(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 October 2017 (19.10.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/180589 A1

(51) International Patent Classification:
C07C 225/20 (2006.01) *A61P 25/00* (2006.01)
C07B 59/00 (2006.01) *A61K 31/135* (2006.01)
A61K 101/00 (2006.01)

(21) International Application Number:
PCT/US2017/026953

(22) International Filing Date:
11 April 2017 (11.04.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/320,914 11 April 2016 (11.04.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

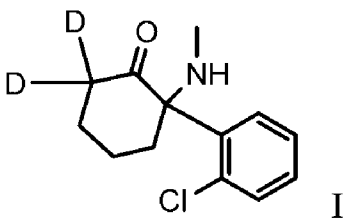
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/180589 A1

(54) Title: DEUTERATED KETAMINE DERIVATIVES



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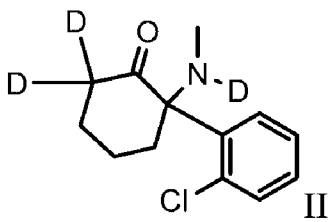


II

(57) Abstract: The present disclosure provides compounds of Formula I and/or Formula II, or pharmaceutically acceptable salts thereof: wherein D is deuterium and each deuterium has deuterium enrichment of no less than about 10%, compositions containing these compounds, and methods of using these compounds.

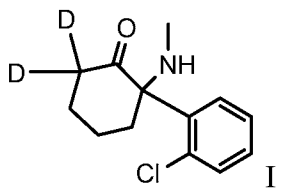
DEUTERATED KETAMINE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/320,914, filed April 11, 2016, the entirety of which is incorporated herein by reference.

FIELD

[0002] The present disclosure provides compounds of Formula I and/or II, or pharmaceutically acceptable salts thereof:



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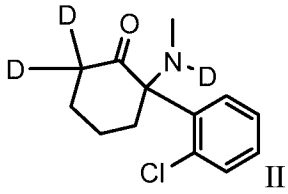


II

wherein D is deuterium; and each deuterium has deuterium enrichment of no less than about 10%, compositions containing these compounds, and methods of using these compounds.

BACKGROUND

[0003] Ketamine is a racemic mixture of S-ketamine and R-ketamine. It is classed as a Schedule III Controlled Substance due to its potential for physical and psychological dependence, as well as its potential for abuse. At high doses, such as in Ketalor®, Ketaject®, and Ketalar®, it can be used as a general anesthetic. At subanesthetic doses (for example 0.2 mg/kg, 0.5 mg/kg), ketamine has been used experimentally, either intranasally or intravenously (IV), for the treatment of depression, specifically treatment resistant depression. However IV and intranasal ketamine, unlike current treatment options for depression, such as mono-amine oxidase inhibitors, tricyclic antidepressants, serotonin specific reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, and noradrenaline reuptake inhibitors, produces a rapid antidepressant effect, acting within two hours and having an extended effect. While ketamine is a racemic mixture of S-ketamine and R-ketamine, there is some controversy regarding the specific role of each enantiomer, as well as the mechanism of action.

[0004] In addition to treatment for depression, human studies of low-dose ketamine for use in the treatment of Rett syndrome is being explored. Rett syndrome (RTT) is a rare genetic postnatal neurological disorder of the grey matter of the brain.

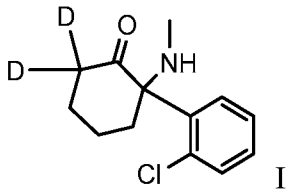
[0005] When administered orally, ketamine is subject to the first-pass liver metabolism *via* N-demethylation and conversion to the active metabolite *N*-desmethylketamine, usually referred to as norketamine. The elimination half-life of ketamine has been estimated at 2-3 hours, and 4 hours for norketamine. Due to extensive first pass metabolism which results in poor oral bioavailability, ketamine is typically administered parenterally or intranasally. Both of these routes of administration are inconvenient for a patient [Peltoniemi 2012, Basic & Clinical Pharmacology & Toxicology, 111, 325-332].

[0006] Oral administration of ketamine has been investigated to some extent (*see* Blonk, European Journal of Pain, 2010, 14, 466-472 and Fanta, European Journal of Clinical Pharmacology, 2015, 71, 441-447). Ketamine has been administered as an oral solution prepared from the commercially available injectable formulation (1 or 10% ketamine in water). Solid dose forms of ketamine have also been reported (Yanagihara, Biopharmaceutics & Drug Disposition, 2003, 24, 37-43) with pharmacokinetics in humans similar to the orally administered syrup formulation. Furthermore, oral and sublingual formulations of ketamine have been disclosed by Salama et al., WO 2014020155 and Chong 2009, Clinical Drug Investigation, 29(5), 317-324.

[0007] As such, there remains a need for more convenient, efficient, controllable, oral ketamine and ketamine-like products that mimic the results of ketamine IV for treatment of conditions such as pain, depression, traumatic brain injury, stroke, epilepsy, alcohol dependence, Rett or Alzheimer's disease.

SUMMARY OF THE INVENTION

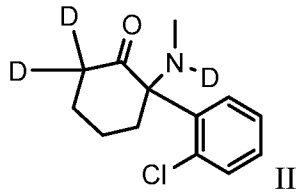
[0008] The present disclosure provides compounds of Formula I, or pharmaceutically acceptable salts thereof:



I

wherein D is deuterium and each deuterium has deuterium enrichment of no less than about 10%.

[0009] The present disclosure also provides compounds of formula II:



II

wherein, D is deuterium; and each deuterium has deuterium enrichment of no less than about 10%.

[0010] The present disclosure provides compositions comprising a compound of formula I and/or II or a pharmaceutically acceptable salt thereof. Further provided are pharmaceutical compositions comprising a compound of formula I and/or II or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

[0011] The present disclosure provides methods for treating, preventing, or ameliorating one or more symptoms of disorders including, but not limited to alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic disorder and the like using the compounds and compositions discussed herein.

[0012] Further provided is a compound of formula I and/or II or a pharmaceutically acceptable salt thereof, for use in treating a disorder. Further provided is a compound of formula I and/or II or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treatment of a disorder. In a further embodiment of the compound or use, the disorder includes, but is not limited to a ketamine responsive disorder for example, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic disorder and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 shows the stability of the compound of Example 1 in phosphate-buffered saline, at the indicated solution pH and time points.

[0014] FIG. 2 shows the plasma concentration time profile for S-ketamine and a deuterated *d*2-S-ketamine compound of the disclosure after oral administration to rats at 60 mg/kg.

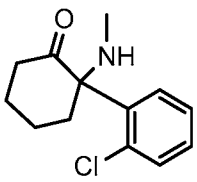
[0015] FIG. 3 shows the plasma concentration time profile for norketamine after oral administration of S-ketamine and a deuterated *d*2-S-ketamine compound to rats at 60 mg/kg.

[0016] FIG. 4 shows the plasma concentration time profile for 6-OH-norketamine after oral administration of S-ketamine and a deuterated *d*2-S-ketamine compound to rats at 60 mg/kg.

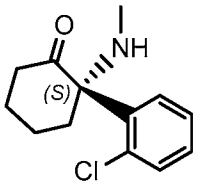
DETAILED DESCRIPTION

[0017] 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.

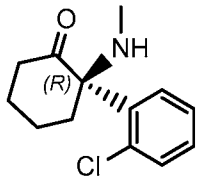
[0018] Unless specifically defined otherwise, references to ketamine in this disclosure are to be understood to refer to racemic ketamine and/or its individual enantiomers, S-(esketamine) or R-ketamine.



Racemic Ketamine

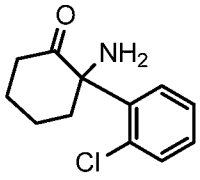


(S)-Ketamine



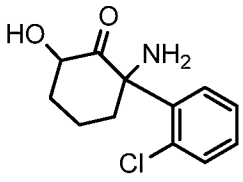
(R)-Ketamine

[0019] As used herein, "norketamine" or "N-desmethylketamine" are used interchangeably and have the below structure. Norketamine is an active metabolite of ketamine.



Norketamine

[0020] "Hydroxynorketamine" discussed herein refers to 6-hydroxynorketamine, having the below structure, as well as its four stereoisomers. Hydroxynorketamine is a metabolite of ketamine.



Hydroxynorketamine

[0021] As used herein, the singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0022] 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, etc. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human patient.

[0023] The terms "treat," "treating," and "treatment" are meant to include improving, preventing, alleviating or abrogating a disorder; or alleviating, preventing or abrogating one or more of the symptoms associated with the disorder; and/or preventing, alleviating or eradicating the cause(s) of the disorder itself, i.e., causing a clinical symptom to not significantly develop in a mammal that may be predisposed to the disease but does not yet experience or display symptoms of the disease. This may include improving the subject's ability to perform activities of daily living, perform domestic chores, manage finances, and/or perform an occupation or reduce the level of care needed by the subject. Treat, treating or treatment may include improvement of the symptom by at least 20%, 30%, 50%, 80%, 90%, or by 100%. Symptoms associated with a specific disorder depend on the specific disorder at hand. For example, in Rett syndrome, the symptom may be any one of more of the following: delay, partial or complete loss in acquiring mobility skills such as delayed or decreased motor coordination as in ability to sit, crawl, and/or walk; abnormal gait, ataxia, apraxia, muscle weakness, spasticity, rigidity; impaired gait initiation; abnormal muscle tone; hypotonia; peripheral vasomotor disturbance;

scoliosis; delay, partial or complete loss in acquiring purposeful hand skills; abnormal hand movement such as wringing, squeezing, clapping, washing, tapping, rubbing, and/or repeatedly bringing hands to mouth; delay in acquiring communication skill such as a partial or complete loss of acquired communication skill such as eye contact, abnormal eye movement (staring, excessive blinking, crossed eyes, and/or closing one eye at a time); delay in acquiring language skill such as spoken language; breathing irregularity such as hyperventilation while may occur while awake as bruxism or while asleep as apnea. In one embodiment, the sympom is a breathing irregularity; increased irritability, decreased alertness, and/or decreased attention span; inappropriate laughing and/or screaming; seizure; cardiac abnormality such as bradycardia or tachycardia; decreased response to pain; growth retardation; microcephaly; impaired sleeping pattern; or hypotrophic cold blue feet.

[0024] "Treating" or "treatment" of a condition or disease includes: (1) preventing at least one symptom of the conditions, or (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its symptoms, or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms. Treatment, prevention and ameliorating a condition, as used herein, can include, for example decreasing or eradicating a deleterious or harmful condition associated with Rett syndrome. Examples of such treatment include: decreasing breathing abnormalities, decreasing motor dysfunction, and improving respiratory and neurological function. The terms "prevent," "preventing," and "prevention" refer to a method of delaying or precluding the onset of a disorder; delaying or precluding its attendant symptoms; barring a subject from acquiring a disorder; and/or reducing a subject's risk of acquiring a disorder.

[0025] The term "therapeutically effective amount" refers to the amount of a compound that, when administered, is sufficient to prevent development of, alleviate to some extent or delay or prevent worsening of at least 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.

[0026] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must

be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenecity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. S*ee, Remington: The Science and Practice of Pharmacy*, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition; Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004).

[0027] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy.

[0028] The term "is/are deuterium," when used to describe a given position in a molecule or a drawing of a molecular structure, such as the symbol "D," means that the specified position is deuterium or that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In some embodiments, deuterium enrichment is no less than about 1%, in other embodiments, no less than about 5%, in further embodiments, no less than about 10%, in still other embodiments, no less than about 20%, in yet further embodiments, no less than about 50%, in other embodiments, no less than about 70%, in further embodiments, no less than about 80%, in yet other embodiments, no less than about 90%, or in still further embodiments, no less than about 98% of deuterium, at the specified position.

