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(71) Applicant: **ALEXANDER SHULGIN RESEARCH INSTITUTE, INC.** [US/US]; 1483 Shulgin Road, Lafayette, California 94549 (US).

(72) Inventor: **SZABO, Thomas** (deceased).

(72) Inventors: **MARTINI, Mark J.**; c/o Alexander Shulgin Research Institute, Inc., 1483 Shulgin Road, Lafayette, California 94549 (US). **COZZI, Nicholas V.**; 505 Saras Ct., Slinger, Wisconsin 53086 (US). **DALEY, Paul F.**; 4241 Harmon Rd., El Sobrante, California 94803 (US).

(74) Agent: **DWULET, Gregory et al.**; 78 Virgil Street, San Francisco, California 94110 (US).

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(54) Title: ASYMMETRIC PHENYLALKYLAMINES

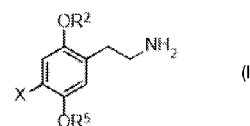
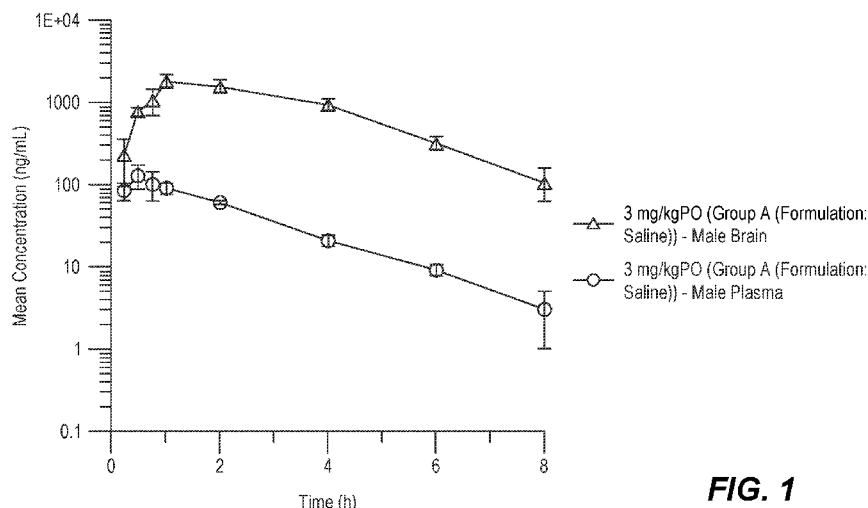


FIG. 1

(57) Abstract: Provided herein are substituted phenylalkylamine analogs, such as 2,5-dialkoxyphenethylamines that are asymmetrically substituted (e.g., wherein the 2-alkoxy and 5-alkoxy substituents are different). Also provided are methods of making such compounds, pharmaceutical compositions thereof, and methods of their use, such as in the treatment of mental health disorders, neurodegenerative conditions, pain disorders, and inflammation, including as part of psychedelic-assisted therapy.



ASYMMETRIC PHENYLALKYLAMINES

INVENTORS: Thomas Szabo, Mark J. Martini, Nicholas V. Cozzi, Paul F. Daley

CROSS-REFERENCE

[01] Priority is claimed under PCT Art. 8(1) and Rule 4.10 to U.S. Prov. App. No. 63/468,956, filed May 25, 2023, and fully incorporated by reference for all purposes.

TECHNICAL FIELD

[02] This disclosure relates in some aspects to substituted phenylalkylamine analogs, such as asymmetrically substituted phenethylamines. The disclosure also relates to methods of making such compounds, pharmaceutical compositions thereof, and methods of using the same.

BACKGROUND OF THE INVENTION

[03] Psychedelics have gained attention as potential therapeutic tools for various mental health conditions, such as depression, anxiety, PTSD, and addiction. Aside from remarkable subjective effects on consciousness, there is increasing interest in their physiological effects and their potential application in the treatment of physical and neurological disorders. While much progress has been made in recent years towards understanding the structure-activity relationships underlying the effects of classical psychedelics, many open questions remain concerning the efficacy of these compounds for the treatment of complex diseases that may lack effective treatments, such as depression and attention-deficit/hyperactivity disorder (ADHD). As such, there is an ongoing unmet need for novel alternative treatments, especially those which minimize side effects, increase access, and optimize efficacy. Provided herein are phenylalkylamine compounds to meet these needs and others, and that have such advantages and improvements as will become readily apparent through the disclosure below.

INCORPORATION BY REFERENCE

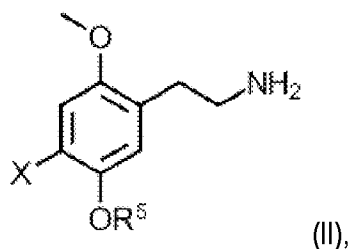
[04] Each cited patent, publication, and non-patent literature is incorporated by reference in its entirety, as if each was incorporated by reference individually, and as if each is fully set forth herein. However, no such citation should be construed as an admission that a cited reference is from an area that is analogous or directly applicable to the invention, nor should any citation be construed as an admission that a document or underlying information, in any jurisdiction, is prior art or part of the common general knowledge in the art.

BRIEF SUMMARY OF THE INVENTION

[05] The following is a simplified summary of some embodiments of the invention in order to provide a basic understanding thereof. This summary is not an extensive overview of the invention, nor intended to identify key or critical elements of the invention or to delineate its scope. Its sole purpose is to present some embodiments

and aspects of the invention in a simplified form as a prelude to the more detailed description that follows.

[06] In one aspect, provided is a compound of Formula (II):



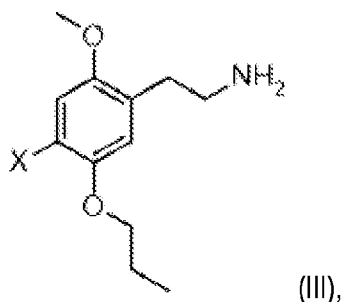
or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

X is Br, F, Cl, I, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkylthio; and

R⁵ is n-propyl, n-butyl, n-pentyl, n-hexyl, or C₃-C₆ alkenyl.

[07] In some embodiments, R⁵ is n-propyl, n-butyl, n-pentyl, or n-hexyl. In some embodiments, R⁵ is n-propyl.

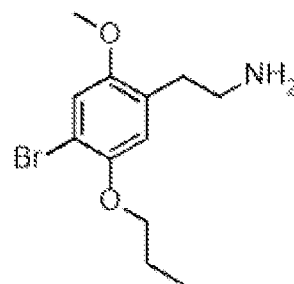
[08] In some embodiments, the compound has the structure of Formula (III):



or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein X is Br, F, Cl, I, or CF₃.

[09] In some embodiments, X is Br.

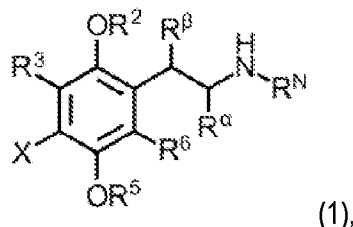
[10] In another aspect, provided is a compound selected from **TABLE 1**, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.



[11] In another aspect, provided is a compound having the structure: , or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.

[12] In another aspect, provided is a compound selected from **TABLE 2**, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.

[13] In another aspect, provided is a compound having the structure of Formula (1),



or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

R^a is H or C_1 - C_6 alkyl;

R^b is H, OH, or C_1 - C_6 alkoxy;

X is Br, F, Cl, I, C_1 - C_6 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, nitro, or amino; wherein each C_1 - C_6 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino is independently optionally substituted by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, $—OP(O)(OH)_2$, $—OC(O)H$, $—OSO_2OH$, or $—OC(O)NH_2$; and

one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylene-3- to 6-membered cycloalkyl, C_1 - C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1 - C_6 alkylene-aryl, or C_1 - C_6 alkylene-heteroaryl; and R^3 and R^6 are both H; or R^2 and R^3 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^5 is C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylene-3- to 6-membered cycloalkyl, C_1 - C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1 - C_6 alkylene-aryl, or C_1 - C_6 alkylene-heteroaryl; and R^6 is H; or

R^5 and R^6 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^2 is C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylene-3- to 6-membered cycloalkyl, C_1 - C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1 - C_6 alkylene-aryl, or C_1 - C_6 alkylene-heteroaryl; and R^3 is H.

