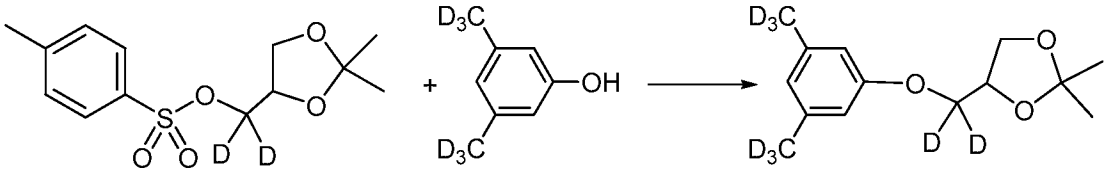
[00243] 5-[(3,5-Dimethylphenoxy)methyl-d_2]oxazolidin-2-one: The procedure of Example 1, Step 2 was followed, but substituting 3-(3,5-dimethylphenoxy)propane-3,3-d_2-1,2-diol for 3-(3,5-dimethylphenoxy)propane-3,3-1,2-diol. The title compound was isolated as a white solid (0.070 g, 10%). m.p. 120-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.61 (dd, J = 8.5, 6.2 Hz, 1H), 3.72-3.78 (m, 1H), 4.94 (dd, J = 8.6, 6.1 Hz, 1H), 5.29 (br, exchangeable with D_2O, 1H), 6.54 (s, 2H), 6.64 (s, 1H); IR (KBr) υ 3285, 1734, 1599, 1322, 1239 cm^{-1}; MS 224 (M + 1).

EXAMPLE 4

5-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]oxazolidin-2-one

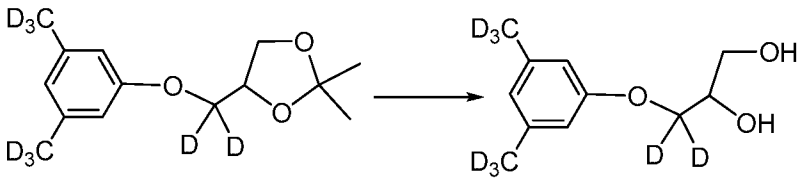


Step 1



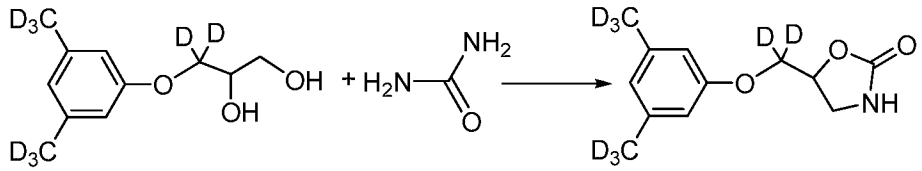
[00244] 4-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]-2,2-dimethyl-1,3-dioxolane: The procedure of Example 3, Step 5 was followed, but substituting 3,5-dimethyl-d_6-phenol (1.30 g, 10.14 mmol) for 3,5-dimethyl-phenol (1.30 g, 10.14 mmol). The title product was isolated as a pale yellow liquid (1.70 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 2.28 (s, 6H), 3.89 (dd, J = 8.2, 6.1 Hz, 1H), 4.11-4.17 (m, 1H), 4.21-4.26 (m, 1H), 6.54 (s, 0.34H), 6.61 (s, 0.16H); IR (film) υ 2987, 2924, 2866, 2203, 2095, 1599, 1468, 1375, 1320 cm^{-1}; MS 239 (M + 1).

Step 2



[00245] 3-(3,5-Dimethyl-d_6-phenoxy)propane-3,3-d_2-1,2-diol: The procedure of Example 3, Step 6 was followed, but substituting 4-[(3,5-dimethyl-d_6-phenoxy)methyl-d_2]-2,2-dimethyl-1,3-dioxolane for 4-[(3,5-dimethylphenoxy)methyl-d_2]-2,2-dimethyl-1,3-dioxolane. The title compound was isolated as a low-melting solid (0.900 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.69-3.86 (m, 2H), 4.05-4.11 (m, 1H), 6.55 (s, 0.34H), 6.63 (s, 0.16H); IR (KBr) υ 3418, 3331, 2926, 1597, 1445, 1316 cm^{-1}; MS 199 (M + 1).

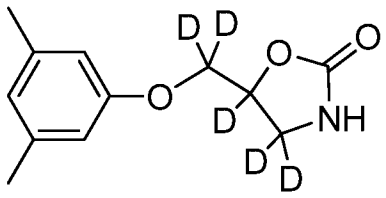
Step 3



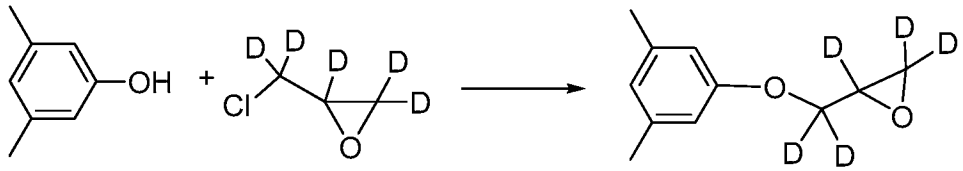
[00246] 5-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]oxazolidin-2-one: The procedure of Example 3, Step 7 was followed, but substituting 3-(3,5-dimethyl-d_6-phenoxy)propane-3,3-d_2-1,2-diol for 3-(3,5-dimethylphenoxy)propane-3,3-d_2-1,2-diol. The title compound was isolated as a white solid (0.080 g, 9%). m.p. 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (dd, J = 8.1, 6.5 Hz, 1H), 3.72-3.78 (m, 1H), 4.94 (dd, J = 8.7, 6.2 Hz, 1H), 5.15 (br, exchangeable with D_2O, 1H), 6.54 (s, 0.62H), 6.64 (s, 0.4H); IR (KBr) υ 3281, 1733, 1584, 1391, 1328, 1237 cm^{-1}; MS 230 (M + 1).

EXAMPLE 5

5-[(3,5-Dimethylphenoxy)methyl-d_2]oxazolidin-4,4,5-d_3-2-one



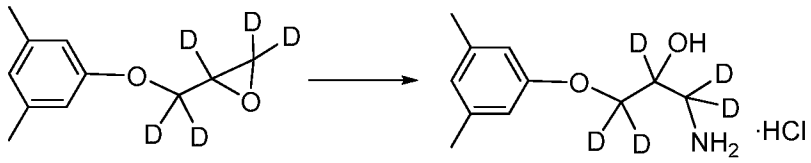
Step 1



[00247] 2-[(3,5-Dimethylphenoxy)methyl-d_2]oxirane-1,1,2-d_3: Potassium hydroxide (0.689 g, 12.28 mmol) was added portionwise to a mixture of 3,5-dimethylphenol (0.750 g, 6.14 mmol), epichlorohydrin-d_5 (1.20 g, 12.30 mmol) and poly(ethyleneglycol) (3 mL) at ambient temperature. The mixture was stirred at about 45 °C for about 6 hours, at ambient temperature for 18 hours, and then diluted with deuterium oxide (15 mL). Following standard extractive workup with ethyl acetate, the crude residue which was purified by silica gel column chromatography (1% ethyl acetate in petroleum ether) to give the title product as an oil (0.450 g,

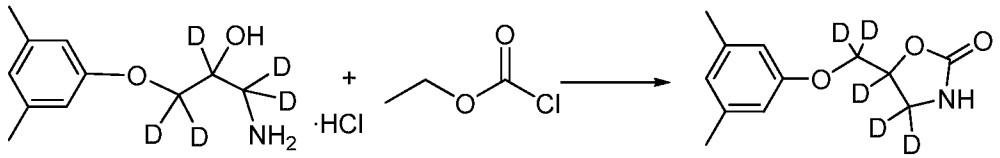
40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 6.55 (s, 2H), 6.62 (s, 1H); IR (film) υ 3023, 2921, 2862, 2188, 2097, 1598, 1471, 1319 cm^{-1}; MS 184 (M + 1).