[0029] 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. For example, "non-isotopically enriched ketamine" refers to ketamine in which the percentages of the various isotopes, including deuterium, are substantially the same as the naturally occurring percentages.

[0030] The term "about" or "approximately" should be considered as disclosing the range defined by the absolute values of the two endpoints. The term "about" or "approximately" also means an acceptable error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, "about" can mean 1 or more standard deviations. For example, the expression "from about 2 to about 4" also discloses the range "from 2 to 4." When used to modify a single number, the term "about" may refer to plus or minus 10% of the indicated number and includes the indicated number. For example, "about 10%" may indicate a range of 9% to 11%, and "about 1" means from 0.9-1.1.

[0031] The term "isomers" refers to different compounds that have the same molecular formula. The term "stereoisomers" refers to isomers that differ only in the way the atoms are arranged in space. The term "enantiomers" refers to stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog *R*-*S* system.

[0032] The terms "active ingredient" and "active substance" refer to a compound, which is administered alone, or in combination with one or more pharmaceutically acceptable excipients and/or carriers, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0033] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0034] The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease," "syndrome," and "condition" (as in medical condition), in that all reflect an abnormal condition of the body or one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

[0035] The term "release controlling excipient" refers to an excipient having a primary function to modify the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0036] The term "nonrelease controlling excipient" refers to an excipient having a primary function that does not include modifying the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0037] The term "NMDA" refers to the N-methyl d-aspartate receptor. NMDA is a protein that facilitates the transport of ions, particularly calcium, sodium, and potassium, across certain cell membranes.

[0038] The term "AMPA" refers to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. AMPA is a non-NMDA-type ionotropic transmembrane protein for glutamate that mediates fast synaptic transmission in the central nervous system.

[0039] The term "NMDA receptor-mediated disorder" refers to a disorder that is characterized by abnormal NMDA receptor (NMDAR) activity or normal NMDA receptor activity that, when that activity is modified, leads to the amelioration of other abnormal biological processes. An NMDA receptor-mediated disorder may be completely or partially mediated by the abnormal NMDA receptor. In particular, a NMDA receptor-mediated disorder is one in which modulation of the NMDA receptor activity results in some effect on the underlying disorder, e.g., an NMDA receptor modulator results in some improvement in at least some of the patients being treated.

[0040] The term "AMPA receptor-mediated disorder" refers to a disorder that is characterized by abnormal AMPA receptor (AMPAR) activity or normal AMPA receptor activity that, when that activity is modified, leads to the amelioration of other abnormal biological processes. An AMPA receptor-mediated disorder may be completely or partially mediated by the abnormal AMPA receptor. In particular, an AMPA receptor-mediated disorder is one in which modulation of the AMPA receptor activity results in some effect on the underlying disorder, e.g., an AMPA receptor modulator results in some improvement in at least some of the patients being treated.

[0041] The term "ketamine responsive disorder" refers to a disorder wherein the symptoms of the disorder can be alleviated by the administration of an effective amount of ketamine or wherein ketamine produces an effect on the subject.

[0042] The term "NMDA receptor modulator" or "modulation of NMDA receptors" refers to the ability of a compound disclosed herein to alter the function of an NMDA receptor. A modulator may activate the activity of an NMDA receptor, may activate or inhibit the activity of an NMDA receptor depending on the concentration of the compound exposed to the NMDA receptor, or may inhibit the activity of an NMDA receptor. Such activation or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction

pathway, and/or may be manifest only in particular cell types. The term "NMDA receptor modulator" or "modulation of NMDA receptors" also refers to altering the function of an NMDA receptor by increasing or decreasing the probability that a complex forms between an NMDA receptor and a natural binding partner. A NDMA receptor modulator may increase the probability that such a complex forms between the NMDA receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the NMDA receptor and the natural binding partner depending on the concentration of the compound exposed to the NMDA receptor, and or may decrease the probability that a complex forms between the NMDA receptor and the natural binding partner. In some embodiments, modulation of the NMDA receptor may be assessed using Receptor Selection and Amplification Technology (R-SAT) as described in U.S. Patent No. 5,707,798, the disclosure of which is incorporated herein by reference in its entirety.

[0043] The term "AMPA receptor modulator" or "modulation of AMPA receptors" refers to the ability of a compound disclosed herein to alter the function of an AMPA receptor. A modulator may activate the activity of an AMPA receptor, may activate or inhibit the activity of an AMPA receptor depending on the concentration of the compound exposed to the AMPA receptor, or may inhibit the activity of an AMPA receptor. Such activation or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types. The term "AMPA receptor modulator" or "modulation of AMPA receptors" also refers to altering the function of an NMDA receptor by increasing or decreasing the probability that a complex forms between an AMPA receptor and a natural binding partner. An AMPA receptor modulator may increase the probability that such a complex forms between the AMPA receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the AMPA receptor and the natural binding partner depending on the concentration of the compound exposed to the AMPA receptor, and or may decrease the probability that a complex forms between the AMPA receptor and the natural binding partner. One skilled in the art would be able to utilize known assays to assess modulation of the AMPA receptor

[0044] The term "halide" or "halo" includes fluorine, chlorine, bromine, and iodine.

[0045] The term "alkyl" includes substituted, optionally substituted and unsubstituted C_1-C_{10} straight chain saturated aliphatic hydrocarbon groups, substituted, optionally substituted and

unsubstituted C_2-C_{10} straight chain unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_2-C_{10} branched saturated aliphatic hydrocarbon groups, substituted and unsubstituted C_2-C_{10} branched unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_3-C_8 cyclic saturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_5-C_8 cyclic unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, the definition of "alkyl" shall include but is not limited to: methyl (Me), trideuteromethyl (-CD_3), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, ethenyl, propenyl, butenyl, pentyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, adamantyl, norbornyl and the like.

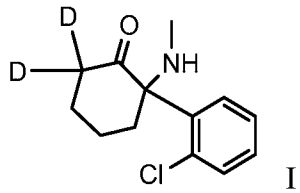
[0046] The term "lower alkyl" means an alkyl having between 1 and 6 carbon atoms, i.e., C_{1-6}alkyl.

[0047] "Pharmaceutically acceptable salt" as used herein refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Preferably, the salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. In some embodiments, the salts include acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentane propionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like. In other embodiments, the salts are formed when an acidic proton is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or

coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. In some embodiments, the salt contains one or more deuterium. In other embodiments, the salt is a DCl salt. In further embodiments, the salt is a HCl salt.

[0048] The term "prodrug" as used herein refers to a precursor of ketamine that, following administration to a subject, yields ketamine *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula I and/or II). Preferably, the prodrug is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "*Design of Prodrugs*", ed. H. Bundgaard, Elsevier, 1985. In some embodiments, the prodrug is inter alia, an ester, glucuronide, or amino acid residue.

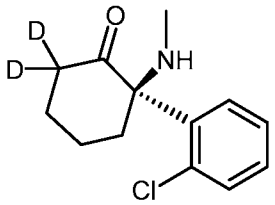
[0049] In some embodiments, the present disclosure provides compounds of Formula I, or pharmaceutically acceptable salts thereof:



I

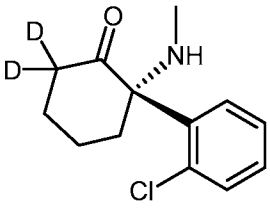
wherein, D is deuterium and each deuterium has deuterium enrichment of no less than about 10%.

[0050] In certain embodiments, the compound is *d*2-R-ketamine, or a pharmaceutically acceptable salt thereof:



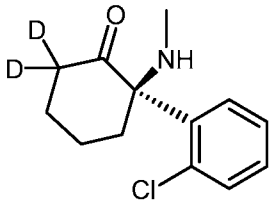
Formula Ia: *d*2-R-ketamine.

[0051] In other embodiments, the compound is *d*2-S-ketamine, or a pharmaceutically acceptable salt thereof:

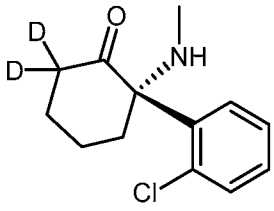


Formula Ib: *d*2-S-ketamine.

[0052] In further embodiments, the compound is a mixture of *d*2-R-ketamine:

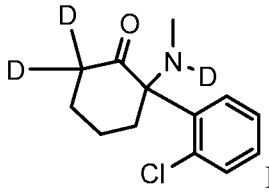


, or a pharmaceutically acceptable salt thereof; and *d*2-S-ketamine:



, or a pharmaceutically acceptable salt thereof.

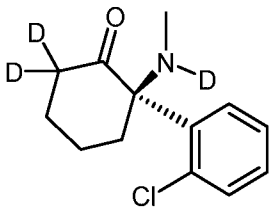
[0053] In yet further embodiments, the present disclosure provides compounds of formula II:



II

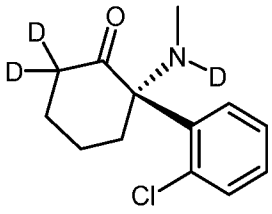
wherein, D is deuterium; and each deuterium has deuterium enrichment of no less than about 10%.

[0054] In certain embodiments, the compound is *d*3-R-ketamine, or a pharmaceutically acceptable salt thereof:



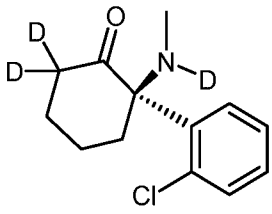
Formula IIa: *d*3-R-ketamine.

[0055] In other embodiments, the compound is *d*3-S-ketamine, or a pharmaceutically acceptable salt thereof:

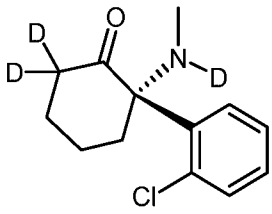


Formula IIb: *d*3-S-ketamine.

[0056] In further embodiments, the compound is a mixture of *d*3-R-ketamine:



, or a pharmaceutically acceptable salt thereof; and *d*3-S-ketamine:



, or a pharmaceutically acceptable salt thereof.

[0057] In still other embodiments, the compound is a mixture of *d*2-R-ketamine or a pharmaceutically acceptable salt thereof and *d*3-R-ketamine or a pharmaceutically acceptable salt thereof.

[0058] In yet further embodiments, the compound is a mixture of *d*2-S-ketamine or a pharmaceutically acceptable salt thereof and *d*3-S-ketamine or a pharmaceutically acceptable salt thereof.

[0059] In other embodiments, the compound is a mixture of *d*2-S-ketamine or a pharmaceutically acceptable salt thereof and *d*3-R-ketamine or a pharmaceutically acceptable salt thereof.

[0060] In further embodiments, the compound is a mixture of *d*2-R-ketamine or a pharmaceutically acceptable salt thereof and *d*3-S-ketamine or a pharmaceutically acceptable salt thereof.

[0061] In yet other embodiments, the compound is a mixture of *d*2-S-ketamine or a pharmaceutically acceptable salt thereof, *d*2-R-ketamine or a pharmaceutically acceptable salt thereof, and *d*3-S-ketamine or a pharmaceutically acceptable salt thereof.

[0062] In still further embodiments, the compound is a mixture of *d*2-S-ketamine or a pharmaceutically acceptable salt thereof, *d*2-R-ketamine or a pharmaceutically acceptable salt thereof, and *d*3-R-ketamine or a pharmaceutically acceptable salt thereof.