[14] Also provided is a pharmaceutical composition comprising the compound of any of the disclosed embodiments, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[15] In some embodiments, the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration.

[16] In some embodiments, the composition is provided in unit dosage form.

[17] In some embodiments, the pharmaceutical composition comprises the compound in a total amount of between 1 and 200 mg, or between 5 and 100 mg.

[18] In some embodiments, the pharmaceutical composition comprises the compound in a total amount of between 10 and 75 mg, or between 20 and 50 mg.

[19] In some embodiments, the unit dosage form is an immediate release, controlled release, sustained release, extended release, or modified release formulation.

[20] In some embodiments, the pharmaceutical composition further comprises a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof. In some embodiments, the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins. In some embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, or alter pharmacokinetics or pharmacodynamics. In some embodiments, the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.

[21] Also provided is a method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the compound or composition of any of the disclosed embodiments.

[22] In some embodiments, the medical condition is a disorder linked to dysregulation or inadequate functioning of neurotransmission. In some embodiments, the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of monoaminergic neurotransmission. In some embodiments, the disorder linked to dysregulation or inadequate functioning of monoaminergic neurotransmission is that of serotonergic, dopaminergic, or noradrenergic neurotransmission.

[23] In some embodiments, the medical condition is a mental health disorder. In some embodiments, the

mental health disorder is selected from the group consisting of post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders, attachment disorders, and dissociative disorders. In some embodiments, depression is major depressive disorder (MDD) or treatment-resistant depression (TRD). In some embodiments, anxiety is generalized anxiety disorder (GAD). In some embodiments, the mental health disorder is PTSD. In some embodiments, the substance use disorder is alcohol use disorder (AUD), nicotine dependence or tobacco use disorder, opioid use disorder (OUD), stimulant use disorder, or sedative, hypnotic, or anxiolytic use disorder.

[24] In some embodiments, the medical condition is a neurodegenerative disorder, pain or a pain disorder, or inflammation or an inflammatory disorder.

[25] In some embodiments, the medical condition is an ischemic injury. In some embodiments, the ischemic injury is a stroke or an ischemia-reperfusion injury.

[26] In some embodiments, the compound or composition is administered together with one or more sessions of psychotherapy or psychological support.

[27] Also provided is a method of modulating neurotransmission in a subject, comprising administering to the subject a therapeutically effective amount of the compound or composition of the disclosed embodiments. In some embodiments, modulating neurotransmission comprises activating a monoamine neurotransmitter receptor and/or modulating the uptake activity of a monoamine transporter. In some embodiments, the monoamine neurotransmitter receptor is any of a serotonin receptor, a dopamine receptor, and a norepinephrine receptor. In some embodiments, the serotonin receptor is the 5-HT_{2A} receptor. In some embodiments, the monoamine transporter is a serotonin transporter (SERT).

[28] Also provided is the use of the compound or composition of any of the disclosed embodiments for the manufacture of a medicament for the treatment of a medical condition.

[29] Also provided is the compound or composition of any of the disclosed embodiments, for use in treating a medical condition.

[30] The foregoing has outlined broadly and in summary certain pertinent features of the disclosure so that the detailed description of the invention that follows may be better understood, and so that the present contribution to the art can be more fully appreciated. Hence, this summary is to be considered as a brief and

general synopsis of only some of the objects and embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the claims are lawfully entitled. Additional features of the invention are described hereinafter. It should be appreciated by those in the art that all disclosed specific compositions and methods are only exemplary, and may be readily utilized as a basis for modifying or designing other compositions and methods for carrying out the same purposes. Such equivalent compositions and methods will be appreciated to be also within the scope and spirit of the invention as set forth in the claims. The headings in this document are utilized only to expedite its review by a reader and must not be construed as limiting the invention in any manner.

BRIEF SUMMARY OF THE DRAWINGS

[31] To further clarify various aspects of the invention, a more particular description thereof will be rendered by reference to certain exemplary embodiments thereof which are illustrated in the figures. It will be understood and appreciated that the figures depict only illustrated embodiments of the invention and are not to be considered limiting of its scope. They are simply provided as exemplary illustrations of some embodiments of the invention. Certain aspects of the invention are therefore further described and explained with additional specificity and detail, but still by way of example only, with reference to the following accompanying figures.

[32] **FIG. 1** shows mean concentration (ng/mL) of **ASR2001** vs. time in C57BL/6 mouse brain and plasma.

[33] **FIG. 2** shows (3 mg/kg) predicted and observed mean concentrations (ng/mL) of **ASR2001** vs. time in C57BL/6 mouse plasma. $Rsq = 0.9982$; $Rsq_adjusted = 0.9978$; Half-life = 1.4423; 6 points used in calculation.

[34] **FIG. 3** shows (3 mg/kg) predicted and observed mean concentrations (ng/mL) of **ASR2001** vs. time in C57BL/6 mouse brain. $Rsq = 1.0$; $Rsq_adjusted = 1.0$; Half-life = 1.2882; 3 points used in calculation.

[35] **FIG. 4** shows mean concentration (ng/mL) of psilocin vs. time in C57BL/6 mouse brain and plasma.

[36] **FIG. 5** shows predicted and observed mean concentrations (ng/mL) of psilocin vs. time in C57BL/6 mouse plasma. $Rsq = 0.8687$; $Rsq_adjusted = 0.8425$; Half-life = 1.6977; 7 points used in calculation.

[37] **FIG. 6** shows predicted and observed mean concentrations (ng/mL) of psilocin vs. time in C57BL/6 mouse brain. $Rsq = 0.9592$; $Rsq_adjusted = 0.9184$; Half-life = 4.4741; 3 points used in calculation.

[38] **FIG. 7** shows mean receptor occupancy of **ASR2001** at mouse frontal cortex 5-HT_{2A} receptors at 15, 30, 45, 60, 120, 360, and 480 minutes post dosing determined by inhibition of 0.071 nM [³H]Cimbi-56 binding. Results are expressed as adjusted mean receptor occupancy as a percentage of control taken as 0% (n=3-4). For statistical analyses data were square root transformed and analyzed by robust regression followed by Dunnett's test to compare each timepoint to the naïve group. *p<0.05.

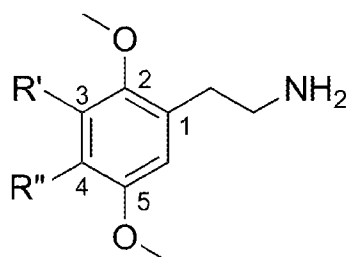
[39] **FIG. 8** shows mean specific binding (% of control) of **ASR2001** at mouse frontal cortex 5-HT_{2A}

receptors at 15, 30, 45, 60, 120, 360, and 480 minutes post dosing determined by inhibition of 0.071 nM [3 H]Cimbi-56 binding determined by inhibition of 0.071 nM [3 H]Cimbi-56 binding. Results are expressed as adjusted mean receptor occupancy as a percentage of control taken as 0% (n=3-4). For statistical analyses data were square root transformed and analyzed by robust regression followed by Dunnett's test to compare each timepoint to the naïve group. *p<0.05.

[40] **FIG. 9** shows mean specific binding (disintegrations per minute) of **ASR2001** at mouse frontal cortex 5-HT_{2A} receptors at 15, 30, 45, 60, 120, 360, and 480 minutes post dosing. Results are expressed as adjusted means + SEM (n=3-4). For statistical analyses data were square root transformed and analyzed by robust regression followed by Dunnett's test to compare each timepoint to the naïve group. *p<0.05.

DETAILED DESCRIPTION OF THE INVENTION

[41] The phenethylamine pharmacophore is one of the most well-known chemical scaffolds found in bioactive molecules, including as neurotransmitters (e.g., dopamine) and psychoactive drugs (e.g., the empathogen 3,4-methylenedioxymethamphetamine, also known as MDMA). Among the phenethylamines, the class known as the "2C" or "2C-X" compounds are well-known ring-substituted phenethylamines that have 2,5-dimethoxy substitution on the core phenyl ring, and commonly an additional substituent at the 4 position (i.e., R" below):



[42] Some 2C compounds have effects that are similar to those of empathogens (e.g., MDMA), while others produce effects similar to those of classic psychedelics (e.g., LSD, psilocybin). Although some 2C compounds are generally well-tolerated within certain dose ranges, adverse effects have been reported, and many 2C compounds are known to be generally associated with heavy "body load" and gastrointestinal effects (see, e.g., Dean et al., J Med Toxicol, 2013; 9(2), 172–178).