Step 2



[00248] 1-Amino-3-(3,5-dimethylphenoxy)propan-2-ol-1,1,2,3,3-d_5 hydrochloride: At –40 °C, liquid ammonia (7 mL) was carefully added to a solution of 2-[(3,5-dimethylphenoxy)methyl-d_2]oxirane-1,1,2-d_3 (0.500 g, 2.73 mmol) in 2-propanol (8 mL) in a pressure tube. The tube was sealed and stirred for about 24 hours at ambient temperature. After the volatiles were removed *in vacuo*, the resulting residue was dissolved in diethyl ether (5 mL). Diethyl ether saturated with hydrochloric gas was then added until the pH reached 2. The resulting precipitate was filtered and dried to give the title product as a white solid (0.450 g, 70%). m.p. 175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 6H), 6.57 (s, 2H), 6.61 (s, 1H); IR (film) υ 3358, 3023, 1598, 1490, 1322 cm^{-1}; MS 200 (M–HCl + 1).

Step 3

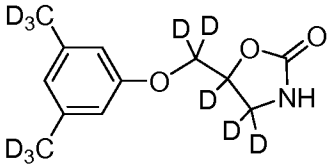


[00249] 5-[(3,5-Dimethylphenoxy)methyl-d_2]oxazolidin-4,4,5-d_3-2-one: A mixture of 1-amino-3-(3,5-dimethylphenoxy)propan-2-ol-1,1,2,3,3-d_5 hydrochloride (0.130 g, 0.549 mmol), anhydrous potassium carbonate (0.229 g, 1.657 mmol), poly(ethyleneglycol) (1 mL) and dry toluene (10 mL) was heated at reflux for about 1 hour and then cooled to about 40 °C. Ethyl chloroformate (64 μL, 0.669 mmol) was added and the mixture was heated at about 60 °C for about 1 hour, and then at reflux for about 6 hours. Following standard extractive workup with ethyl acetate, the crude residue was purified by Preparative HPLC on a Zodiacsil C18 (250 × 33 mm, 10 μ column; eluting with acetonitrile / 0.01M ammonium acetate (gradient) at a flow rate of 48 mL/min). The title compound eluted at 6.13 min. Standard extractive workup with ethyl acetate gave the title compound as a white solid (0.095 g, 76%). m.p. 119-122 °C; ^{1}H NMR (400

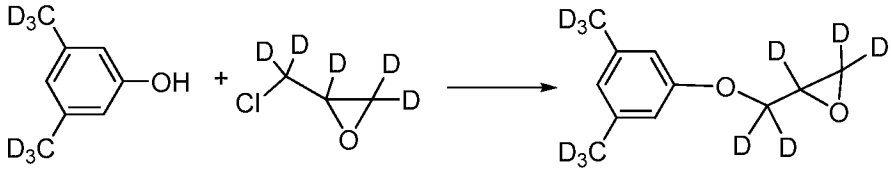
MHz, $CDCl_3$) δ 2.29 (s, 6H), 4.90 (br, exchangeable with D_2O, 1H), 6.54 (s, 2H), 6.64 (s, 1H); IR (film) υ 3282, 1733, 1600, 1335 cm^{-1}; MS 226 (M + 1).

EXAMPLE 6

5-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]oxazolidin-4,4,5-d_3-2-one

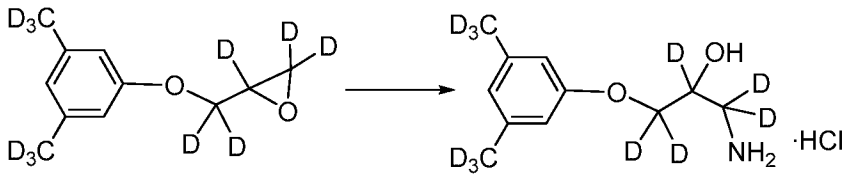


Step 1



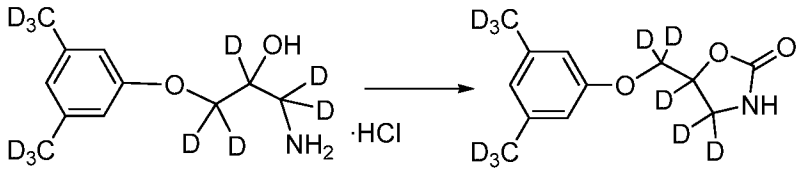
[00250] 2-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]oxirane-1,1,2-d_3: The procedure of Example 5, Step 1 was followed but substituting 3,5-dimethyl-d_6-phenol for 3,5-dimethylphenol. The title compound was isolated as an oil (0.350 g, 47%). IR (film) υ 2926, 2225, 2071, 1577, 1392 cm^{-1}; MS 190, 191, 192, 193 (M + 1, M + 2, M + 3, M + 4).

Step 2



[00251] 1-Amino-3-(3,5-dimethyl-d_6-phenoxy)propan-2-ol-1,1,2,3,3-d_5 hydrochloride: The procedure of Example 5, Step 2 was followed, but substituting 2-[(3,5-dimethyl-d_6-phenoxy)methyl-d_2]oxirane-1,1,2-d_3 for 2-[(3,5-dimethylphenoxy)methyl-d_2]oxirane-1,1,2-d_3. The title product was isolated as a white solid (0.340 g, 88%). m.p. 170 °C; IR (film) υ 3356, 3035, 1582, 1494, 1397, 1328 cm^{-1}; MS 209, 210 (M–HCl + 3, M–HCl + 4).

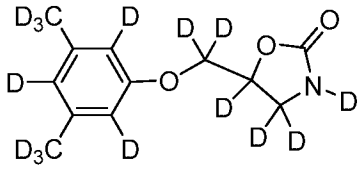
Step 3



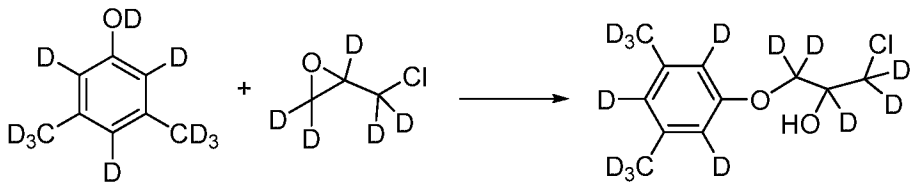
[00252] 5-[(3,5-Dimethyl-d_6-phenoxy)methyl-d_2]oxazolidin-4,4,5-d_3-2-one: The procedure of Example 5, Step 3 was followed, but substituting 1-amino-3-(3,5-dimethyl-d_6-phenoxy)propan-2-ol-1,1,2,3,3-d_5 hydrochloride for 1-amino-3-(3,5-dimethylphenoxy)propan-2-ol-1,1,2,3,3-d_5 hydrochloride. The title compound was isolated as a white solid (0.085 g, 30%). m.p. 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (br, exchangeable with D_2O, 1H), 6.54 (s, 0.38H), 6.64 (s, 0.23H); IR (film) υ 3282, 1731, 1578, 1397, 1337 cm^{-1}; MS 233, 234, 235 (M + 1, M + 2, M + 3).