[0063] In other embodiments, the compound is a mixture of *d*3-R-ketamine or a pharmaceutically acceptable salt thereof, *d*3-S-ketamine or a pharmaceutically acceptable salt thereof, and *d*2-S-ketamine or a pharmaceutically acceptable salt thereof.

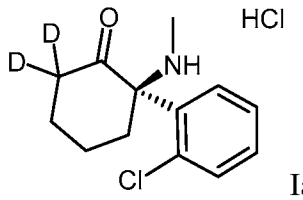
[0064] In further embodiments, the compound is a mixture of *d*3-R-ketamine or a pharmaceutically acceptable salt thereof, *d*3-S-ketamine or a pharmaceutically acceptable salt thereof, and *d*2-R-ketamine or a pharmaceutically acceptable salt thereof.

[0065] In yet other embodiments, the compound is a mixture of *d*2-R-ketamine or a pharmaceutically acceptable salt thereof, *d*2-S-ketamine or a pharmaceutically acceptable salt thereof, *d*3-R-ketamine or a pharmaceutically acceptable salt thereof, and *d*3-S-ketamine or a pharmaceutically acceptable salt thereof.

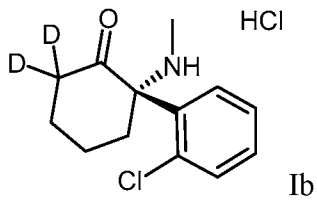
[0066] In further embodiments, each compound of Formula I, Ia, Ib, II, IIa, or IIb is a free base.

[0067] In other embodiments, each compound of Formula I, Ia, Ib, II, IIa, or IIb is a pharmaceutically acceptable salt. In some preferred embodiments, the compound is an HCl salt of Formula I, Ia, Ib, II, IIa, or IIb. In other preferred embodiments, the compound is a DCl salt of Formula I, Ia, Ib, II, IIa, or IIb.

[0068] In preferred embodiments, the compound of Formula Ia or Ib is a hydrogen chloride salt of *d*2-R-ketamine, *d*2-S-ketamine, or mixtures thereof:

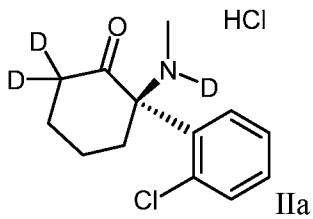


Ia

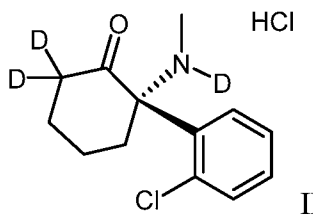


Ib.

[0069] In other preferred embodiments, the compound of Formula IIa or IIb is a hydrogen chloride salt of *d*3-R-ketamine, *d*3-S-ketamine or mixtures thereof:

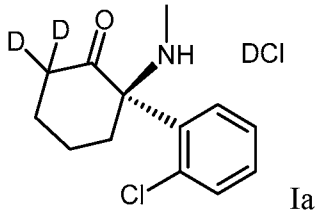


IIa

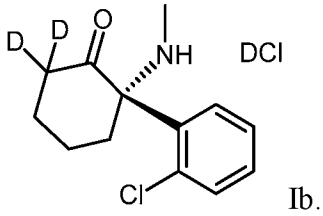


IIb.

[0070] In preferred embodiments, the compound of Formula Ia or Ib is a deuterium chloride salt of *d*2-R-ketamine, *d*2-S-ketamine, or mixtures thereof:

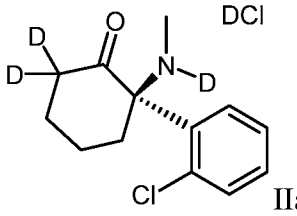


Ia

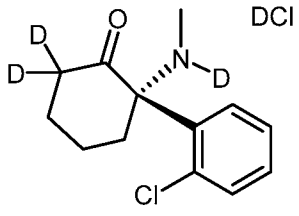


Ib.

[0071] In other preferred embodiments, the compound of Formula IIa or IIb is a deuterium chloride salt of *d*3-R-ketamine, *d*3-S-ketamine or mixtures thereof:



IIa



IIb.

[0072] As discussed above, the compound of Formula I and/or II provides a deuterium substituted ketamine. In some embodiments, each deuterium of the compound of Formula I and/or II 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%. In other embodiments, both deuteriums in the compound of Formula I have deuterium enrichment of no less than about 1% or 10%. In other embodiments, two or three deuteriums in the compound of Formula II have deuterium enrichment of no less than about 1 or 10%. In some embodiments, the compositions disclosed herein comprise the compound of Formula I and/or II as a single enantiomer. In other embodiments, the compounds and compositions are racemic comprising a mixture of the enantiomers. For example, in some aspects, compositions comprise about 90% or more by weight of the (R) enantiomer. In other aspects, compositions comprise about 80% by weight of the (R) enantiomer. In other aspects, compositions comprise about 70% by weight of the (R) enantiomer. In other aspects, compositions comprise about 60% by weight of the (R) enantiomer. In other aspects, compositions comprise about 50% by weight of the (R) enantiomer. In other aspects, compositions comprise about 40% by weight of the (R) enantiomer. In other aspects, compositions comprise about 30% by weight of the (R) enantiomer. In other aspects, compositions comprise about 20% by weight of the (R)

enantiomer. In other aspects, compositions comprise about 10% by weight of the (R) enantiomer. In other aspects, compositions comprise about 5% by weight of the (R) enantiomer.

[0073] In some aspects, compositions comprise about 90% or more by weight of the (S) enantiomer. In other aspects, compositions comprise about 80% by weight of the (S) enantiomer. In other aspects, compositions comprise about 70% by weight of the (S) enantiomer. In other aspects, compositions comprise about 60% by weight of the (S) enantiomer. In other aspects, compositions comprise about 50% by weight of the (S) enantiomer. In other aspects, compositions comprise about 40% by weight of the (S) enantiomer. In other aspects, compositions comprise about 30% by weight of the (S) enantiomer. In other aspects, compositions comprise about 20% by weight of the (S) enantiomer. In other aspects, compositions comprise about 10% by weight of the (S) enantiomer. In other aspects, compositions comprise about 5% by weight of the (S) enantiomer.

[0074] In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 60% or more by weight of the (S)-enantiomer of the compound and about 40% or less by weight of (R)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 70% or more by weight of the (S)-enantiomer of the compound and about 30% or less by weight of (R)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 80% or more by weight of the (S)-enantiomer of the compound and about 20% or less by weight of (R)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 90% or more by weight of the (S)-enantiomer of the compound and about 10% or less by weight of the (R)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 95% or more by weight of the (S)-enantiomer of the compound and about 5% or less by weight of (R)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 99% or more by weight of the (S)-enantiomer of the compound and about 1% or less by weight of (R)-enantiomer of the compound.

[0075] In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 60% or more by weight of the (R)-enantiomer of the compound and about 40% or less by weight of (S)-enantiomer of the compound. In certain embodiments, the compound of

Formula I and/or II as disclosed herein contains about 70% or more by weight of the (R)-enantiomer of the compound and about 30% or less by weight of (S)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 80% or more by weight of the (R)-enantiomer of the compound and about 20% or less by weight of (S)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 90% or more by weight of the (R)-enantiomer of the compound and about 10% or less by weight of the (S)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 95% or more by weight of the (R)-enantiomer of the compound and about 5% or less by weight of (S)-enantiomer of the compound. In certain embodiments, the compound of Formula I and/or II as disclosed herein contains about 99% or more by weight of the (R)-enantiomer of the compound and about 1% or less by weight of (S)-enantiomer of the compound.

[0076] The compound of Formula I and/or II 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.

[0077] In certain embodiments, without being bound by any theory, the compounds disclosed herein, including compounds of Formula I and/or II, 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.

[0078] In some embodiments, 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), modifying AUC, lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

[0079] 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.

[0080] Further provided are processes for preparing a compound as disclosed herein as a NMDA receptor modulator, or other pharmaceutically acceptable derivatives such as prodrug derivatives, or individual isomers and mixture of isomers or enantiomers thereof. 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 Examples section herein and routine modifications thereof, and/or procedures found in Hopfgartner et al., *J. Mass. Spectrom.* **1996**, *31*, 69-76, U.S. Patent No. 3,254,124, 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. For example, certain compounds as disclosed herein can be prepared as shown in Example 1 hereinbelow.

Pharmaceutical Compositions

[0081] 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. The pharmaceutical compositions that comprise a compound disclosed herein may be formulated in various dosage forms for oral, intranasal, parenteral, or topical administration. The pharmaceutical compositions may also be formulated as an immediate or modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms, and

may be optionally coated. 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 Delivery Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

[0082] The pharmaceutical compositions disclosed herein may be provided 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. In some embodiments, the pharmaceutical composition comprises a tablet or capsule. 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 or packages comprising tablets or capsules, or bottles of pints or gallons.

[0083] 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.

[0084] The pharmaceutical compositions disclosed herein may be administered as single or multiple doses at intervals of time.

[0085] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[0086] 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").

[0087] Once improvement of the patient's conditions has occurred, a maintenance dose may be administered. Subsequently, the dosage or the frequency of administration, or both, can be modified, 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.

[0088] A. Oral Administration

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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 polyvinylpyrrolidine. 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.

[0095] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0096] The pharmaceutical compositions disclosed herein may be formulated as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or coated forms such as enteric-coated tablets, sugar-coated, or film-coated tablets.

[0097] In some embodiments, the oral dosage form is coated. In some embodiments, the oral dosage form is coated with an enteric coating. 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. In some embodiments, disclosed 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.

[0098] 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.

[0099] 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, consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule 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. Patent 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.

[00100] 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, 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.

[00101] 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, butylated hydroxyanisole, 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.

[00102] 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, e.g., U.S. Patent No. 6,350,458.

[00103] 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. In some embodiments, the pharmaceutical compositions are provided in an effervescent dosage forms, which comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients or carriers for use in an effervescent dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[00104] Coloring and flavoring agents can be used in all of the above dosage forms.

[00105] 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.

[00106] 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.

[00107] In other embodiments, pharmaceutical compositions in a dosage form for oral administration are provided. Such compositions 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.

[00108] In further embodiments, the pharmaceutical compositions comprise about 0.1 to about 1000 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg of one or more compounds as disclosed herein. In some embodiments, the compounds are formulated as enteric-coated granules, as delayed-release capsules for oral administration. In some embodiments, the pharmaceutical composition further comprises cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hypromellose, lactose, mannitol, and sodium lauryl sulfate. In other embodiments, the pharmaceutical composition further comprises glyceryl monostearate 40-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate.

[00109] In some embodiments, the pharmaceutical composition further comprises carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide. In other embodiments, the pharmaceutical composition further comprises calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

[00110] B. Parenteral Administration

[00111] 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.

[00112] 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).

[00113] 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.

[00114] 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.

[00115] 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).

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] C. Topical Administration

[00123] The pharmaceutical compositions disclosed herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00124] 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.

[00125] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations disclosed herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing

agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00126] 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).

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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 inhalation or /intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00137] 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.

[00138] D. Modified Release

[00139] 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. In some embodiments, the pharmaceutical composition comprises 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. Thus, in certain embodiments, the pharmaceutical composition comprises one or more release-controlling excipients. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers. In some embodiments, the pharmaceutical composition further comprises one or more non-release controlling excipients.