[43] While there has been a resurgence of interest in the therapeutic application of psychedelics, including 2C compounds, in treating a variety of medical diseases and disorders, there is also a need for novel compounds that have limited or no hallucinogenic or psychedelic effects. For example, certain individuals may be contraindicated for traditional psychedelics due to a personal or family history of psychotic disorders (Reiff et al. Am. J. Psychiatry 2020, 177(5), 391-410). These conditions are characterized by alterations in perception, thinking, and cognition, and the hallucinogenic effects of psychedelics could potentially exacerbate or trigger

these symptoms. Developing compounds with therapeutic properties but without hallucinogenic effects (or with reduced hallucinogenic effects) is crucial for providing safe and effective treatment options for individuals who may be vulnerable to adverse psychiatric reactions. Moreover, chronic or daily administration of psychedelics for conditions such as depression may not be feasible or practical due to the potential for tolerance and the extended duration of psychedelic experiences. Daily dosing with compounds that produce strong hallucinogenic effects could be disruptive to daily functioning and could pose challenges for individuals seeking to integrate treatment into their daily lives. For these and other reasons, developing less-hallucinogenic alternatives could provide a more sustainable approach for long-term treatment, enhancing adherence and optimizing therapeutic outcomes.

[44] Provided herein are asymmetrically substituted phenylalkylamines. Also provided are methods of making the disclosed compounds, such as by chemical synthesis. Additionally provided are compositions, such as pharmaceutical compositions, comprising the disclosed compounds. Further provided are kits containing such compositions with instructions for use. In other aspects, provided are methods of using the disclosed compounds and compositions thereof, such as in the treatment of a mental health disorder or other medical condition.

[45] While various aspects and features of certain embodiments are summarized above, the following detailed description illustrates several exemplary embodiments in further detail to enable one of skill in the art to practice such embodiments, and to make and use the full scope of the invention claimed. The described examples are provided for illustrative purposes and are not intended to limit the scope of the invention or its applications. It will be understood that many modifications, substitutions, changes, and variations in the described examples, embodiments, applications, and details of the invention illustrated herein can be made by those in the art without departing from the spirit of the invention, or the scope of the invention as described in the claims. It also will be appreciated that the headings within this document are being utilized only to expedite its review by a reader. They should not be construed as limiting the invention in any manner.

[46] The scope of the invention includes all embodiments and formulations thereof, not only those expressly described below, and it will be understood that many modifications, substitutions, changes, and variations in the described embodiments, applications, and details of the invention illustrated herein can be made by those in the art without departing from the spirit of the invention, or the scope of the invention as set forth in the claims.

A. General Definitions and Terms

[47] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an active agent” includes reference to a combination of two or more active agents, and reference to “an excipient” includes

reference to a combination of two or more excipients. While the term “one or more” may be used, its absence (or its replacement by the singular) does not signify the singular only, but simply underscores the possibility of multiple agents or ingredients in particular embodiments.

[48] The terms “comprising,” “including,” “such as,” and “having” are inclusive and not exclusive (i.e., there may be other elements in addition to the recited elements). Thus, the term “including” means, and is used interchangeably with, the phrase “including but not limited to.” The term “or” means, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise.

[49] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term “about,” even where not so stated explicitly. In alternative embodiments, such numbers will be understood as not being modified by the term “about.” In some embodiments (equivalently, and as shorthand, “in embodiments”), the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In embodiments, “about” may refer to plus or minus five percent ($\pm 5\%$) of the recited unit of measure. In other embodiments, “about” may refer to plus or minus ten percent ($\pm 10\%$) of the recited unit of measure. Where “about” is used to modify one number in a series or range, it is understood to modify all numbers in the series or range, including, for a range, both the upper and lower bounds of the range; thus, the term “about 1, 2, or 3” is understood to mean “about 1, about 2, or about 3” and the term “about 1 to 10” means “about 1 to about 10.”

[50] The term “substantially,” where it is applied to modify a feature or limitation herein, will be read in the context of the invention and in light of the knowledge in the art to provide the appropriate certainty, e.g., by using a standard that is recognized in the art for measuring the meaning of “substantially” as a term of degree, or by ascertaining the scope as would one of skill in the art.

[51] In some embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[52] A comprehensive list of the abbreviations utilized by organic chemists of skill appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations; the current list as of the date of this filing is incorporated by reference as if fully set forth

herein.

[53] Unless defined otherwise, all technical and scientific terms herein have the meaning as commonly understood by one having ordinary skill in the art to which this invention belongs, who as a shorthand may be referred to simply as “one of skill.” Further definitions that may assist the reader in understanding the disclosed embodiments are as follows; however, it will be appreciated that such definitions are not intended to limit the scope of the invention, which shall be properly interpreted and understood by reference to the full specification (as well as any plain meaning known to one of skill) in view of the language used in the claims. The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[54] Generally, the nomenclature used and procedures performed herein are those known in fields relating to one or more aspects of the invention, e.g., biology, pharmacology, neuroscience, organic chemistry, synthetic chemistry, and/or medicinal chemistry, and that are well known and commonly employed in such fields. Standard techniques and procedures are those generally performed according to conventional methods in the art.

[55] “Alkyl” will be understood to include straight-chain or branched radicals having any degree or level of saturation, i.e., groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions “alkanyl,” “alkenyl,” and “alkynyl” can also be used. In some embodiments, an alkyl group comprises from 1-10 carbon atoms, from 1-6 carbon atoms, from 1-4 carbon atoms, or from 1-3 carbon atoms (inclusive). For any alkyl, the alkyl may be optionally substituted at one or more positions by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, cycloalkyl, heterocycloalkyl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, —OP(O)(OH)₂, —OC(O)H, —OSO₂OH, —OC(O)NH₂, or —SONH₂.

[56] “Alkanyl” refers to saturated straight-chain, branched, or cyclic alkyl radicals derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), and cyclopropan-1-yl; butanyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), and cyclobutan-1-yl; etc.

[57] “Alkenyl” refers to an unsaturated straight-chain, branched, or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the cis or trans conformation about the double bond(s). Typical alkenyl groups include ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl),

prop-2-en-2-yl, cycloprop-1-en-1-yl, and cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, and cyclobuta-1,3-dien-1-yl; and the like.

[58] “Alkynyl” refers to an unsaturated straight-chain, branched, or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include ethynyl; propynyls such as prop-1-yn-1-yl, and prop-2-yn-1-yl; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, and but-3-yn-1-yl; and the like.

[59] “Aryl” refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen (H) atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like. In some embodiments, an aryl group comprises from 6-20 carbon atoms, or from 6-12 carbon atoms.

[60] “Amino” refers to —NR_2 , wherein each R is independently H, OH, or $\text{C}_1\text{—C}_6$ alkyl, wherein the $\text{C}_1\text{—C}_6$ alkyl is optionally substituted. An amino group can be a primary amino group (—NH_2), a secondary amino group (—NHR), a tertiary amino group (—NR_2), or a quaternary amino group (—NR_3^+), wherein R is independently H or $\text{C}_1\text{—C}_6$ alkyl, wherein the $\text{C}_1\text{—C}_6$ alkyl is optionally substituted.