EXAMPLE 7

d_{15}-5-[(3,5-dimethylphenoxy)methyl]oxazolidin-2-one

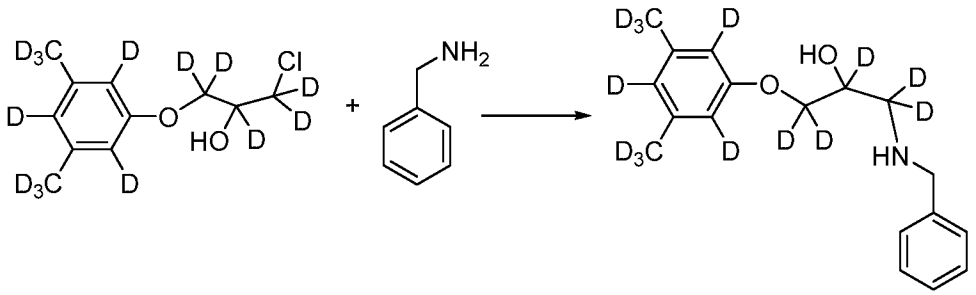


Step 1



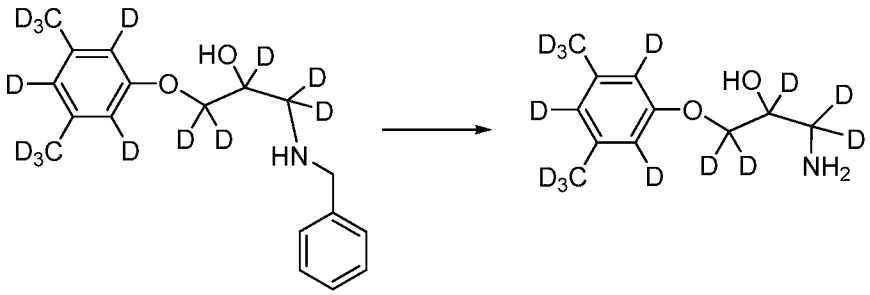
[00253] d_{14}-1-(3,5-dimethylphenoxy)-3-chloro-2-propanol: The procedure of Step 1 is carried out using the methods described in US 6,538,142 B1. Tetrabutylammonium bromide, d_5-epichlorohydrin (available commercially from Sigma-Aldrich, St. Louis MO 63103), d_{10}-3,5-dimethylphenol (available commercially from C/D/N Isotopes, Pointe-Claire, Quebec, Canada H9R 1H1) are loaded into a reaction vessel and heated at reflux for about 3 hours. Volatiles are removed *in vacuo* to yield the title product, which is used in the following step without purification.

Step 2



[00254] d_{14}-1-Benzylamino-3-(3,5-dimethyl-phenoxy)-propan-2-ol: The procedure of Step 2 is carried out using the methods described in US 6,538,142 B1. At about 80 °C, d_{14}-1-(3,5-Dimethylphenoxy)-3-chloro-2-propanol is added dropwise to benzylamine. The mixture is heated to 130 °C - 135 °C for about 8 hours. After cooling to about 40 °C, a mixture of sodium hydroxide (30% w/w, 20 mL) and water (10 mL) is added dropwise. Volatiles are removed *in vacuo* to yield the title product, which is used in the following step without purification.

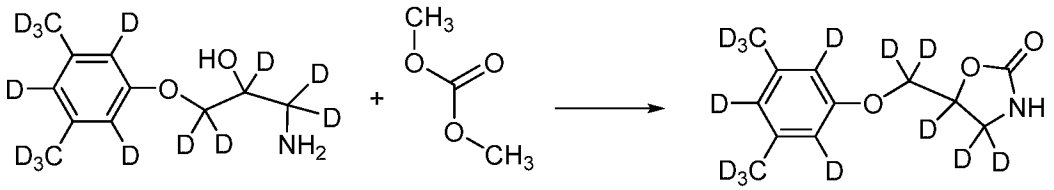
Step 3



[00255] d_{14}-1-Amino-3-(3,5-dimethylphenoxy)-2-propanol: The procedure of Step 3 is carried out using the methods described in US 6,538,142 B1. A mixture of ammonia (30% w/w), 10% palladium on carbon, d_{14}-1-benzylamino-3-(3,5-dimethyl-phenoxy)-propan-2-ol and d_4-methanol is heated at about 130 °C for about 8 hours under 12-13 atm of deuterium gas. The mixture is filtered, and the volatiles are removed *in vacuo*. The resulting residue is diluted with toluene and the pH is adjusted to 12 with 30% sodium hydroxide. Following a second extraction with toluene, water is added to the organic phase and the pH is adjusted to 4 with acetic acid. The organic phase is extracted and the aqueous phase is treated with charcoal, filtered, and diluted with toluene. The pH is adjusted to 12 with 30% sodium hydroxide. The aqueous phase

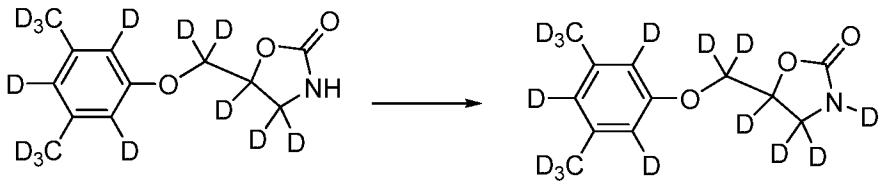
is extracted, and the volatiles are removed *in vacuo* to yield the title product, which is used in the following step without purification.