[00140] The pharmaceutical compositions disclosed herein may be formulated as an abuse deterrent dosage form. Examples of modified release include, but are not limited to, those described in US20170035707, WO2015151259, US20150118302; US20150118303, US20160250203, US20160256392, US20160317457.

[00141] 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).

[00142] Examples of modified release include, but are not limited to, those described in U.S. Patent 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.

[00143] 1. Matrix Controlled Release Devices

[00144] 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).

[00145] 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.

[00146] 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.

[00147] 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.

[00148] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, and the particle sizes of the polymer and/or the active ingredient, the ratio of the active ingredient versus the polymer, and other excipients or carriers in the compositions. 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.

[00149] 2. Osmotic Controlled Release Devices

[00150] 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).

[00151] 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), PEG, polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, PVP, crosslinked PVP, 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, HEC, HPC, HPMC, CMC and carboxyethyl, cellulose, sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00152] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00153] 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.

[00154] 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.

[00155] 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 CA, cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, 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, hydroxylated 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.

[00156] 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. Patent 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.

[00157] 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. Patent Nos. 5,612,059 and 5,698,220.

[00158] 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.

[00159] 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.

[00160] 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).

[00161] 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. Patent No. 5,612,059 and International Patent Publication No. 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.

[00162] 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.

[00163] 3. Multiparticulate Controlled Release Devices

[00164] 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.

[00165] 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.

[00166] 4. Targeted Delivery

[00167] 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. Patent 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.

[00168] 5. Immediate release delivery

[00169] The compounds or compositions discussed herein may be formulated for delivery to a subject by immediate-release. In some embodiments, the compounds or compositions are formulated as discussed in U.S. Patent Publication No. 2016-0317457.

[00170] 6. Combined Release Delivery

[00171] Additionally disclosed are pharmaceutical compositions in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions comprise a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling and non-release controlling excipients or carriers, such as those excipients or carriers suitable for a disruptable semi-permeable membrane and as swellable substances.

[00172] **Methods of Use**

[00173] Any one of the compounds of formula I, Ia, Ib, II, Ia and IIb disclosed herein are useful in inducing a response in a subject, where a similar response is achieved when using ketamine. Accordingly, disclosed are methods for treating, preventing, or ameliorating one or more symptoms of a ketamine responsive 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. In some embodiments, the ketamine responsive disorder can be lessened, alleviated, or prevented by using an agent which is an anesthetic, analgesic, entheogen, therapeutic cataleptic, and neuroprotectant. Preferably, the anesthetic promotes general anesthesia.

[00174] It has been determined that various receptors can be modulated by ketamine. Thus, also within the scope of the disclosure, are methods of modulating the activity of one or more type of receptors that are modulated by ketamine. Also disclosed herein are methods of modulating the activity of receptors that respond to the action of ketamine. In some embodiments, these methods include contacting the receptors with at least one compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00175] Ketamine responsive disorders include, but are not limited to, to alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function

depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic disorder and the like. In some embodiments, the disorder is Rett syndrome. In some embodiments the disorder is depression, more preferably, major depressive disorder, refractory depression, treatment resistant depression, or depression associated with a genetic disorder.

[00176] Examples of receptors that are modulated by ketamine are the NMDA receptors and the AMPA receptors. In some embodiments, disclosed are methods for treating, preventing, or ameliorating one or more symptoms of an NMDA receptor mediated-disorder, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In other embodiments, disclosed are methods for treating, preventing, or ameliorating one or more symptoms of an AMPA receptor mediated-disorder, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00177] NMDA receptor mediated-disorders include, but are not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic disorder. In some embodiments, NDMA receptor-mediated disorder is nociceptive pain, neuropathic pain, phantom limb pain, ischemic pain, stroke, sepsis, inflammation, opioid tolerance, Alzheimer's disease, or burn. In some embodiments, the disorder is depression and, preferably, major depressive disorder, refractory depression, treatment resistant depression, or depression associated with a genetic disorder.

[00178] Also disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder associated with NMDA receptors, by administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00179] Further disclosed are methods of treating, preventing, or ameliorating one or more symptoms of a disorder responsive to modulation of NMDA receptors, comprising administering to a subject having or being suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00180] In some embodiments, the NMDA receptor-mediated disorder can be lessened, alleviated, or prevented by using an agent which is an anesthetic, analgesic, entheogen, therapeutic cataleptic, and neuroprotectant. Preferably, the anesthetic promotes general anesthesia.

[00181] Furthermore, disclosed herein are methods of modulating the activity of NMDA receptors, comprising contacting the receptors with at least one compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the NMDA receptor(s) are expressed by a cell. Also disclosed herein are methods of modulating the activity of AMPA receptors, comprising contacting the receptors with at least one compound as disclosed herein; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the AMPA receptor(s) are expressed by a cell.

[00182] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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

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.

[00183] 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 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, or by greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[00184] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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.

[00185] 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 1510%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

[00186] 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 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than

about 35%, greater than about 40%, greater than about 45%, or greater than about 50% as compared to the corresponding non-isotopically enriched compounds

[00187] Plasma levels of the compound as disclosed herein, or metabolites thereof, are measured using the methods described by Li et al. (*Rapid Communications in Mass Spectrometry* **2005**, *19*, 1943-1950).

[00188] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a ketamine or ketamine metabolite responsive disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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 disease as compared to the corresponding non-isotopically enriched compound.

[00189] 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, or CYP51.Examples of monoamine oxidase isoforms in a mammalian subject include, but are not limited to, MAO_A, and MAO_B.

[00190] 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 15%,greater than about 20%, greater than about 25%,greater

than about 30%, greater than about 35%,greater than about 40%, greater than about 45%,or greater than about 50% as compared to the corresponding non-isotopically enriched compounds.

[00191] 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).

[00192] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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. In other embodiments, the compound has an increased or decreased metabolism by at least one polymorphically-expressed cytochrome P_{450} isoform in the subject per dosage unit thereof as compared to the non-isotopically enriched compound. In further embodiments, the compound is characterized by increased or 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.

[00193] Examples of polymorphically-expressed cytochrome P_{450} isoforms in a mammalian subject include, but are not limited to, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[00194] 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 15%,greater than

about 20%, greater than about 25%,greater than about 30%, greater than about 35%,greater than about 40%, greater than about 45%,or greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[00195] The metabolic activities of the cytochrome P_{450} isoforms are measured, for example, by the method described in Example 4. The metabolic activities of the monoamine oxidase isoforms are measured, for example, by the methods described in Examples 5, and 6.

[00196] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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. Examples of improved disorder-control and/or disorder-eradication endpoints include, but are not limited to, statistically-significant improvement of pain indices, perfusion of ischemic tissues with oxygen, prevention of ischemia, entheogenic effects sufficient to facilitate psychotherapy, cataleptic effects sufficient to enable medical treatment of a non-compliant trauma victim, neuroprotection during an ischemic event, and/or diminution of hepatotoxicity, as compared to the corresponding non-isotopically enriched compound.

[00197] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, nociceptive pain, neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett

syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, traumatic brain injury, treatment resistant depression, tinnitus, and depression associated with genetic disorders and the like, 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 effects include, but are not limited to, statistically-significant improvement of pain or depression indices, perfusion of ischemic tissues with oxygen, prevention of ischemia, entheogenic effects sufficient to facilitate psychotherapy, cataleptic effects sufficient to enable medical treatment of a non-compliant trauma victim, improvement in cognition, neuroprotection during an ischemic event, and/or diminution of hepatotoxicity, or any relevant safety measures as compared to the corresponding non-isotopically enriched compound.

[00198] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, nociceptive pain, neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, traumatic brain injury, treatment resistant depression, tinnitus, and depression associated with genetic disorders and the like., 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.

[00199] Disclosed herein are methods for treating a subject, including a human, having or suspected of having a disorder involving, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, nociceptive pain, neuropathic

pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, traumatic brain injury, treatment resistant depression, tinnitus, and depression associated with genetic disorders and the like. 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, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, nociceptive pain, neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, traumatic brain injury, treatment resistant depression, tinnitus, and depression associated with genetic disorders and the like, while reducing or eliminating deleterious changes in abnormal alimentary, hepatic parameter, or diagnostic hepatobiliary function endpoints as compared to the corresponding non-isotopically enriched compound. In some embodiments, the method affects 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. In some embodiments, the method affects treatment of the disorder while reducing or eliminating an abnormal alimentary or hepatic parameter, as compared to the corresponding non-isotopically enriched compound. 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.

[00200] In some embodiments, the compound has at least one of the following properties: a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound; b) increased average plasma levels of said

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

[00201] In yet further embodiments, the compound has at least two of the following properties: a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound; b) increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[00202] Also provided are methods directed to decreasing the production of metabolites of ketamine, for example, decreasing the production of inactive metabolites of ketamine. In some embodiments, the disclosure provides methods of decreasing the production of hydroxynorketamine in a subject. In other embodiments, the subject had previously been administered ketamine. In further embodiments, the subject had not previously been administered ketamine. Such methods comprise administering to the subject a compound or pharmaceutical composition disclosed herein.

[00203] Further provided are methods of increasing the production of metabolites of ketamine, for example, increasing the producing of active metabolites of ketamine. In some embodiments, the disclosure provides methods of increasing the production of norketamine in a subject. In other embodiments, the subject had been previously administered ketamine. In further embodiments, the subject has not previously been administered ketamine. The methods comprise administering to the subject a compound or pharmaceutical composition described herein.

[00204] Depending on the disease to be treated and the subject's condition, the compound as disclosed herein disclosed herein may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration, and may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[00205] 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 or per week or per month. 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 other embodiments, the compounds are administered in a dose of about 0.5 milligram to about 1000 milligrams. Preferably, the compounds are administered in a dose of about 1 to about 100 milligrams, about 1 to about 50 milligrams, about 5 to about 20 milligrams, or about 50 to about 100milligrams.

[00206] 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

[00207] 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 the disorders for which the compound disclosed herein are useful, including, but not limited to, alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major

depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic 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). The compositions and methods disclosed herein may be used as monotherapy or as adjunct therapy. 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.

[00208] The compounds, compositions and or methods pharmaceutical compositions may further comprise another therapeutic agent for combination therapy. In some embodiments, the therapeutic agent is a NMDA-receptor modulator, opioid, anesthetic, peripherally acting muscle relaxant, benzodiazepine, endothelin converting enzyme (ECE) inhibitor, thromboxane enzyme antagonist, potassium channel opener, thrombin inhibitor, growth factor inhibitor, platelet activating factor (PAF) antagonist, anti-platelet agent, Factor VIIa inhibitor, Factor Xa inhibitor, renin inhibitor, neutral endopeptidase (NEP) inhibitor, vasopepsidase inhibitor, HMG CoA reductase inhibitor, squalene synthetase inhibitor, fibrate, bile acid sequestrant, anti-atherosclerotic agent, MTP inhibitor, calcium channel blocker, potassium channel activator, alpha-PDE5 agent, beta-PDE5 agent, antiarrhythmic agent, diuretic, anti-diabetic agent, PPAR-gamma agonist, mineralocorticoid enzyme antagonist, aP2 inhibitor, protein tyrosine kinase inhibitor, antiinflammatory, antiproliferative, chemotherapeutic agent, immunosuppressant, anticancer agent, cytotoxic agent, antimetabolite, farnesyl-protein transferase inhibitor, hormonal agent, microtubule-disruptor agent, microtubule-stabilizing agent, topoisomerase inhibitor, prenyl-protein transferase inhibitor, cyclosporin, TNF-alpha inhibitor, cyclooxygenase-2 (COX-2) inhibitor, gold compound, or platinum coordination complex.