[61] “Cycloalkyl” refers to a saturated monocyclic, bicyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as from 3 to 6 carbon atoms, 4 to 6 carbon atoms, 5 to 6 carbon atoms, 3 to 8 carbon atoms, 4 to 8 carbon atoms, 5 to 8 carbon atoms, 6 to 8 carbon atoms, 7 to 8 carbon atoms, 3 to 9 carbon atoms, 4 to 9 carbon atoms, 5 to 9 carbon atoms, 6 to 9 carbon atoms, 7 to 9 carbon atoms, 8 to 9 carbon atoms, 3 to 10 carbon atoms, 4 to 10 carbon atoms, 5 to 10 carbon atoms, 6 to 10 carbon atoms, 7 to 10 carbon atoms, 8 to 10 carbon atoms, 9 to 10 carbon atoms, 3 to 11 carbon atoms, 4 to 11 carbon atoms, 5 to 11 carbon atoms, 6 to 11 carbon atoms, 7 to 11 carbon atoms, 8 to 11 carbon atoms, 9 to 11 carbon atoms, 10 to 11 carbon atoms, 3 to 12 carbon atoms, 4 to 12 carbon atoms, 5 to 12 carbon atoms, 6 to 12 carbon atoms, 7 to 12 carbon atoms, 8 to 12 carbon atoms, 9 to 12 carbon atoms, 10 to 12 carbon atoms, and 11 to 12 carbon atoms (all inclusive). Monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Bicyclic compounds include spirocyclic compounds, fused bicyclic compounds and bridged bicyclic compounds. Bicyclic and polycyclic cycloalkyl rings include, for example, norbornane,

bicyclooctane, decahydronaphthalene and adamantane. When cycloalkyl is a monocyclic C₃₋₈ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. When cycloalkyl is a monocyclic C₃₋₆ cycloalkyl, exemplary groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl groups can be substituted or unsubstituted.

[62] "Cycloalkenyl" refers to a mono- or multi-cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring. However, if there is more than one double bond, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. Cycloalkenyl can include any number of carbons, such as from 3 to 6 carbon atoms, 4 to 6 carbon atoms, 5 to 6 carbon atoms, 3 to 8 carbon atoms, 4 to 8 carbon atoms, 5 to 8 carbon atoms, 6 to 8 carbon atoms, 7 to 8 carbon atoms, 3 to 9 carbon atoms, 4 to 9 carbon atoms, 5 to 9 carbon atoms, 6 to 9 carbon atoms, 7 to 9 carbon atoms, 8 to 9 carbon atoms, 3 to 10 carbon atoms, 4 to 10 carbon atoms, 5 to 10 carbon atoms, 6 to 10 carbon atoms, 7 to 10 carbon atoms, 8 to 10 carbon atoms, 9 to 10 carbon atoms, 3 to 11 carbon atoms, 4 to 11 carbon atoms, 5 to 11 carbon atoms, 6 to 11 carbon atoms, 7 to 11 carbon atoms, 8 to 11 carbon atoms, 9 to 11 carbon atoms, 10 to 11 carbon atoms, 3 to 12 carbon atoms, 4 to 12 carbon atoms, 5 to 12 carbon atoms, 6 to 12 carbon atoms, 7 to 12 carbon atoms, 8 to 12 carbon atoms, 9 to 12 carbon atoms, 10 to 12 carbon atoms, and 11 to 12 carbon atoms (all inclusive). Representative cycloalkenyl groups include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. A cycloalkenyl group may be unsubstituted or substituted.

[63] "Halogen" refers to fluorine, chlorine, bromine, and iodine.

[64] "Heterocycloalkyl" and "heterocyclyl" both refer to a cycloalkyl as defined above, having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Heterocycloalkyl and heterocyclyl include bicyclic compounds which include a heteroatom. Bicyclic compounds includes spirocyclic compounds, fused bicyclic compounds, and bridged bicyclic compounds. The heteroatoms can also be oxidized, such as, but not limited to, —S(O)— and —S(O)₂—. Heterocycloalkyl groups can include any number of ring atoms, such as from 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4 (all inclusive). The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine,

dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. Heterocycloalkyl groups can be unsubstituted or substituted. For example, heterocycloalkyl groups can be substituted with C₁₋₆ alkyl or oxo (=O), among many others.

[65] “Heterocycloalkenyl” refers to cycloalkenyl as defined above, having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. The heteroatoms can also be oxidized, such as, but not limited to, —S(O)— and —S(O)₂—. Heterocycloalkenyl groups can include any number of ring atoms, such as from 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkenyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4 (all inclusive). Exemplary heterocycloalkenyl groups include dihydrofuran, dihydropyran, dihydropyridine, tetrahydropyridine, dihydrothiazole, and dihydrothiophene.

[66] “Heteroaryl” refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Heteroaryl groups can include any number of ring atoms, such as from 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

[67] “Alkoxy” refers to the formula —OR, wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, or heterocyclyl, as defined herein. A non-limiting list of alkoxy groups are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzyloxy. An alkoxy may be substituted or unsubstituted.

[68] “Acy” refers to a hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, or heterocyclyl, connected via a carbonyl group as a substituent. Examples include formyl, acetyl, propanoyl,

benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[01] Deuterium (^2H or D), also called “heavy hydrogen,” is a stable isotope of hydrogen (^1H) with a natural abundance in the Earth’s oceans of approximately one atom per 6,500 of hydrogen (~154 ppm). Deuterium thus accounts for approximately 0.0154% (alternately, on a mass basis, 0.0308%) of all naturally occurring hydrogen in the oceans. “Non-substituted,” “non-deuterated,” and “undeuterated” may refer to compounds having no greater than the amount of deuterium expected as a percentage of naturally occurring hydrogen in a compound.

[01] “Deuteroalkyl” will be understood to include any alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a deuterium (i.e., ^2H , or D). Where an alkyl radical is substituted by more than one deuterium, it may be referred to using a prefix corresponding to the number of deuterium substitutions. For example, trideuteroalkyl refers to an alkyl in which three hydrogens have been replaced by deuteriums. A deuteroalkyl can be fully deuterated (i.e., all of the hydrogens have been replaced by deuteriums) or partially deuterated (i.e., only some of the hydrogens have been replaced by deuteriums). For example, a deuteromethyl (i.e., a C_1 deuteroalkyl) group refers to $-\text{CH}_2\text{D}$, $-\text{CHD}_2$, or $-\text{CD}_3$. A deuteroethyl (i.e., a C_2 deuteroalkyl) group refers to $-\text{CH}_2\text{CH}_2\text{D}$, $-\text{CHDCH}_2\text{D}$, $-\text{CD}_2\text{CH}_2\text{D}$, $-\text{CH}_2\text{CHD}_2$, $-\text{CHDCHD}_2$, $-\text{CD}_2\text{CHD}_2$, $-\text{CH}_2\text{CD}_3$, $-\text{CHDCD}_3$, or $-\text{CD}_2\text{CD}_3$. A deuteropropyl group (i.e., a C_3 deuteroalkyl) refers to any partially or fully substituted *n*-propyl or isopropyl group.

[69] “Haloalkyl” will be understood to include any alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen (e.g., a fluorine, a chlorine, a bromine, or an iodine). Where an alkyl radical is substituted by more than one halogen, it may be referred to using a prefix corresponding to the number of halogen substitutions. For example, dihaloalkyl refers to an alkyl substituted by two halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl groups include difluoromethyl ($-\text{CHF}_2$), bromofluoromethyl ($-\text{CHBrF}$), trifluoromethyl ($-\text{CF}_3$), and 2-fluoroethyl ($-\text{CH}_2\text{CH}_2\text{F}$). Additional examples of haloalkyl groups include $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}(\text{CH}_3)(\text{CF}_3)$, $-\text{CH}(\text{CH}_3)(\text{CHF}_2)$, and $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{F})$.

[70] “Hydroxyalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include, for example, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[71] “Haloalkoxy” refers to an $-\text{O}$ -alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). The halogens may be the same or different in each instance. Such groups include chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[72] "Alkylthio" refers to the formula —SR , wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, or heterocyclyl, as defined herein. A non-limiting list of alkylthio are methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, phenylthio, and benzylthio. An alkylthio may be substituted or unsubstituted.

[73] "Sulfenyl" refers to an —SR group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. A sulfenyl may be substituted or unsubstituted.

[74] "Sulfinyl" refers to an —S(=O)—R group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[75] "Sulfonyl" refers to an $\text{—SO}_2\text{R}$ group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[76] "O-carboxy" refers to a —RC(=O)O— group in which R can be H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[77] "Ester" and "C-carboxy" refer to a —C(=O)OR group in which R can be the same as defined with respect to O-carboxy. Ester and C-carboxy groups may be substituted or unsubstituted.

[78] "Thiocarbonyl" refers to a —C(=S)R group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[79] "Trihalomethanesulfonyl" refers to an $\text{X}_3\text{CSO}_2\text{—}$ group wherein each X is a halogen.

[80] "Trihalomethanesulfonamido" refers to an $\text{X}_3\text{CS(O)}_2\text{N(R}_A\text{)—}$ group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein.