Step 4



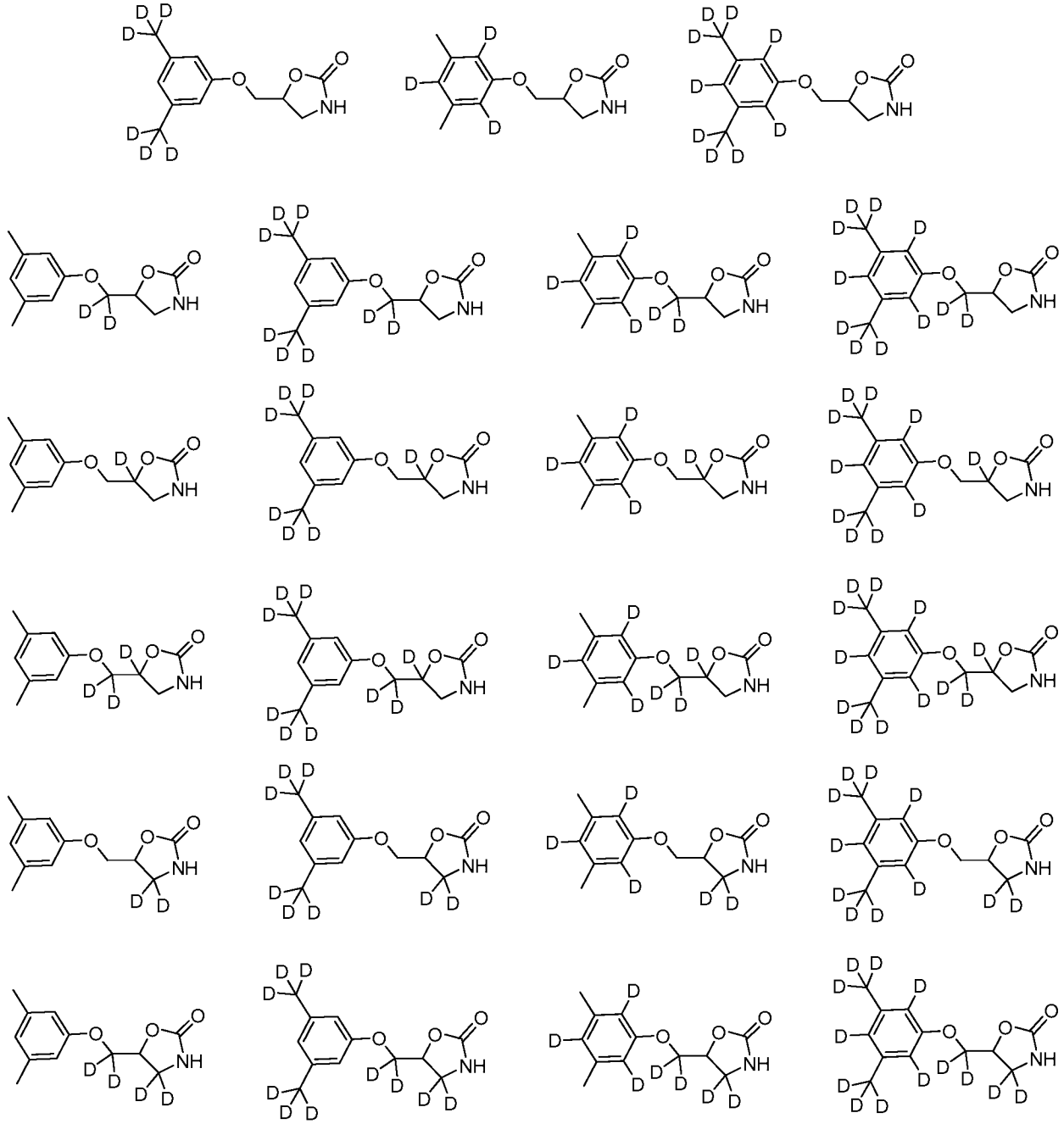
[00256] d_{14}-5-[(3,5-Dimethylphenoxy)methyl]oxazolidin-2-one: The procedure of Step 4 is carried out using the methods described in US 6,538,142 B1. d_{14}-1-Amino-3-(3,5-dimethylphenoxy)-2-propanol is added to dimethyl carbonate and sodium methoxide (30% solution in d_4-methanol). The mixture is heated at reflux for 3 to 5 hours. Volatiles are removed *in vacuo*, and the resulting residue is diluted with toluene and water. The pH is adjusted to 0.5 with 35% hydrochloric acid. The aqueous layer is extracted at about 60 °C and discarded. Water is added to the organic phase and the pH is adjusted to 7 with 30% sodium hydroxide. The aqueous layer is extracted at about 60 °C and discarded. The organic phase is dried, treated with charcoal, and filtered at an elevated temperature. The mother liquor is slowly cooled to about 0 °C for about 3 hours. The resulting precipitate is collected by filtration and washed with cold toluene, dried in vacuo and recrystallized from hot toluene to yield the title product.