[00209] In certain embodiments, the compounds, compositions and or methods disclosed herein can be combined with one or more modulators of NMDA-receptors known in the art, including, but not limited to, phencyclidine (PCP), amantadine, ibogaine, memantine, nitrous oxide, and dextromethorphan. In some embodiments, the NMDA receptor-mediated disorder can be lessened, alleviated, or prevented by administering a NDMA receptor modulator. In other embodiments, the ketamine responsive disorder can be lessened, alleviated, or prevented by administering a NDMA receptor modulator.

[00210] In certain embodiments, the compounds, compositions and or methods disclosed herein can be combined with one or more natural, semisynthetic, or fully synthetic opioids known in the art, including, but not limited to, morphine, codeine, thebain, diacetylmorphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, nicomorphine, fentanyl, α-methylfentanyl, alfentanil, sufentanil, remifentanyl, carfentanyl, ohmefentanyl, pethidine, ketobemidone, propoxyphene, dextropropoxyphene, methadone, loperamide, pentazocine, buprenorphine, etorphine, butorphanol, nalbufine, levorphanol, naloxone, naltrexone, and tramadol.

[00211] In certain embodiments, the compounds, compositions and or methods provided herein can be combined with one or more local or general anesthetics known in the art, including, but not limited to, diethyl ether, vinyl ether, halothane, chloroform, methoxyflurane, enflurane, trichloroethylene, isoflurane, desflurane, sevoflurane, methohexital, hexobarbital, thiopental, narcobarbital, fentanyl, alfentanil, sufentanil, phenoperidine, anileridine, remifentanil, droperidol, non-deuterated ketamine, propanidid, alfaxalone, etomidate, propofol, hydroxybutyric acid, nitrous oxide, non-deuterated esketamine, metabutethamine, procaine, tetracaine, chloroprocaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, butanilicaine, cinchocaine, etidocaine, articaine, ropivacaine, levobupivacaine, cocaine, ethyl chloride, dyclonine, phenol, and capsaicin.

[00212] In certain embodiments, the compounds, compositions and or methods disclosed herein can be combined with one or more peripherally acting muscle relaxants known in the art, including, but not limited to alcuronium, dimethyltubocurarine, tubocurarine, suxamethonium, atracurium, cisatracurium, doxacurium chloride, fazadinium bromide, gallamine, hexafluronium, mivacurium chloride, pancuronium, pipecuronium bromide, rocuronium bromide, vecuronium, and botulinum toxin.

[00213] In certain embodiments, the compounds, compositions and or methods disclosed herein can be combined with one or more benzodiazepines ("minor tranquilizers") known in the art, including, but not limited to alprazolam, bromazepam, clonazepam, diazepam, estazolam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, triazolam, temazepam, and chlordiazepoxide. The compounds disclosed herein can also be administered in combination with other classes of compounds, including, but not limited to, endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists, such as ifetroban; potassium channel openers; thrombin inhibitors, such as hirudin; growth factor inhibitors, such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents, such as GPIIb/IIIa blockers (e.g., abdximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants, such as warfarin; low molecular weight heparins, such as enoxaparin; Factor VIIa Inhibitors and Factor Xa Inhibitors; renin inhibitors; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants, such as questran; niacin; anti-atherosclerotic agents, such as ACAT inhibitors; MTP Inhibitors; calcium channel blockers, such as amlodipine besylate; potassium channel activators; alpha-adrenergic agents; beta-adrenergic agents, such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothlazide, hydrochiorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichioromethiazide, polythiazide, benzothlazide, ethacrynic acid, tricrynafen, chlorthalidone, furosenilde, musolimine, bumetanide, triamterene, amiloride, and spironolactone; thrombolytic agents, such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC); anti-diabetic agents, such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, and glipizide), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; growth hormone secretagogues; aP2 inhibitors; phosphodiesterase inhibitors, such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors

(e.g., sildenafil, tadalafil, vardenafil); protein tyrosine kinase inhibitors; antiinflammatories; antiproliferatives, such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil; chemotherapeutic agents; immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes); antimetabolites, such as folate antagonists, purine analogues, and pyridine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; microtubule-disruptor agents, such as ecteinascidins; microtubule-stabilizing 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

[00214] 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. In some embodiments, the kit or article of manufacture includes a container (such as a bottle) with a desired amount of at least one compound (or pharmaceutical composition of a compound) as disclosed herein.

[00215] 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.

[00216] 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.

[00217] Such a kit or article of manufacture can further include instructions for using said compound (or pharmaceutical composition of a compound) disclosed herein. In some embodiments, a set of instructions is included. In other embodiments, the instructions are attached to the container, or are included in a package (such as a box or a plastic or foil bag) holding the container.

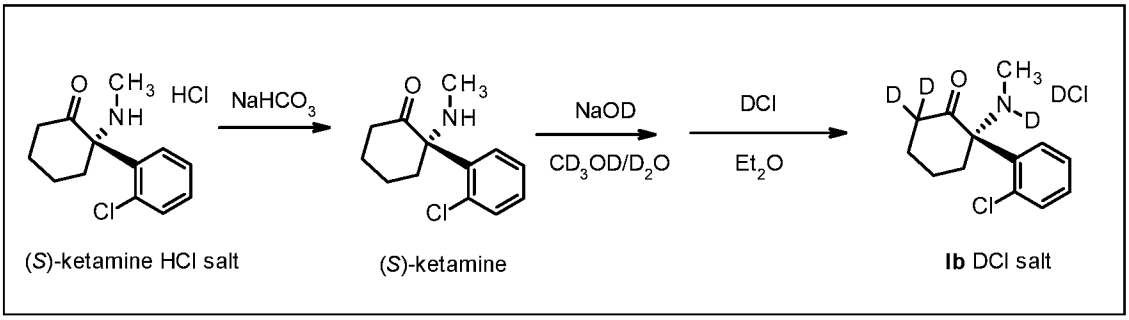
[00218] In another embodiment, the kit or article of manufacture is a tamper resistant kit or article of manufacture.

[00219] 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.

[00220] This invention will be better understood by reference to the Experimental section which follows, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Example 1: Synthesis of (2S)-2-(2-chlorophenyl)-6,6-dideuterio-2-[deuterio(methyl)amino]cyclohexanone, deuterium chloride(D2-(S)-ketamine DCl

[00221] A. Route 1



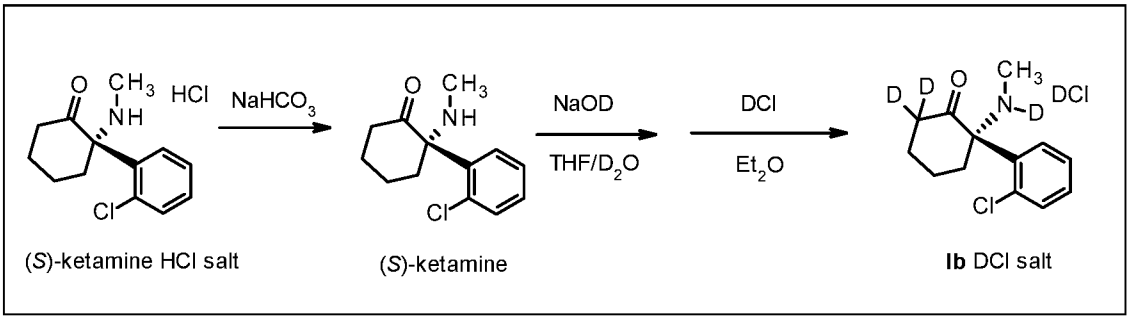
[00222] To a 500 mL single neck flask, equipped with a stirrer bar, thermocouple, and nitrogen line, was charged 4.9695 g (18.1 mmol) of (*S*)-(+)-ketamine HCl salt, 100 mL of ethyl acetate and 100 mL of $NaHCO_3$ saturated aqueous solution. The mixture was stirred for 10 minutes at room temperature before transferring into a separation funnel. After partition, the bottom aqueous layer was back-extracted with additional 100 mL of ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate. This was filtered, and the filtrate was concentrated to dryness, affording 4.2023 g (17.7 mmol) of (S)-ketamine as a white solid, representing a 97.8% yield in 99.4% purity.

[00223] A 25 mL sealed tube was charged with 0.25 g (1.05 mmol) of esketamine free amine (**2**), 2.5 mL of CD_3OD, 9 mL of D_2O and 1 mL of NaOD in D_2O (40 wt%). After capping the tube, the mixture was heated to 40 ^oC for 14-24 hours. The resultant mixture was extracted with 3×10 mL of ethyl acetate. The combined extractions were concentrated to dryness. The residue was re-subjected to the same reaction for additional two times, allowing the D-H exchange to be over 98% determined by ^1H NMR analysis. The residue was dissolved in 40 mL of anhydrous ethyl ether, filtered on a Buchner filter with a fine frit into a 250 mL three neck flask. The filter cake was washed with 10 mL of ethyl ether, the wash was combined with the filtrate. DCl gas was blown over the surface of the solution with stirring. The product precipitated, and the slurry was stirred at room temperature for 1 hour before filtering on a Buchner funnel. The filter cake was washed with 2×10 mL of ethyl ether, and dried under vacuum overnight at room temperature, affording 0.2017 g of d2-(*S*)-ketamine DCl salt (formula **Ib DCl salt**), representing a 69.6% yield in 100 A% chemical purity and > 99% ee. LC-MS analysis indicated the

deuterium incorporation was 96.0% D2, 2.7% D1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.57-1.64 (m, 1H), 1.84-1.91 (m, 2H), 2.02-2.04 (m, 1H), 2.47-2.57 (m, 1H), 2.58-2.60 (m, 3H), 3.57-3.58 (m, 1H), 7.46-7.48 (m, 2H), 7.50-7.57 (m, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 9.53 (brm, 1H), 10.71 (brm, 1H); HRMS-ESI (*m/z*): $[M+H]^+$ Calcd for $C_{13}H_{14}D2ClNO$: 240.1046; found 240.1126.

[00224] Changes in the metabolic properties of the compounds of Example 1 and its analogs as compared to its non-isotopically enriched analogs can be shown using the following assays. Other compounds listed above, which have not yet been made and/or tested, are predicted to have changed metabolic properties as shown by one or more of these assays as well.

[00225] B. Route 2



[00226] A 1000 ml, round bottom flask, equipped with a stir bar and nitrogen, was charged with 23.82 g (0.0915 mol, 1.0 eq) of (S)-ketamine HCl. The flask was charged with 450 mL (20V) of ethyl acetate, and 450 mL (20V) of a saturated sodium bicarbonate solution. The mixture was stirred for 15 minutes. The mixture was poured into a separatory funnel, and the layers were separated. The aqueous layer was washed with 450 mL of ethyl acetate. The organic layers were combined and dried over Na_2SO_4. The solution was filtered, and concentrated to dryness. Obtained was 20.05 g of (S)-ketamine, representing a 98% yield, and 100 A% purity.

[00227] A 500 mL round bottom flask, equipped with a stir bar, and nitrogen, was charged with 5.15 g (0.0216 mol, 1.0 eq) of (S)-ketamine and 25 ml (5V) of anhydrous THF, and stirred until all the solids went into solution. Then was added 100 mL (20 V) of deuterium oxide, and 20 mL (4V) of sodium deuterate. The reaction was heated at 65°C for 24 hours. The reaction was complete with 24 hours, and checked by taking an aliquot from the reaction, and running an NMR. The reaction was cooled to room temperature, the mixture was poured into a separatory funnel and extracted with ethyl acetate (3 X 100 mL). Concentrated the organic layer to dryness. Obtained 4.64 g of d2-(*S*)-ketamine free base with 89.2% yield.