[81] "S-sulfonamido" refers to a $\text{—SO}_2\text{N(R}_A\text{R}_B\text{)}$ group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An S-sulfonamido may be substituted or unsubstituted.

[82] "N-sulfonamido" refers to a $\text{RSO}_2\text{N(R}_A\text{)—}$ group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An N-sulfonamido may be substituted or unsubstituted.

[83] "Oxo" refers to =O .

[84] "O-carbamyl" refers to a $\text{—OC(=O)N(R}_A\text{R}_B\text{)}$ group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An O-carbamyl may be substituted or unsubstituted.

[85] "N-carbamyl" refers to an $\text{ROC(=O)N(R}_A\text{)—}$ group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An N-carbamyl may be substituted or unsubstituted.

[86] "O-thiocarbamyl" refers to a $\text{—OC(=S)—N(R}_A\text{R}_B\text{)}$ group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An O-thiocarbamyl may be substituted or unsubstituted.

[87] "N-thiocarbamyl" refers to an $\text{ROC(=S)N(R}_A\text{)—}$ group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An N-thiocarbamyl may be substituted or unsubstituted.

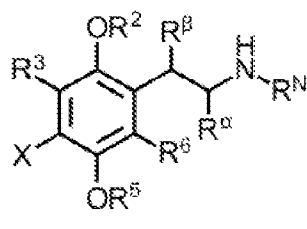
[88] "C-amido" group refers to a $\text{—C(=O)N(R}_A\text{R}_B\text{)}$ group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. A C-amido may be substituted or unsubstituted.

[89] "N-amido" refers to a $\text{RC(=O)N(R}_A\text{)—}$ group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, or heterocyclyl, as defined herein. An N-amido may be substituted or unsubstituted.

[90] "Optionally substituted" unless otherwise specified means that a group may be unsubstituted, or substituted by one or more of the substituents listed for that group. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more of the indicated substituents. When there are more than one substituents, the substituents may be the same or different. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. If no substituents are indicated for an "optionally substituted" or "substituted" group, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, oxo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group, a di-substituted amino group, and a tri-substituted amino group.

B. Compounds

[91] In a first aspect, provided is a compound of Formula (1):



or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

R^{α} is H or C_1-C_6 alkyl;

R^{β} is H, OH, or C_1-C_6 alkoxy;

X is Br, F, Cl, I, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, nitro, or amino;

wherein each C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino is independently optionally substituted by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, $—OP(O)(OH)_2$, $—OC(O)H$, $—OSO_2OH$, or $—OC(O)NH_2$; and

one of R^2 and R^5 is methyl, and the other is C_3-C_6 alkyl, C_3-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkylene-3- to 6-membered cycloalkyl, C_1-C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; and R^3 and R^6 are both H; or

R^2 and R^3 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^5 is C_3-C_6 alkyl, C_3-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-3- to 6-membered cycloalkyl, C_1-C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; and R^6 is H; or

R^5 and R^6 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^2 is C_3-C_6 alkyl, C_3-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-3- to 6-membered cycloalkyl, C_1-C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; and R^3 is H.

[92] In some embodiments of Formula (1), R^{α} is H or C_1-C_6 alkyl. In some embodiments, R^{α} is H. In some embodiments, R^{α} is C_1-C_6 alkyl. In some embodiments, R^{α} is methyl. In some embodiments, R^{α} is ethyl.

[93] In some embodiments of Formula (1), R^{β} is H, OH, or C_1-C_6 alkoxy. In some embodiments, R^{β} is H. In some embodiments, R^{β} is OH. In some embodiments, R^{β} is C_1-C_6 alkoxy. In some embodiments, R^{β} is methoxy.

[94] In some embodiments of Formula (1), X is H, Br, F, Cl, I, C₁-C₆ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, nitro, or amino; wherein each C₁-C₆ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino is independently optionally substituted by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, —OP(O)(OH)₂, —OC(O)H, —OSO₂OH, or —OC(O)NH₂. In some embodiments, X is H. In some embodiments, X is halogen (i.e., F, Cl, Br, I). In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C₁-C₆ alkyl. In some embodiments, X is methyl (—CH₃). In some embodiments, X is ethyl (—CH₂CH₃). In some embodiments, X is C₂-C₈ alkenyl. In some embodiments, X is C₂-C₈ alkynyl. In some embodiments, X is C₁-C₆ alkoxy. In some embodiments, X is methoxy. In some embodiments, X is ethoxy. In some embodiments, X is propoxy. In some embodiments, X is isopropoxy. In some embodiments, X is C₁-C₆ alkylthio. In some embodiments, X is —SCH₃. In some embodiments, X is —SCH₂CH₃. In some embodiments, X is —SCH₂CH₂CH₃. In some embodiments, X is C₁-C₆ haloalkyl. In some embodiments, X is C₁-C₆ haloalkoxy. In some embodiments, X is 3- to 6-membered cycloalkyl. In some embodiments, X is 4- to 6-membered heterocycloalkyl. In some embodiments, X is cyano. In some embodiments, X is nitro. In some embodiments, X is amino (i.e., —NR₂, wherein each R is independently H, OH, or C₁-C₆ alkyl, wherein the C₁-C₆ alkyl is optionally substituted according to embodiments described below).

[95] In some embodiments of Formula (1), wherein X is C₁-C₆ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino, each C₁-C₆ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino is independently optionally substituted by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, —OP(O)(OH)₂, —OC(O)H, —OSO₂OH, or —OC(O)NH₂. In some embodiments, X is unsubstituted C₁-C₆ alkyl, unsubstituted C₂-C₈ alkenyl, unsubstituted C₂-C₈ alkynyl, unsubstituted C₁-C₆ alkoxy, unsubstituted C₁-C₆ alkylthio, unsubstituted C₁-C₆ haloalkyl, unsubstituted C₁-C₆ haloalkoxy, unsubstituted 3- to 6-membered cycloalkyl, unsubstituted 4- to 6-membered heterocycloalkyl, or unsubstituted amino (i.e., —NH₂). In some embodiments, X is substituted C₁-C₆ alkyl, substituted C₂-C₈ alkenyl, substituted C₂-C₈ alkynyl, substituted C₁-C₆ alkoxy, substituted C₁-C₆ alkylthio, substituted C₁-C₆ haloalkyl, substituted C₁-C₆ haloalkoxy, substituted 3- to 6-membered cycloalkyl, substituted 4- to 6-membered

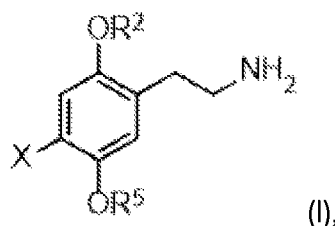
heterocycloalkyl, or substituted amino (i.e., —NR_2 , wherein each R is independently deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyle, arylcarbamoyle, nitro, cyano, nitrate, —OP(O)(OH)_2 , —OC(O)H , $\text{—OSO}_2\text{OH}$, or —OC(O)NH_2).

[96] In some embodiments of Formula (1), one of R^2 and R^5 is methyl, and the other is $\text{C}_3\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ alkenyl, $\text{C}_2\text{—C}_8$ alkynyl, $\text{C}_1\text{—C}_6$ haloalkyl, $\text{C}_1\text{—C}_6$ alkylene-3- to 6-membered cycloalkyl, $\text{C}_1\text{—C}_6$ alkylene-4- to 6-membered heterocycloalkyl, or $\text{C}_1\text{—C}_6$ alkylene-aryl, or $\text{C}_1\text{—C}_6$ alkylene-heteroaryl; and R^3 and R^6 are both H. In some embodiments, R^2 is methyl; R^5 is $\text{C}_3\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ alkenyl, $\text{C}_2\text{—C}_8$ alkynyl, $\text{C}_1\text{—C}_6$ haloalkyl, $\text{C}_1\text{—C}_6$ alkylene-3- to 6-membered cycloalkyl, $\text{C}_1\text{—C}_6$ alkylene-4- to 6-membered heterocycloalkyl, or $\text{C}_1\text{—C}_6$ alkylene-aryl, or $\text{C}_1\text{—C}_6$ alkylene-heteroaryl; and R^3 and R^6 are both H. In some embodiments, R^5 is methyl; R^2 is $\text{C}_3\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ alkenyl, $\text{C}_2\text{—C}_8$ alkynyl, $\text{C}_1\text{—C}_6$ haloalkyl, $\text{C}_1\text{—C}_6$ alkylene-3- to 6-membered cycloalkyl, $\text{C}_1\text{—C}_6$ alkylene-4- to 6-membered heterocycloalkyl, or $\text{C}_1\text{—C}_6$ alkylene-aryl, or $\text{C}_1\text{—C}_6$ alkylene-heteroaryl; and R^3 and R^6 are both H.