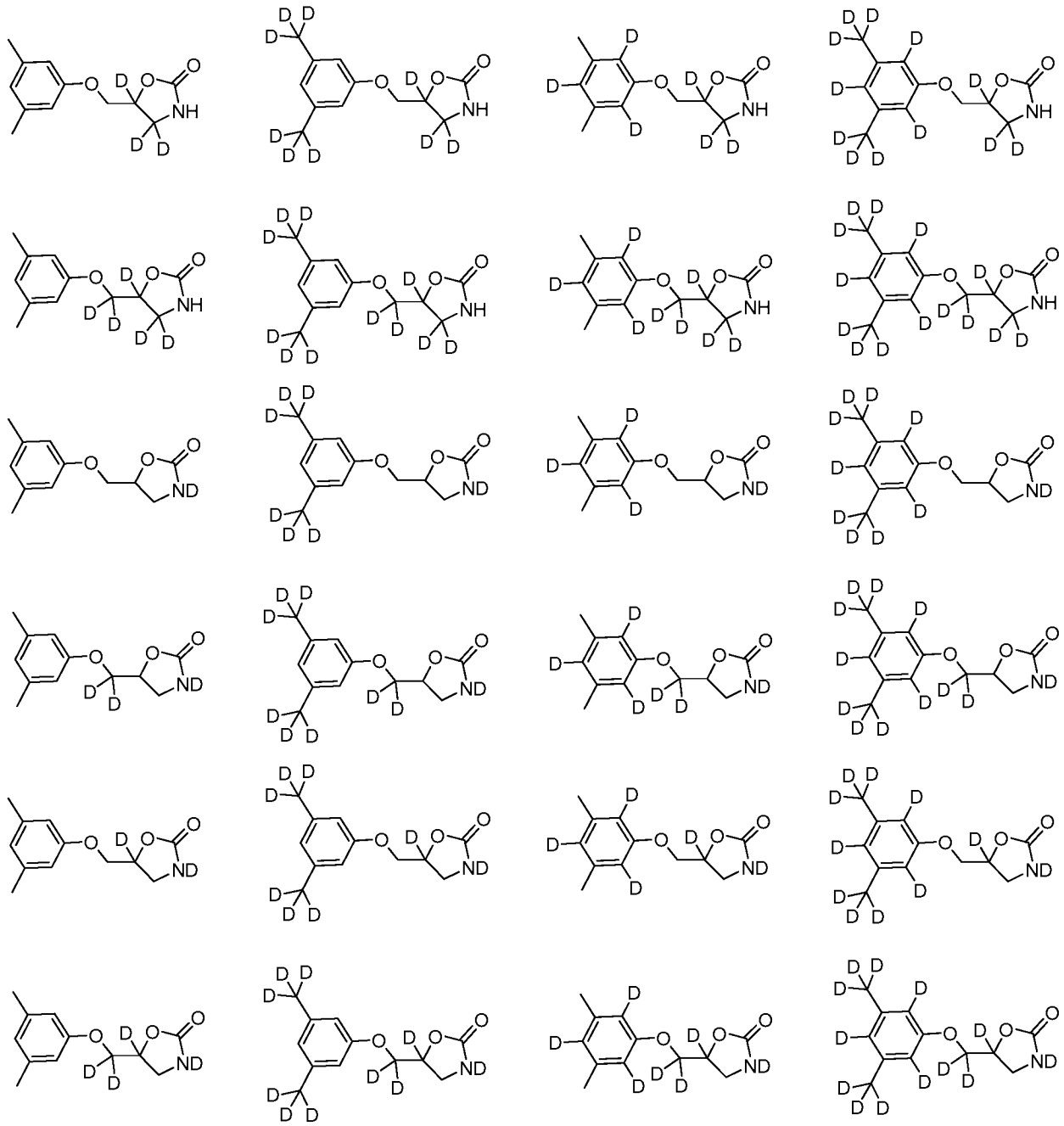
Step 5

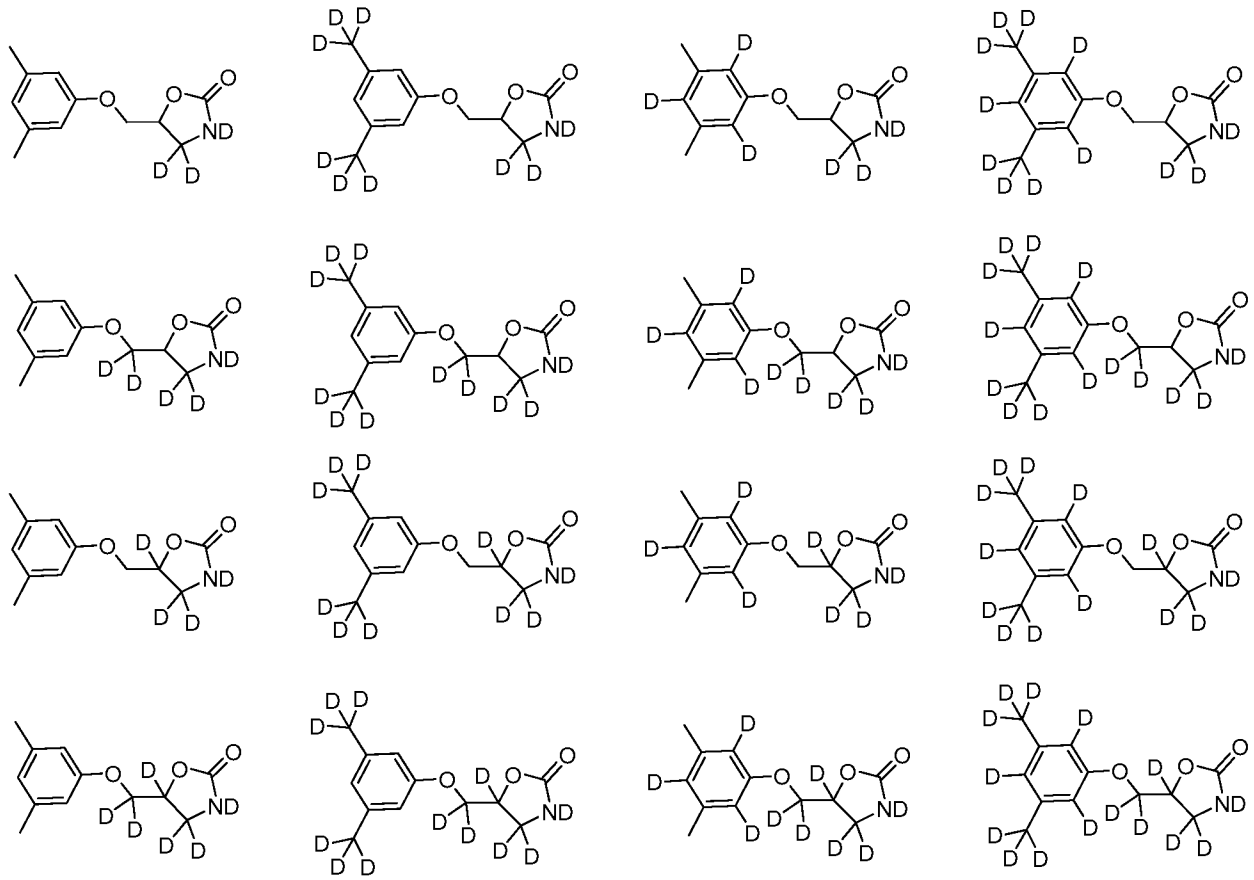


[00257] d_{15}-5-[(3,5-Dimethylphenoxy)methyl]oxazolidin-2-one: The procedure of Step 5 is carried out using the methods described in Hopfgartner et al., *J. Mass. Spectrom.* **1996**, *31*, 69-76. d_{14}-5-[(3,5-dimethylphenoxy)methyl]oxazolidin-2-one is taken up in a 1:1 mixture of deuterium oxide and dioxane and kept at ambient temperature and monitored by ^{1}H-NMR for the disappearance of the exchangeable oxazolidinone proton.

[00258] The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.







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

[0001] Changes in the metabolic properties of the compounds disclosed herein as compared to their non-isotopically enriched analogs can be shown using the following assays. 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.

Biological Assays

EXAMPLE 8

In vitro Liver Microsomal Stability Assay

[00259] Liver microsomal stability assays were conducted at 1 mg per mL liver microsome protein with an NADPH-generating system in 2% $NaHCO_3$ (2.2 mM NADPH, 25.6 mM glucose 6-phosphate, 6 units per mL glucose 6-phosphate dehydrogenase and 3.3 mM MgCl2). Test compounds were prepared as solutions in 20% acetonitrile-water. These solutions were added to the assay mixture (final assay concentration 1 μM) and incubated at 37 °C. Final

concentration of acetonitrile in the assay should be <1%. Aliquots (50μL) were collected at the these timpoints: 0, 0.25, 0.30, and 1 hours, and diluted with ice cold acetonitrile (200 μL) to stop the reactions. Samples were centrifuged at 12,000 RPM for 10 minutes 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. Compounds as disclosed in the present invention which have been tested in this assay, showed improved degradation half-life as compared to the non-isotopically enriched drug. Some of the compounds showed at least a 37% increase in degradation half-life, as compared with the non-isotopically enriched drug. The degradation half-lives of Examples 1 through 6 (Metaxalone and isotopically enriched drugs) are shown in table 1.

Results of *in vitro* human liver microsomal (HLM) stability assay

Table 1.

	% increase of HLM degradation half-life			
	-25% - 0%	0% - 50%	50% - 150%	>150%
Example 1	+			
Example 2		+		
Example 3		+		
Example 4		+		
Example 5		+		
Example 6		+		

EXAMPLE 9

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

[00260] The cytochrome P_{450} enzymes are expressed from the corresponding human cDNA using a baculovirus expression system (BD Biosciences, San Jose, CA). A 0.25 milliliter reaction mixture containing 0.8 milligrams per milliliter protein, 1.3 millimolar $NADP^+$, 3.3 millimolar glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 millimolar magnesium chloride and 0.2 millimolar of a compound of Formula I, the corresponding non-isotopically enriched compound or standard or control in 100 millimolar potassium phosphate (pH 7.4) is incubated at 37 °C for 20 min. After incubation, the reaction is stopped by the addition of an appropriate solvent (e.g., acetonitrile, 20% trichloroacetic acid, 94%

acetonitrile/6% glacial acetic acid, 70% perchloric acid, 94% acetonitrile/6% glacial acetic acid) and centrifuged (10,000 g) for 3 min. The supernatant is analyzed by HPLC/MS/MS.