[00228] A 250 mL, three neck round bottom flask equipped with a stir bar and nitrogen, was charged with 2.31 g (9.64 mmol, 1.0 eq) of D2-(*S*)-ketamine free base and 70 mL (30 V) of diethyl ether was added. The reaction was placed into an ice bath, and cooled to 0°C. DCl gas was added. A white precipitate started forming in the flask. The completion of the reaction was monitored by testing the pH of the reaction, an acidic reaction deemed the reaction complete. After the addition of DCl gas was complete, the ice bath was removed and the reaction was allowed to warm to room temperature, and stirred for 1 hour. After 1 hour, the reaction was filtered through a sintered funnel, and the solids were washed with 20 mL (10 V) of diethyl ether. The white solid was dried under vacuum with a canopy of nitrogen. Obtained was 2.44 g of alpha d2-(*S*)-ketamine DCl salt (formula **Ib DCl salt**) in a 90% yield, 100 A% purity, and 1.6% D1, 98.4% D2, 0.0% D3.

Example 2: *In vitro* Liver Microsomal Stability Assay

[00229] Liver microsomal stability was measured using 0.5 mg per mL of liver microsomal protein with a NADPH-generating system (1 mM NADPH, 5 mM glucose 6-phosphate and 1 unit per mL glucose 6-phosphate dehydrogenase) in potassium phosphate buffer (50 mM, pH 7.4) containing $MgCl_2$ (3 mM) and EDTA (1 mM, pH 7.4). Test articles were added for a final assay concentration of 1 μM and incubated at about 37°C. Reactions were started by addition of the cofactor, and were stopped at four designated time points (0, 15, 30 and 60 min) by the addition of an equal volume of stop reagent (*e.g.*, acetonitrile containing an internal standard, 0.2 mL). Samples were then centrifuged at 920 x g centrifugal force for 10 min at 10°C to precipitate the proteins. Supernatants were analysed by LC/MS/MS. It has thus been found that the compounds as disclosed herein according to the present disclosure that have been tested in this assay showed an increase of 10% or more in the degradation half-life, as compared to the non-isotopically enriched drug. The degradation half-lives of Example 1 were increased by 18%, as compared to non-isotopically enriched ketamine.

Example 3: Stability of alpha-d2-(R/S)-ketamine (Example 1 racemate) in phosphate-buffered saline at various pH levels

[00230] The stability of alpha-deuterium-substituted (d2) (R/S)-ketamine (Example 1 as a racemate) in phosphate-buffered saline at pH 2.0, 7.4 and 8.4 at 37 ± 1°C was evaluated.

Incubations of (d2) (R/S)-ketamine (*e.g.*, 1 μM) with PBS (pH 2.0, 7.4 and 8.4) were carried out using a Tecan Liquid Handling System (Tecan), or equivalent, at 37 ± 1°C in 0.2-mL incubation mixtures (final volume) containing PBS, at the final concentrations indicated in a 96-well plate format. The test article was added to the incubation mixtures in water. Reactions were started by addition of the test article, and stopped at four designated time points (*e.g.*, 0, 30, 60 and 120 min) by the addition of an equal volume of stop reagent (*e.g.*, acetonitrile, 0.2 mL containing an internal standard). Incubations were carried out in triplicate with an exception for zero-time samples (which were incubated in quadruplicate). The samples were centrifuged (*e.g.*, 920 x *g* for 10 min at 10°C) and the supernatant fractions analyzed by LC-MS/MS. Non-deuterated (d0) (R/S)-ketamine was used as an internal standard. The amount of unchanged test article and formation of non-deuterated (d0) (R/S)-ketamine was monitored based on peak area ratio of the analyte/internal standard.

[00231] Data are shown below in Table 1 and 2. The data for Table 1 are presented graphically in Figure 1.

[00232] Table 1: Incubations of d2-ketamine with phosphate-buffered saline

PBS pH	Mean percent remaining (0 min)	Mean percent remaining (30 min)	Mean percent remaining (60 min)	Mean percent remaining (120 min)
2.0	100%	94.6%	98.8%	93.9%
7.4	100%	98.3%	99.0%	96.0%
8.4	100%	96.4%	99.6%	95.1%

[00233] Table 2: Incubations of d2-ketamine with phosphate-buffered saline (analyte D0-ketamine)

PBS pH	Mean area ratio (0 min)	Mean area ratio (30 min)	Mean area ratio (60 min)	Mean area ratio (120 min)
2.0	NA	ND	ND	ND
7.4	NA	ND	ND	ND
8.4	NA	0.00367	ND	ND
Mean area ratio values were blank corrected to subtract the detection in zero-minute samples. NA Not applicable ND Not detected (value was zero or negative)				

Example 4: *In vitro* metabolism using human cytochrome P_{450} enzymes

[00234] 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 as disclosed herein, 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 5: Monoamine Oxidase A Inhibition and Oxidative Turnover

[00235] The procedure is carried out as described in Weyler, *Journal of Biological Chemistry* **1985**, *260*, 13199-13207. Monoamine oxidase A activity is measured spectrophotometrically by monitoring the increase in absorbance at 314 nm on oxidation of kynuramine with formation of 4-hydroxyquinoline. The measurements are carried out, at 30 °C, in 50mM NaP_i buffer, pH 7.2, containing 0.2% Triton X-100 (monoamine oxidase assay buffer), plus 1 mM kynuramine, and the desired amount of enzyme in 1 mL total volume.

Example 6: Monoamine Oxidase B Inhibition and Oxidative Turnover

[00236] The procedure is carried out as described in Uebelhack, *Pharmacopsychiatry* **1998**, *31*, 187-192.

Example 7: Inhibition of [^{3}H]TCP Binding to the Rat NMDA Receptor

[00237] The procedure is carried out as described in Goldman et al, *FEBS Letters* **1985**, *190*(2), 333-336.

Example 8: Rat Model for Hypoxia-Induced Neurodegeneration and NMDA-Antagonist Neuroprotection

[00238] The procedure is carried out as described in Reeker et al, *Canadian Journal of Anaesthesia* **2000**, *37*(6), 572-578.

Example 9: Determination of the *In Vitro* Metabolism of *S*-Ketamine and alpha d2 S-ketamine in Microsomes

[00239] A. Incubation Conditions

[00240] *S*-Ketamine and *alpha d2 S*-Ketamine (10 μM) were incubated with liver microsomes (2 mg/mL in 0.1 M potassium phosphate buffer containing 1 mM EDTA, assay buffer) for 0 and 15 minutes (rat) or 0 and 30 minutes (human) at 37°C. Incubations were initiated by the addition of nicotinamine adenine dinucleotide phosphate (NADPH, 1 mM) and terminated by the addition of methanol. Samples were vortex mixed, stored on ice, and the samples were centrifuged at 1400 × g for 5 minutes. Supernatants were removed from the microsome pellets and stored in new tubes at approximately -20°C until analysis. Metabolic controls were conducted by incubating *S*-ketamine (10 μM) in microsomes (2 mg/mL) in the absence of NADPH at 0 and 15 or 30 minutes, respectively, to determine the stability of the test article under the incubation conditions.

[00241] B. Characterization of Metabolites

[00242] Metabolites generated in microsome incubation samples were characterized by LC-MS/MS using a LTQ Orbitrap XL with electrospray ionization in positive ion mode. Semi-quantitation of the metabolites present in the samples was based on LC MS peak areas of the putative metabolites. The structural elucidation of metabolites of S-ketamine and the d2 S-

ketamine was accomplished through the use of standards (6-OH-norketamine, norketamine and dehydronorketamine), references to reported metabolites in the scientific literature (Turfus et al., 2009; Bijlsma et al., 2011), high resolution accurate mass spectrometry, interpretation of product ion spectra and comparison of chromatographic retention times among metabolites.

Table 3: % Peak Area after incubation of S-ketamine and d2 S-ketamine in rat and human liver microsomes

Component	Rat liver microsomes (15 min)		Human liver microsomes (30 min)	
	S-ketamine	d2 S-ketamine	S-ketamine	d2 S-ketamine
S-ketamine	4.6	2.6	31.2	33.6
6-OH-ketamine	0.8	ND	3.9	1.0
OH-ketamine	ND	0.1	ND	ND
OH-ketamine1	6.3	3.7	0.2	0.4
OH-ketamine2	ND	ND	ND	0.1
norketamine	35.1	75.9	59.8	60.8
6-OH-norketamine	40.7	7.1	1.6	0.7
OH-norketamine1	0.9	ND	ND	ND
OH-norketamine2	10.5	8.3	2.0	1.5
OH-norketamine3	ND	1.7	ND	0.4
dehydro-norketamine1	1.3	0.5	0.1	ND
dehydro-norketamine2	ND	0.1	ND	ND
phenol-ketamine1	ND	ND	0.2	0.1
phenol-ketamine2	ND	ND	0.9	1.1
phenol-norketamine	ND	ND	0.1	0.1

[00243] ND=Not detected or below the limit of quantitation (0.1% of the total chromatographic peak area)

[00244] [1] deuterated analog for incubations with d2S-ketamine

[00245] C. Results

[00246] In rat liver microsomal incubation, S-ketamine and its d2 analog were extensively metabolized, with approximately 5 and 3% of the parent compound remaining, respectively, after 15 minutes. In human liver microsomal incubation, catalytic rates were lower compared to rat liver microsomal incubations with approximately 31 and 34% of the parent compound remaining, respectively, after 30 minutes. The major metabolites formed from S-ketamine by rat liver microsomes were norketamine and 6-OH-norektamine with 35.1 and 40.7%, respectively. The deuteration at the 6-position in d2 S-ketamine resulted in a marked decrease in formation of

the 6-OH-norketamine analog indicating that the deuterium abstraction is the rate-limiting step for the 6-hydroxylation reaction. Alternate hydroxylation sites were not favored and therefore norketamine was the dominant metabolite in rat liver microsomal incubations of d2 S-ketamine with 75.9%.

[00247] In human liver microsomal incubations, norketamine was the dominant metabolite formed from both S-ketamine and d2 S-ketamine. Apparently, 6-OH-hydroxylation is a slow process in liver microsomal incubations and only small amounts were observed, although it is a major circulating metabolite in human in vivo. Because only small amounts of 6-OH-ketamine and 6-OH-norketamine were formed from S-ketamine under the test conditions, the impact of the deuteration at the 6-position was only marginally apparent in human liver microsomes.

[00248] **Example 10: Oral Single Dose PK Study in Rats**

[00249] A. Study design

[00250] Six male Sprague-Dawley rats per group received a single oral dose of S-ketamine or d2 S-ketamine at 15 or 60 mg/kg. The formulation was prepared in saline and animals received a dose volume of 5 mL/kg. Blood samples for the preparation of plasma were collected from 3 animals per group per time point at 10 min, 30 min, and 1, 2, 4, 7, 12, 24, and 30 hours postdose. Samples were analyzed for S-ketamine, norketamine, 6-OH-norketamine and dehydronorketamine with a LC/MS/MS method using reference standards. The respective metabolites from d2 S-ketamine were also quantified against the same standard curve prepared from the non-deuterated metabolites.