[97] In some embodiments of Formula (1), R^2 and R^3 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^5 is $\text{C}_3\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ alkenyl, $\text{C}_2\text{—C}_8$ alkynyl, $\text{C}_1\text{—C}_6$ haloalkyl, $\text{C}_1\text{—C}_6$ alkylene-3- to 6-membered cycloalkyl, $\text{C}_1\text{—C}_6$ alkylene-4- to 6-membered heterocycloalkyl, or $\text{C}_1\text{—C}_6$ alkylene-aryl, or $\text{C}_1\text{—C}_6$ alkylene-heteroaryl; and R^6 is H. In some embodiments, R^2 and R^3 together with the intervening atoms form a dihydrofuranyl. In some embodiments, R^2 and R^3 together with the intervening atoms form a furanyl.

[98] In some embodiments of Formula (1), R^5 and R^6 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R^2 is $\text{C}_3\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ alkenyl, $\text{C}_2\text{—C}_8$ alkynyl, $\text{C}_1\text{—C}_6$ haloalkyl, $\text{C}_1\text{—C}_6$ alkylene-3- to 6-membered cycloalkyl, $\text{C}_1\text{—C}_6$ alkylene-4- to 6-membered heterocycloalkyl, or $\text{C}_1\text{—C}_6$ alkylene-aryl, or $\text{C}_1\text{—C}_6$ alkylene-heteroaryl; and R^3 is H. In some embodiments, R^5 and R^6 together with the intervening atoms form a dihydrofuranyl. In some embodiments, R^5 and R^6 together with the intervening atoms form a furanyl.

[99] In another aspect, provided is a compound of Formula (I):



or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

X is F, Cl, Br, I, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_1\text{—C}_6$ haloalkyl, or $\text{C}_1\text{—C}_6$ alkylthio; and

one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl or C_3 - C_6 alkenyl.

[100] In some embodiments of Formula (I), X is F, Cl, Br, I, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkylthio. In some embodiments, X is F, Cl, Br, or I. In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C_1 - C_6 alkyl. For example, in some embodiments, X is methyl. In some embodiments, X is ethyl. In some embodiments, X is C_1 - C_6 haloalkyl. For example, in some embodiments, X is CF_3 . In some embodiments, X is C_1 - C_6 alkylthio. For example, in some embodiments, X is $-S-CH_3$.

[101] In some embodiments of Formula (I), one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl or C_3 - C_6 alkenyl. In some embodiments, one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl. In some embodiments, R^2 is methyl and R^5 is C_3 - C_6 alkyl. In some embodiments, R^2 is methyl and R^5 is propyl, butyl, pentyl, or hexyl. In some embodiments, R^2 is methyl and R^5 is propyl. In some embodiments, R^2 is methyl and R^5 is butyl. In some embodiments, R^2 is methyl and R^5 is pentyl. In some embodiments, R^2 is methyl and R^5 is hexyl. In some embodiments, R^2 is methyl and R^5 is n-propyl, isopropyl (1-methylethyl), n-butyl, sec-butyl (butan-2-yl), isobutyl (2-methylpropyl), tert-butyl, n-pentyl, tert-pentyl (2-methylbutan-2-yl), neopentyl (2,2-dimethylpropyl), isopentyl (3-methylbutyl), sec-pentyl (pentan-2-yl), pentan-3-yl, sec-isopentyl (3-methylbutan-2-yl), or 2-methylbutyl. In some embodiments, R^2 is methyl and R^5 is n-propyl. In some embodiments, R^2 is methyl and R^5 is isopropyl (1-methylethyl). In some embodiments, R^2 is methyl and R^5 is n-butyl. In some embodiments, R^2 is methyl and R^5 is sec-butyl (butan-2-yl). In some embodiments, R^2 is methyl and R^5 is isobutyl (2-methylpropyl). In some embodiments, R^2 is methyl and R^5 is tert-butyl. In some embodiments, R^2 is methyl and R^5 is n-pentyl. In some embodiments, R^2 is methyl and R^5 is tert-pentyl (2-methylbutan-2-yl). In some embodiments, R^2 is methyl and R^5 is neopentyl (2,2-dimethylpropyl). In some embodiments, R^2 is methyl and R^5 is isopentyl (3-methylbutyl). In some embodiments, R^2 is methyl and R^5 is sec-pentyl (pentan-2-yl). In some embodiments, R^2 is methyl and R^5 is pentan-3-yl. In some embodiments, R^2 is methyl and R^5 is sec-isopentyl (3-methylbutan-2-yl). In some embodiments, R^2 is methyl and R^5 is 2-methylbutyl. In some embodiments, R^2 is methyl and R^5 is hexyl (including n-hexyl and all other hexyl isomers). In some embodiments, R^2 is methyl and R^5 is n-propyl, n-butyl, n-pentyl, or n-hexyl.

[102] In some embodiments of Formula (I), R^2 is methyl and R^5 is C_3 - C_6 alkenyl. In some embodiments, R^2 is methyl and R^5 is ethenyl (i.e., vinyl), propenyl (e.g., allyl), butenyl, penenyl, or hexenyl. In some embodiments, R^2 is methyl and R^5 is vinyl. In some embodiments, R^2 is methyl and R^5 is allyl.

[103] In some embodiments of Formula (I), R^5 is methyl and R^2 is C_3 - C_6 alkyl. In some embodiments, R^5 is methyl and R^2 is propyl, butyl, pentyl, or hexyl. In some embodiments, R^5 is methyl and R^2 is propyl. In some embodiments, R^5 is methyl and R^2 is butyl. In some embodiments, R^5 is methyl and R^2 is pentyl. In some

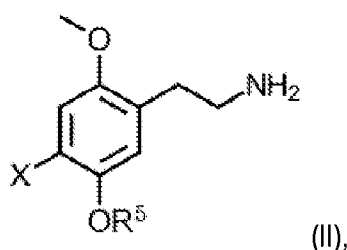
embodiments, R^5 is methyl and R^2 is hexyl. In some embodiments, R^5 is methyl and R^2 is n-propyl, isopropyl (1-methylethyl), n-butyl, sec-butyl (butan-2-yl), isobutyl (2-methylpropyl), tert-butyl, n-pentyl, tert-pentyl (2-methylbutan-2-yl), neopentyl (2,2-dimethylpropyl), isopentyl (3-methylbutyl), sec-pentyl (pentan-2-yl), pentan-3-yl, sec-isopentyl (3-methylbutan-2-yl), or 2-methylbutyl. In some embodiments, R^5 is methyl and R^2 is n-propyl. In some embodiments, R^5 is methyl and R^2 is isopropyl (1-methylethyl). In some embodiments, R^5 is methyl and R^2 is n-butyl. In some embodiments, R^5 is methyl and R^2 is sec-butyl (butan-2-yl). In some embodiments, R^5 is methyl and R^2 is isobutyl (2-methylpropyl). In some embodiments, R^5 is methyl and R^2 is tert-butyl. In some embodiments, R^5 is methyl and R^2 is n-pentyl. In some embodiments, R^5 is methyl and R^2 is tert-pentyl (2-methylbutan-2-yl). In some embodiments, R^5 is methyl and R^2 is neopentyl (2,2-dimethylpropyl). In some embodiments, R^5 is methyl and R^2 is isopentyl (3-methylbutyl). In some embodiments, R^5 is methyl and R^2 is sec-pentyl (pentan-2-yl). In some embodiments, R^5 is methyl and R^2 is pentan-3-yl. In some embodiments, R^5 is methyl and R^2 is sec-isopentyl (3-methylbutan-2-yl). In some embodiments, R^5 is methyl and R^2 is 2-methylbutyl. In some embodiments, R^5 is methyl and R^2 is hexyl (including n-hexyl and all other hexyl isomers).