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

EXAMPLE 10

Monoamine Oxidase A Inhibition and Oxidative Turnover

[00261] 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_i buffer, pH 7.2, containing 0.2% Triton X-100 (monoamine oxidase assay buffer), plus 1 mM kynuramine, and the desired amount of enzyme in 1 mL total volume.

EXAMPLE 11

Monooamine Oxidase B Inhibition and Oxidative Turnover

[00262] The procedure is carried out as described in Uebelhack, *Pharmacopsychiatry* **1998**, *31*(5), 187-192, which is hereby incorporated by reference in its entirety.

EXAMPLE 12

Liquid chromotagraphy-tandem mass spectroscopy assay for metaxalone

[00263] The procedure is carried out using the methods described by Nirogi et al., *J Anal Toxicol* **2006**, *30*(4), 245-51, which is hereby incorporated by reference in its entirety.

EXAMPLE 13

Quantitative and Qualitative tests for metaxalone

[00264] The procedure is carried out using the methods described in *J Pharmaceutical Sciences* **2006,** *53(12)*, 1522-1523**,** which is hereby incorporated by reference in its entirety.

EXAMPLE 14

Metaxalone Induction/Inhibition of Cytochrome p450 Isozymes

[00265] The procedure is carried out using the methods described in US 20080292584**,** which is hereby incorporated by reference in its entirety.

EXAMPLE 15

Metabolic Phenotyping of Metaxalone

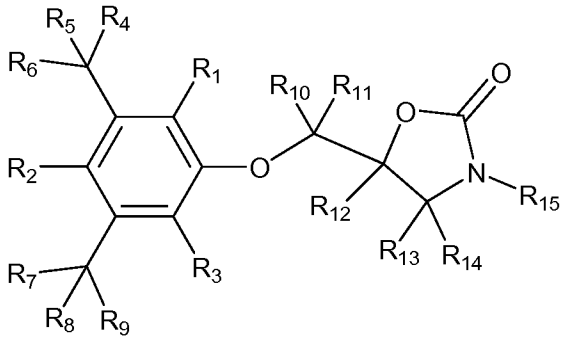
[00266] The procedure is carried out using the methods described in US 20080292584**,** which is hereby incorporated by reference in its entirety.

* * * * *

[00267] The examples set forth above are disclosed to give those of ordinary skill in the art with 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 to persons of skill in the art 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 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.

What is claimed is:

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof; wherein

R_1- R_{15} are each independently selected from the group consisting of hydrogen and deuterium; and

at least one of R_1- R_{15} is deuterium.

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

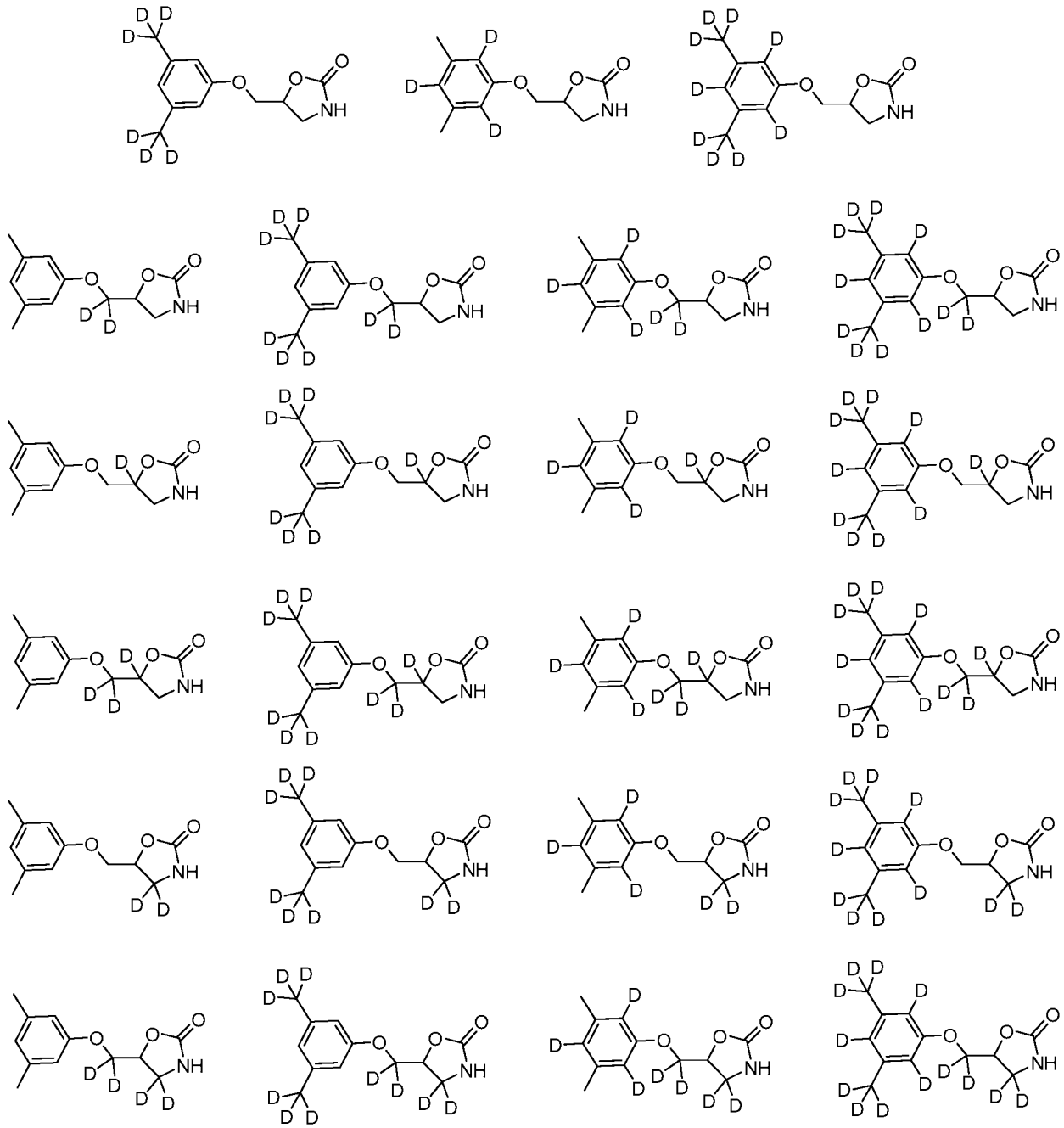
3. The compound as recited in Claim 1 wherein at least one of R_1-R_{15} independently has deuterium enrichment of no less than about 10%.