[00251] B. Results

[00252] After single oral administration of 15 or 60 mg/kg of S-ketamine or S-ketamine D2 to male SD rats, the plasma exposure to the parent compound was essentially unchanged (see FIGs. 2-4). The deuteration in the 6-position increased substantially the exposure to the deuterated norketamine analog while decreasing the exposure to the 6-OH-norketamine and dehydronorketamine analogues. The data are similar for the two dose levels tested. These results are consistent with the observations from the in vitro liver microsomal incubations in rats.

Table 4: PK Parameters for S-ketamine and d2 S-ketamine after single oral administration to rats

Dose	Analyte[1]	C_{max} (ng/mL)		AUC_{0-t} (ng*h/mL)	
		S-ketamine	d2-S-ketamine	S-ketamine	d2 S-ketamine
15 mg/kg	S-ketamine	200	136	183	114
	norketamine	965	1423	2180	5643
	6-OH-norketamine	1943	260	15924	2713
	dehydronorketamine	10	2	25	1
60 mg/kg	S-ketamine	165	163	312	268
	norketamine	1257	4247	5840	17301
	6-OH-norketamine	7140	1173	58707	9677
	dehydronorketamine	33	7	165	49

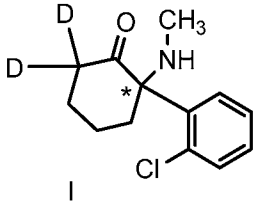
[1]deuterated analog following administration of d2 S-ketamine

[00253] C. Conclusion

[00254] It was shown that the deuteration at the 6-position slows down the metabolism of S-ketamine, resulting in higher norketamine levels while reducing the formation of 6-OH-norketamine and dehydronorketamine. In rats, in vitro and in vivo data align well. In vitro, turnover in human liver microsomes was slower than in rat, and little downstream metabolism was noted. Clinical data showed that, in vivo, in human, both 6-OH-norketamine and dehydronorketamine are major circulating metabolites. Therefore, d2 S-ketamine will increase the norketamine exposure and decrease the 6-OH-norketamine exposure, as well as dehydronorketamine exposure, as was observed in rats.

Aspects of the Disclosure

Aspect 1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



I

Aspect 2. The compound as recited in Aspect 1, wherein at least one position substituted with deuterium has deuterium enrichment of no less than about 98%.

Aspect 3. The compound as recited in Aspect 1, wherein at least one position substituted with deuterium has deuterium enrichment of no less than about 90%.

Aspect 4. The compound as recited in Aspect 1, wherein at least one position substituted with deuterium has deuterium enrichment of no less than about 50%.

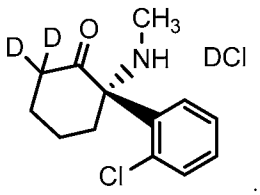
Aspect 5. The compound as recited in Aspect 1, wherein at least one position substituted with deuterium has deuterium enrichment of no less than about 10%.

Aspect 6. A compound of any one of Aspects 1-5, wherein the carbon marked with an asterisk has (R)-configuration.

Aspect 7. A compound of any one of Aspects 1-5, wherein the carbon marked with an asterisk has (S)-configuration.

Aspect 8. A compound of any one of Aspects 1 – 7, wherein the pharmaceutically acceptable salt is a DCl salt.

Aspect 9. The compound which is:



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Aspect 10. A method for the treatment, prevention, or amelioration of one or more symptoms of a disorder selected from the group consisting of Rett syndrome, depression, major depressive disorder, refractory depression, suicidality, treatment resistant depression, obsessive-compulsive disorder, fibromyalgia, post-traumatic stress syndrome, autism spectrum disorder, and depression associated with genetic disorders, in a subject comprising administering a therapeutically effective amount of a compound of any one of Aspects 1-8.

Aspect 11. A method for the treatment, prevention, or amelioration of one or more symptoms of a disorder selected from the group consisting of Rett syndrome, depression, major depressive disorder, refractory depression, suicidality, treatment resistant depression, obsessive-compulsive disorder, fibromyalgia, post-traumatic stress syndrome, autism spectrum disorder, and depression associated with genetic disorders, in a subject comprising administering a therapeutically effective amount of a compound of Aspect 10.

Aspect 12. The method as recited in Aspect 10 or Aspect 11, further comprising the administration of another therapeutic agent.

Aspect 13. The method as recited in Aspect 10 or Aspect 11, wherein said compound has at least one of the following properties:

a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;

b) increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and

e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

Aspect 14. The method as recited in Aspect 10 or Aspect 11, wherein said compound has at least two of the following properties:

a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;

b) increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and

e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

Aspect 15. The method as recited in Aspect 10 or Aspect 11, wherein the method affects a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed cytochrome P450 isoform in the subject, as compared to the corresponding non-isotopically enriched compound.

Aspect 16. The method as recited in Aspect 15, wherein the cytochrome P_{450} isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

Aspect 17. The method as recited in Aspect 10 or Aspect 11, 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.

Aspect 18. The method as recited in Aspect 17, 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.

Aspect 19. The method as recited in Aspect 10 or Aspect 11, 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.

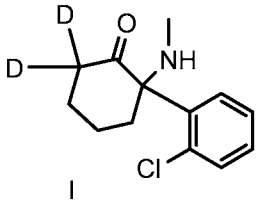
Aspect 20. The method as recited in Aspect 19, wherein the diagnostic hepatobiliary function endpoint is selected from the group consisting of alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline 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.

[00255] The examples set forth above are disclosed to give a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what the inventors regard as what is disclosed herein. Modifications that are obvious are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference. However, with respect to any similar or identical terms found in both the incorporated publications or references and those expressly put forth or defined in

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

What is claimed is:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



wherein:

D is deuterium; and

each deuterium has deuterium enrichment of no less than about 10%.

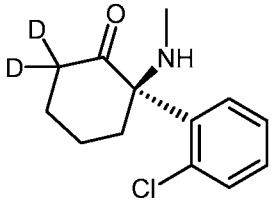
2. The compound of claim 1, wherein at least one deuterium has a deuterium enrichment of no less than about 20%.

3. The compound of any one of the preceding claims, wherein at least one deuterium has a deuterium enrichment of no less than about 50%.

4. The compound of any one of the preceding claims, wherein at least one deuterium has a deuterium enrichment of no less than about 90%.

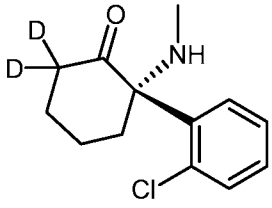
5. The compound of any one of the preceding claims, wherein at least deuterium has a deuterium enrichment of no less than about 98%.

6. The compound of any one of the preceding claims, that is:



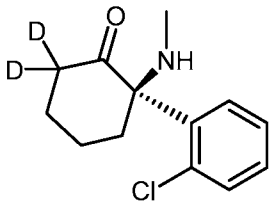
, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1 to 5, that is:



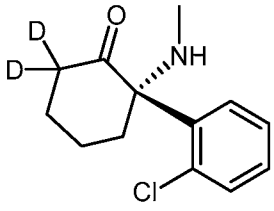
, or a pharmaceutically acceptable salt thereof.

8. The compound of any one of claims 1 to 5, that is a mixture of:



, or a pharmaceutically acceptable salt thereof

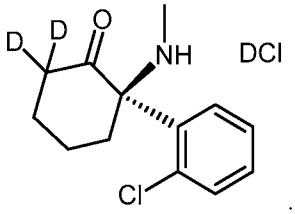
and



, or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1 to 8, wherein the pharmaceutically acceptable salt is a DCl salt or an HCl salt.

10. The compound of claim 6, that is:



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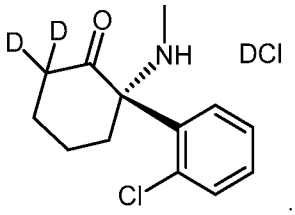
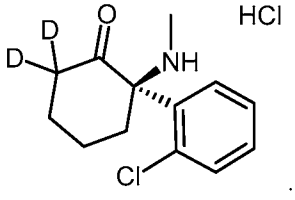
11. The compound of claim 7, that is:



.

12. The compound of claim 6, that is:



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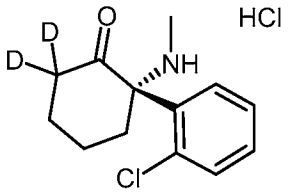
13. The compound of claim 7, that is:



14. A pharmaceutical composition, comprising the compound of any one of claims 1 to 13 and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim 14 which is formulated for oral, transdermal, intravenous, intranasal, or rectal administration.

16. The pharmaceutical composition of claim 14 or claim 15, which is formulated for oral administration.

17. The pharmaceutical composition of any one of claims 14 to 16, which is an oral abuse deterrent formulation.

18. A method for treating, preventing, or ameliorating one or more symptoms of a disorder in a subject, wherein the disorder is alcohol dependence, Alzheimer's disease, anxiety, asthma spectrum disorder, autism, bipolar disorder, Bulbar function depression, burn, diabetic neuropathy, dyskinesia, epilepsy, fibromyalgia, ischemic pain, inflammation, obsessive-compulsive disorder, pain, major depressive disorder, pain such as nociceptive pain or neuropathic pain, opioid tolerance, phantom limb, post-traumatic stress syndrome, pseudobulbar effect, Rett syndrome, refractory depression, schizophrenia, sepsis, stroke, suicidality, tinnitus, traumatic brain injury, treatment resistant depression, or depression associated with a genetic disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 13 or the pharmaceutical composition of any one of claims 14 to 17.

19. The method of claim 18, wherein said disorder is depression.

20. The method of claim 18 or claim 19, wherein said depression is major depressive disorder, refractory depression, treatment resistant depression, or depression associated with a genetic disorder.

21. The method of any one of claims 18 to 20, further comprising administering another therapeutic agent.

22. A compound of any one of claims 1 to 13, or a pharmaceutical composition of any one of claims 12 to 15, for use in treating, preventing, or ameliorating one or more symptoms of a disorder which is Rett syndrome, depression, suicidality, obsessive-compulsive disorder, fibromyalgia, post-traumatic stress syndrome, or autism spectrum disorder, in a subject in need thereof.

23. The compound of claim 22, wherein said disorder is depression.

24. The compound of claim 22 or claim 23, wherein said depression is major depressive disorder, refractory depression, treatment resistant depression, or depression associated with a genetic disorder.

25. The method of claims 18 to 21, wherein the method results in at least one of the following effects:

decreased inter-individual variation in plasma levels of norketamine or a metabolite thereof as compared to the non-isotopically enriched compound;

increased average plasma levels of norketamine per dosage unit thereof as compared to the non-isotopically enriched compound;

decreased average plasma levels of hydroxynorketamine per dosage unit thereof as compared to the non-isotopically enriched compound; or

an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

26. A method of decreasing the production of hydroxynorketamine in a subject to whom ketamine has been administered, comprising administering to the subject a compound of any one of claims 1 to 11 or a pharmaceutical composition of any one of claims 14 to 17.

27. A method of increasing the production of norketamine in a subject to whom ketamine has been administered, comprising administering to the subject a compound of any one of claims 1 to 11 or a pharmaceutical composition of any one of claims 14 to 17.