[104] In some embodiments of Formula (I), R^5 is methyl and R^2 is C_3 - C_6 alkenyl. In some embodiments, R^5 is methyl and R^2 is ethenyl (i.e., vinyl), propenyl (e.g., allyl), butenyl, penenyl, or hexenyl. In some embodiments, R^5 is methyl and R^2 is vinyl. In some embodiments, R^5 is methyl and R^2 is allyl.

[105] In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is not Br. In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is not I. In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is not ethyl. In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is F, Cl, I, or CF_3 . In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is F, Cl, or CF_3 . In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is F. In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is Cl. In some embodiments, wherein R^2 is methyl and R^5 is isopropyl, X is CF_3 . In some embodiments, R^5 is not isopropyl. In some embodiments, wherein X is Br and R^2 is methyl, R^5 is not isopropyl. In some embodiments, wherein X is I and R^2 is methyl, R^5 is not isopropyl. In some embodiments, wherein X is Br and R^2 is methyl, R^5 is n-propyl. In some embodiments, wherein X is I and R^2 is methyl, R^5 is n-propyl. In some embodiments, wherein X is Br and R^2 is methyl, R^5 is butyl, pentyl, or hexyl (including n-butyl, n-pentyl, n-hexyl, and all other isomers). In some embodiments, wherein X is I and R^2 is methyl, R^5 is butyl, pentyl, or hexyl (including n-butyl, n-pentyl, n-hexyl, and all other isomers). In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is not Br. In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is not I. In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is F, Cl, I, or CF_3 . In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is F, Cl, or CF_3 . In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is F. In

some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is Cl. In some embodiments, wherein R^5 is methyl and R^2 is isopropyl, X is CF_3 . In some embodiments, R^2 is not isopropyl. In some embodiments, wherein X is Br and R^5 is methyl, R^2 is not isopropyl. In some embodiments, wherein X is I and R^5 is methyl, R^2 is not isopropyl. In some embodiments, wherein X is Br and R^5 is methyl, R^2 is n-propyl. In some embodiments, wherein X is I and R^5 is methyl, R^2 is n-propyl. In some embodiments, wherein X is Br and R^5 is methyl, R^2 is butyl, pentyl, or hexyl (including n-butyl, n-pentyl, n-hexyl, and all other isomers). In some embodiments, wherein X is I and R^5 is methyl, R^2 is butyl, pentyl, or hexyl (including n-butyl, n-pentyl, n-hexyl, and all other isomers).

[106] In some embodiments, the compound has the structure of Formula (II):



or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

X is Br, F, Cl, I, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkylthio; and

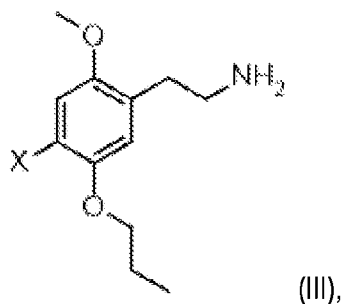
R^5 is C_3 - C_6 alkyl or C_3 - C_6 alkenyl.

[107] In some embodiments of Formula (II), X is F, Cl, Br, I, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkylthio. In some embodiments, X is F, Cl, Br, or I. In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C_1 - C_6 alkyl. For example, in some embodiments, X is methyl. In some embodiments, X is ethyl. In some embodiments, X is C_1 - C_6 haloalkyl. For example, in some embodiments, X is CF_3 . In some embodiments, X is C_1 - C_6 alkylthio. For example, in some embodiments, X is $-S-CH_3$.

[108] In some embodiments of Formula (II), R^5 is C_3 - C_6 alkyl or C_3 - C_6 alkenyl. In some embodiments, R^5 is n-propyl, n-butyl, n-pentyl, n-hexyl, or C_3 - C_6 alkenyl. In some embodiments, R^5 is n-propyl, isopropyl (1-methylethyl), n-butyl, sec-butyl (butan-2-yl), isobutyl (2-methylpropyl), tert-butyl, n-pentyl, tert-pentyl (2-methylbutan-2-yl), neopentyl (2,2-dimethylpropyl), isopentyl (3-methylbutyl), sec-pentyl (pentan-2-yl), pentan-3-yl, sec-isopentyl (3-methylbutan-2-yl), or 2-methylbutyl. In some embodiments, R^5 is n-propyl. In some embodiments, R^5 is isopropyl (1-methylethyl). In some embodiments, R^5 is n-butyl. In some embodiments, R^5 is sec-butyl (butan-2-yl). In some embodiments, R^5 is isobutyl (2-methylpropyl). In some embodiments, R^5 is tert-butyl. In some embodiments, R^5 is n-pentyl. In some embodiments, R^5 is tert-pentyl (2-methylbutan-2-yl). In some embodiments, R^5 is neopentyl (2,2-dimethylpropyl). In some embodiments, R^5 is isopentyl

(3-methylbutyl). In some embodiments, R^5 is sec-pentyl (pentan-2-yl). In some embodiments, R^5 is pentan-3-yl. In some embodiments, R^5 is sec-isopentyl (3-methylbutan-2-yl). In some embodiments, R^5 is 2-methylbutyl. In some embodiments, R^5 is hexyl (including n-hexyl and all other hexyl isomers). In some embodiments, R^5 is ethenyl (i.e., vinyl), propenyl (e.g., allyl), butenyl, penenyl, or hexenyl. In some embodiments, R^5 is vinyl. In some embodiments, R^5 is allyl.

[109] In some embodiments, the compound has the structure of Formula (III):



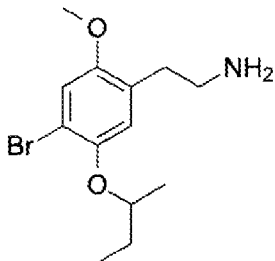
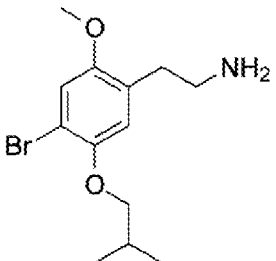
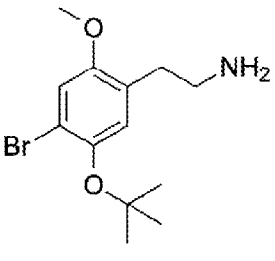
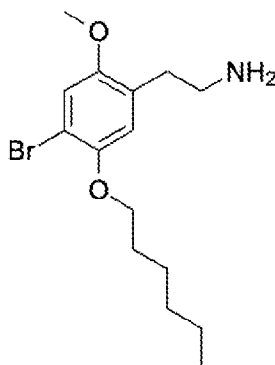
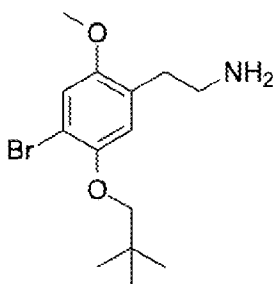
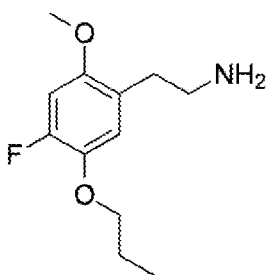
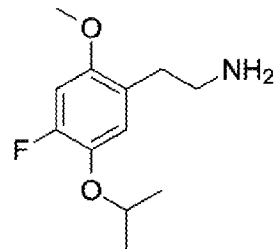
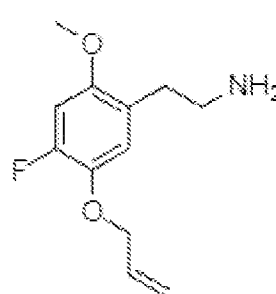
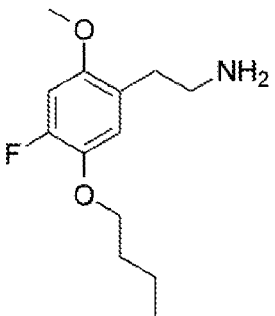
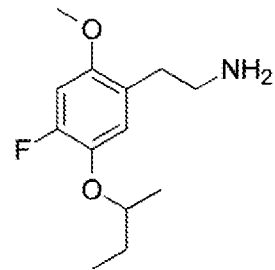
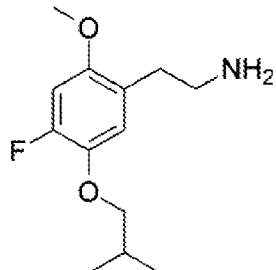
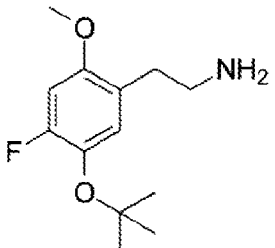
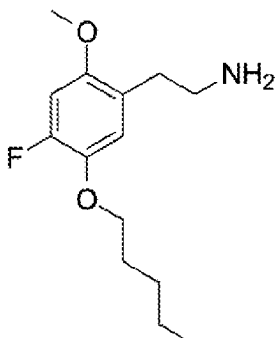
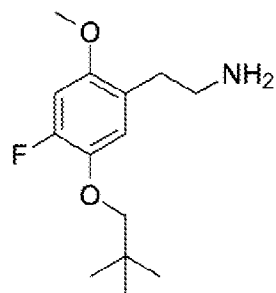
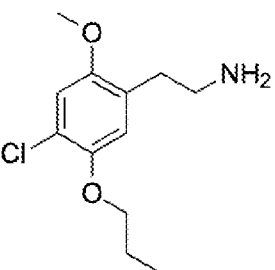
or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein X is F, Cl, Br, I, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkylthio.