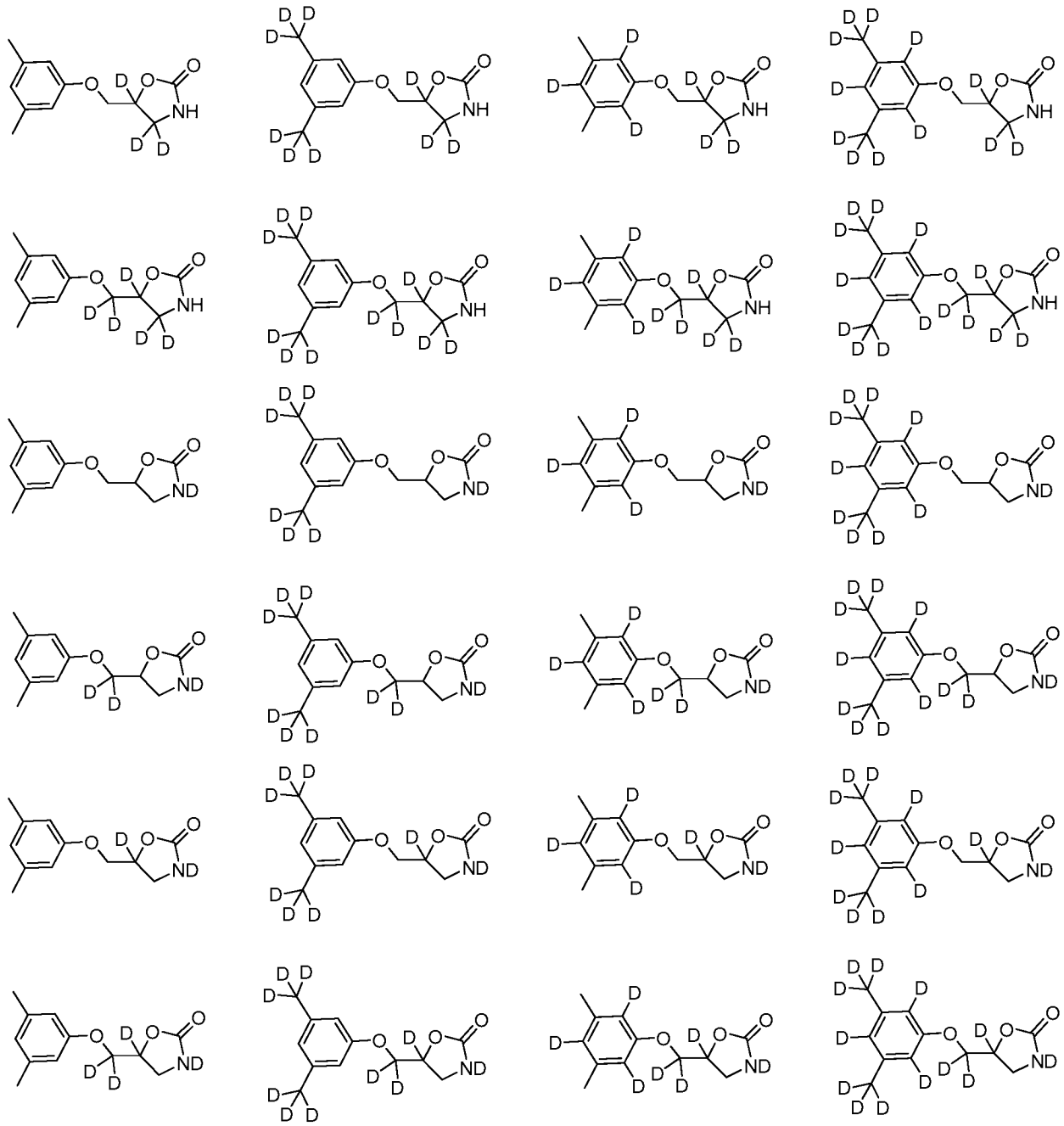
4. The compound as recited in Claim 1 wherein at least one of R_1-R_{15} independently has deuterium enrichment of no less than about 50%.

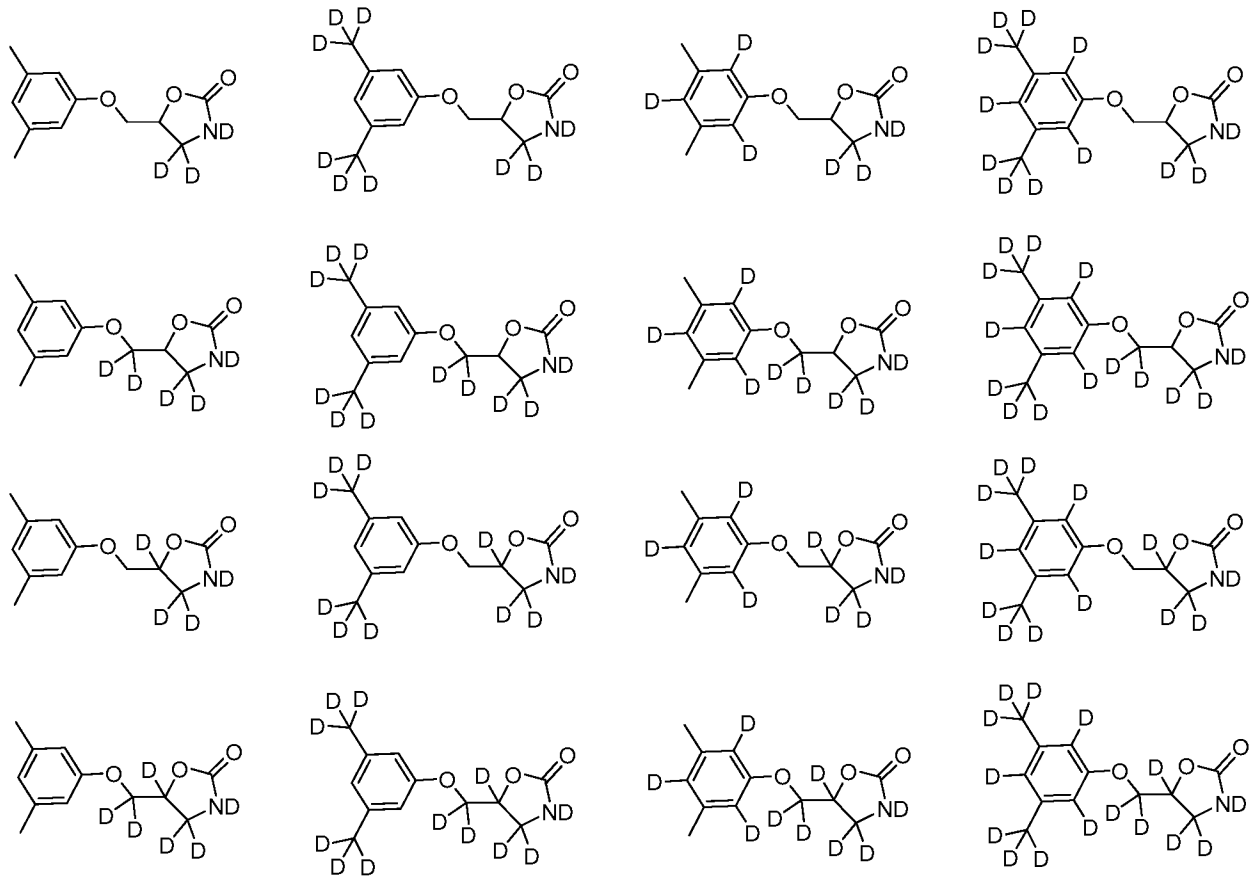
5. The compound as recited in Claim 1 wherein at least one of R_1-R_{15} independently has deuterium enrichment of no less than about 90%.

6. The compound as recited in Claim 1 wherein at least one of R_1-R_{15} independently has deuterium enrichment of no less than about 98%.

7. The compound as recited in Claim 1 wherein said compound has a structural formula selected from the group consisting of







or a pharmaceutically acceptable salt thereof.