FIG. 1

Disappearance of d2-ketamine (1 μM) after incubations with phosphate-buffered saline

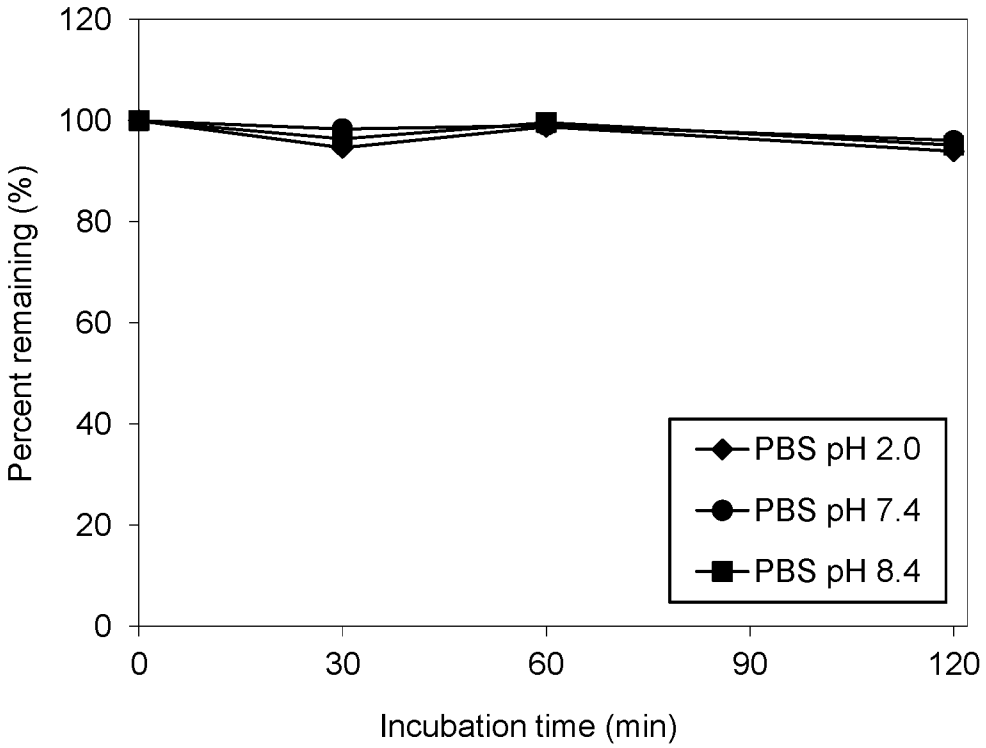


FIG. 2

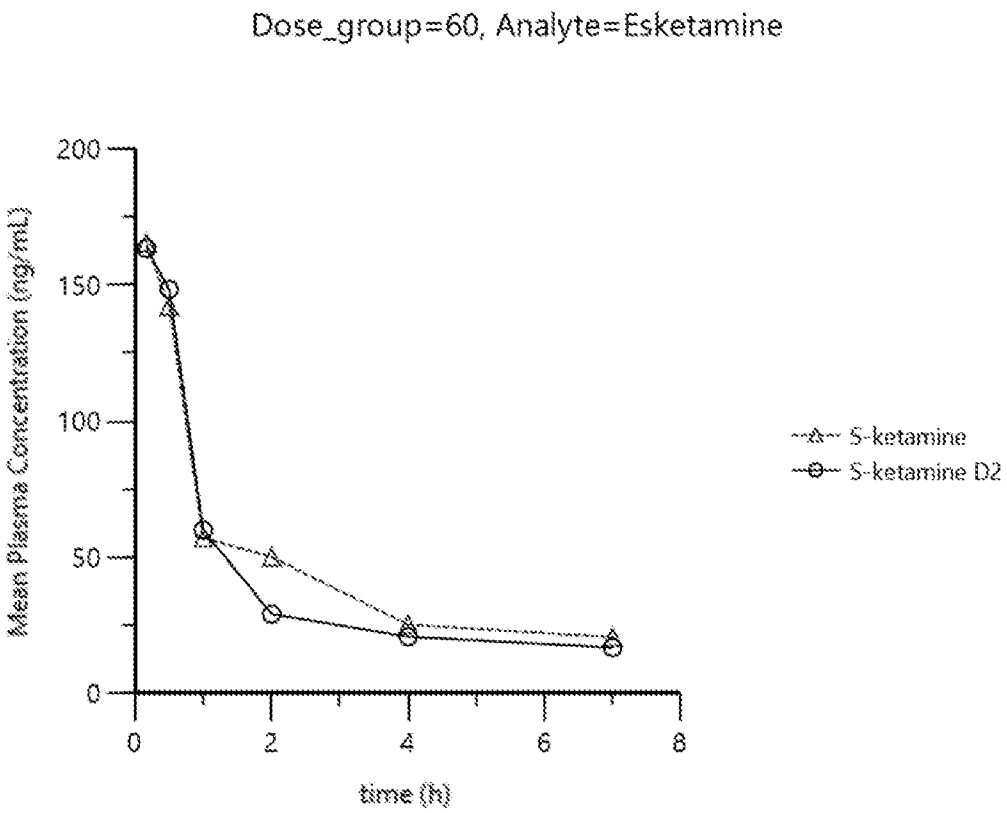

Dose_group=60, Analyte=Esketamine
Mean Plasma Concentration (ng/mL)
200
150
100
50
0
0
2
4
6
8
time (h)
S-ketamine
S-ketamine D2

FIG. 3

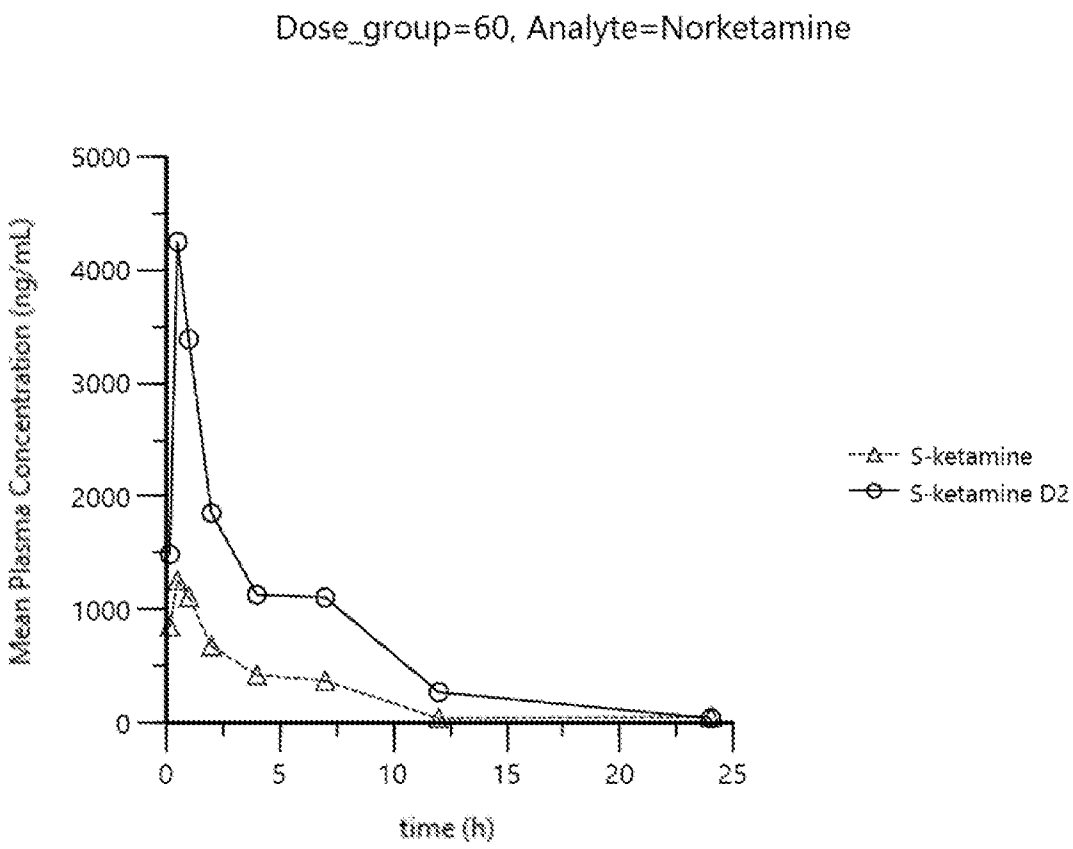
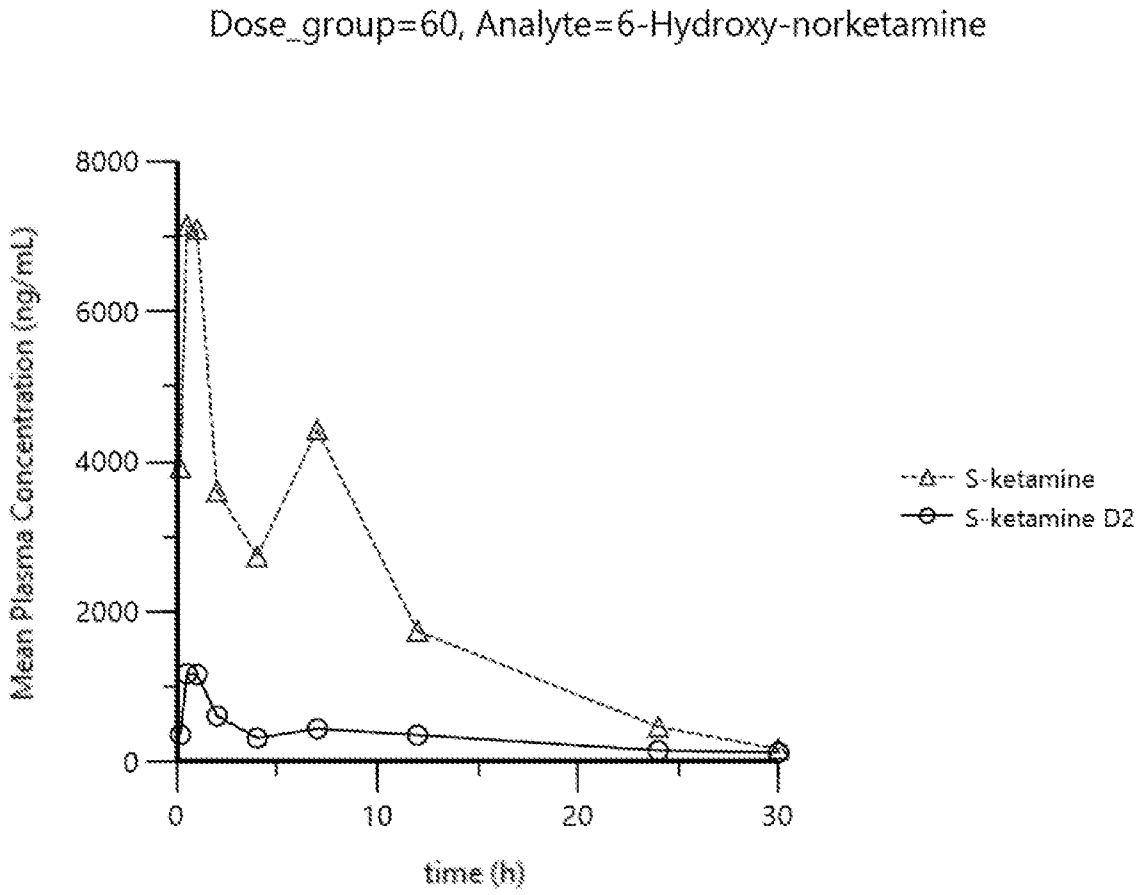

Dose_group=60, Analyte=Norketamine
Mean Plasma Concentration (ng/mL)
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
time (h)
S-ketamine
S-ketamine D2

FIG. 4


Dose_group=60, Analyte=6-Hydroxy-norketamine
Mean Plasma Concentration (ng/mL)
8000
6000
4000
2000
0
0
10
20
30
time (h)
S-ketamine
S-ketamine D2