8. The compound as recited in Claim 7, wherein said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

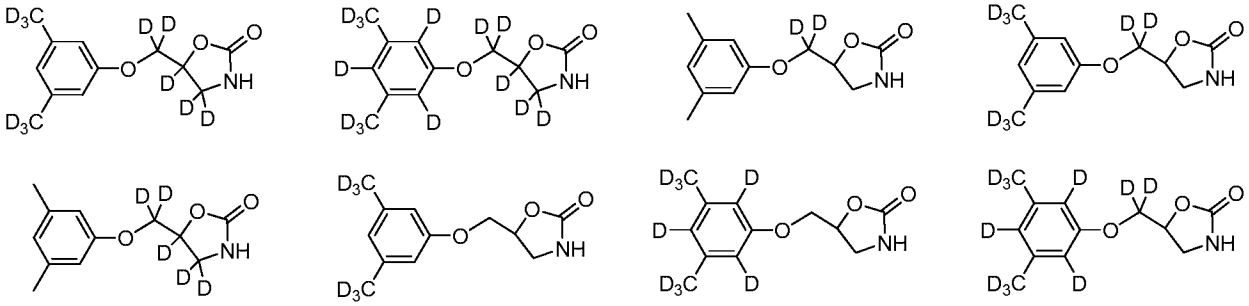
9. The compound as recited in Claim 7 wherein each position represented as D has enrichment of no less than about 10%.

10. The compound as recited in Claim 7 wherein each position represented as D has deuterium enrichment of no less than about 50%.

11. The compound as recited in Claim 7 wherein each position represented as D has deuterium enrichment of no less than about 90%.

12. The compound as recited in Claim 7 wherein each position represented as D has deuterium enrichment of no less than about 98%.

13. The compound as recited in Claim 1 wherein said compound has a structural formula selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

14. The compound as recited in Claim 13, wherein said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

15. The compound as recited in Claim 13 wherein each position represented as D has enrichment of no less than about 10%.

16. The compound as recited in Claim 13 wherein each position represented as D has deuterium enrichment of no less than about 50%.

17. The compound as recited in Claim 13 wherein each position represented as D has deuterium enrichment of no less than about 90%.

18. The compound as recited in Claim 13 wherein each position represented as D has deuterium enrichment of no less than about 98%.

19. A pharmaceutical composition comprising a compound as recited in Claim 1 together with a pharmaceutically acceptable carrier.

20. A method of treatment of a musculoskeletal-mediated disorder comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to a patient in need thereof.

21. The method as recited in Claim 20 wherein said musculoskeletal-mediated disorder is selected from the group consisting of muscle spasms, muscle sprains, dorsalgia,

fibromyalgia, myofascial pain syndrome, radiculopathy, diabetic peripheral neuropathy, and tension headaches.

22. The method as recited in Claim 21, wherein the musculoskeletal-mediated disorder is dorsalgia.

23. The method as recited in Claim 20, wherein said musculoskeletal-mediated disorder can be lessened, alleviated, or prevented by administering a skeletal muscle relaxant.

24. The method as recited in Claim 20 further comprising the administration of an additional therapeutic agent.

25. The method as recited in Claim 24, wherein the therapeutic agent is selected from the group consisting of: non-steroidal anti-inflammatory agents, antiepileptics, anilide analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), diabetic neuropathy treatments, norepinephrine reuptake inhibitors (NRIs), dopamine reuptake inhibitors (DARIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitor (NDRIs), serotonin-norepinephrine-dopamine-reuptake-inhibitors (SNDRIs), monoamine oxidase inhibitors, hypothalamic phospholipids, opioids, antifugal agents, antibacterials, antimycobacterial agents, sepsis treatments, steroidal drugs, anticoagulants, thrombolytics, 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 VIIa Inhibitors, Factor Xa Inhibitors, renin inhibitors, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, anti-atherosclerotic agents, MTP Inhibitors, calcium channel blockers, potassium channel activators, alpha-PDE5 agents, beta-PDE5 agents, antiarrhythmic agents, diuretics, anti-diabetic agents, PPAR-gamma agonists, mineralocorticoid enzyme antagonists, aP2 inhibitors, protein tyrosine kinase inhibitors, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-disruptor agents, microtubule-stablizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors, cyclooxygenase-2 (COX-2) inhibitors, gold compounds, and platinum coordination complexes.

26. The method as recited in Claim 25, wherein the therapeutic agent is a non-steroidal anti-inflammatory agent.

27. The method as recited in Claim 26, wherein the non-steroidal anti-inflammatory agents is selected from the group consisting of aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoracoxib, faislamine, 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.

28. The method as recited in Claim 25, wherein the anilide analgesic is selected from the group consisting of acetaminophen and phenacetin.

29. The method as recited in Claim 28, wherein the anilide analgesic is acetaminophen.

30. The method as recited in Claim 25, wherein the therapeutic agent is an antiepileptic.

31. The method as recited in Claim 30, wherein the antiepileptic is selected from the group consisting of methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, ethosuximide, phensuximide, mesuximide, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, tiagabine, sultiame, phenacemide, lamotrigine, felbamate, topiramate, gabapentin, pheneturide, levetiracetam, zonisamide, pregabalin, stiripentol, and beclamide.

32. The method as recited in Claim 25, wherein the therapeutic agent is a tricyclic antidepressant.

33. The method as recited in Claim 32, wherein the tricyclic antidepressant is selected from the group consisting of amitriptyline, butriptyline, amoxapine, clomipramine, desipramine, dosulepin hydrochloride, doxepin, imipramine, dibenzepin, iprindole, lofepramine, nortriptyline, opipramol, protriptyline, and trimipramine.

34. The method as recited in Claim 25, wherein the therapeutic agent is a SSRI.

35. The method as recited in Claim 34, wherein the SSRI is selected from the group consisting

of alaproclate, citalopram, dapoxetine, escitalopram, etoperidone, fluoxetine, fluvoxamine, paroxetine, sertraline, and zimelidine.

36. The method as recited in Claim 25, wherein the therapeutic agent is a diabetic neuropathy treatment.

37. The method as recited in Claim 36, wherein the diabetic neuropathy treatment is selected from the group consisting of methylcobalamin, α-lipoic acid, epalrestat, and C-peptide.

38. The method as recited in Claim 20, further resulting in 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.

39. The method as recited in Claim 20, further resulting in 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.

40. The method as recited in Claim 20, wherein the method affects a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed

cytochrome P_{450} isoform in the subject, as compared to the corresponding non-isotopically enriched compound.

41. The method as recited in Claim 40, wherein the cytochrome P_{450} isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

42. The method as recited in Claim 20, wherein said compound is characterized by decreased inhibition of at least one cytochrome P_{450} or monoamine oxidase isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

43. The method as recited in Claim 42, wherein said cytochrome P_{450} or monoamine oxidase isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAO_A, and MAO_B.

44. The method as recited in Claim 20, wherein the method affects the treatment of the disease while reducing or eliminating a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

45. The method as recited in Claim 44, 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.

46. A compound as recited in Claim 1 for use as a medicament.

47. A compound as recited in Claim 1 for use in the manufacture of a medicament for the prevention or treatment of a disorder ameliorated by moduating skeletal muscle tone and function.