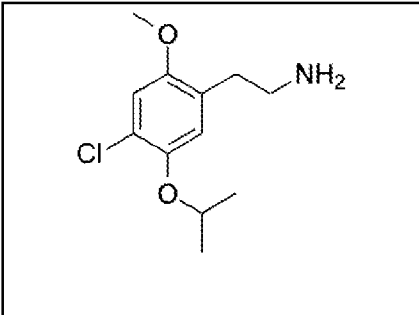
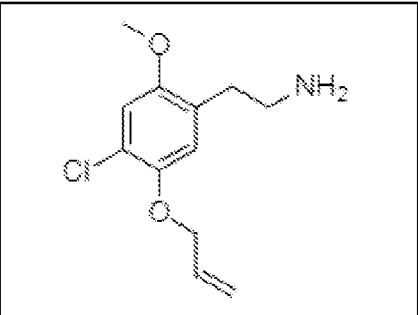
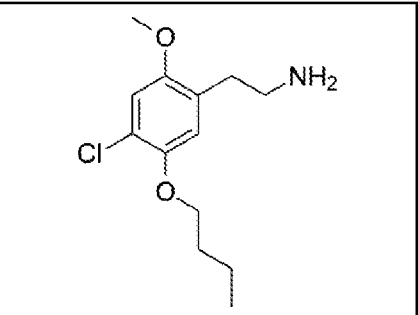
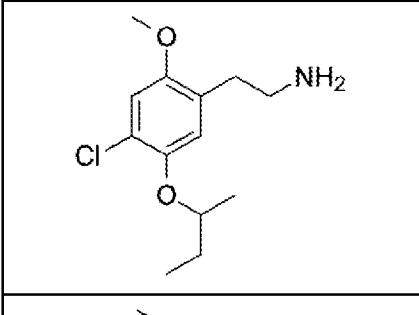
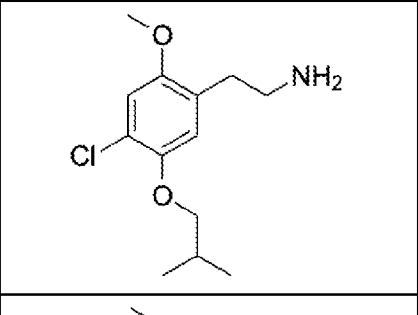
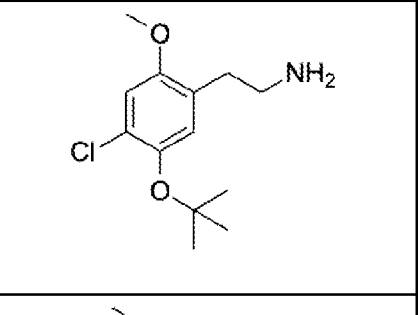
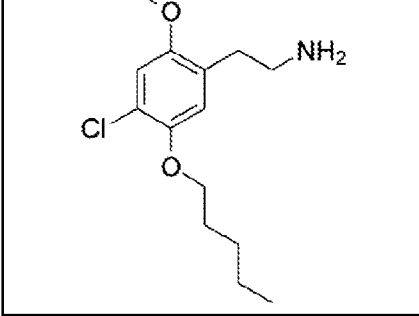
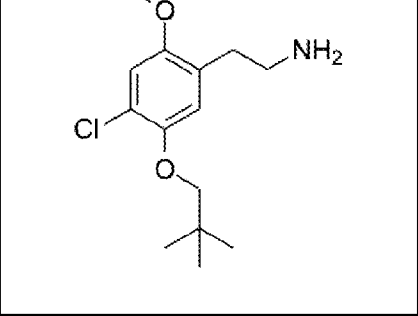
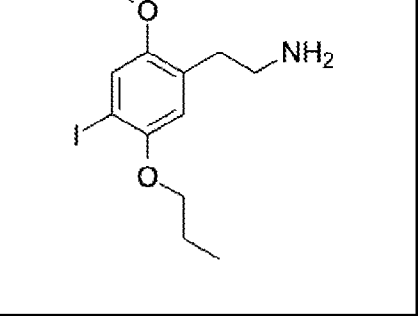
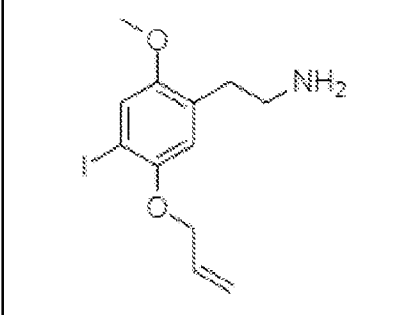
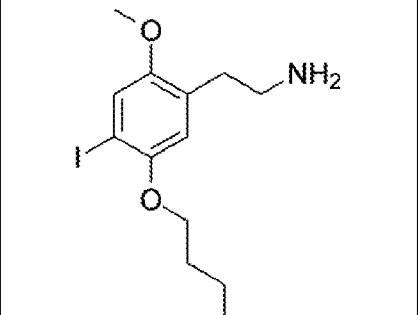
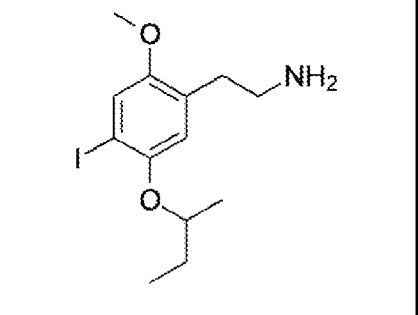
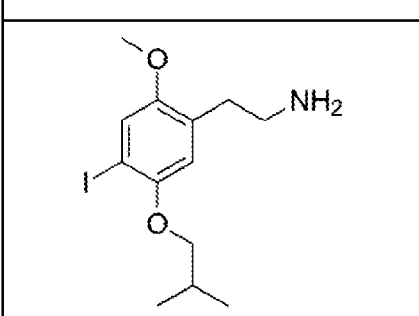
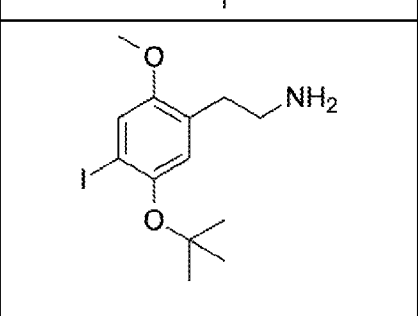
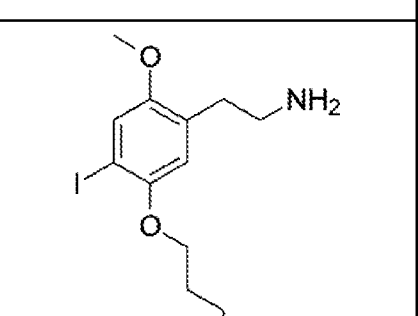
[110] In some embodiments of Formula (III), X is F, Cl, Br, I, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkylthio. In some embodiments, X is F, Cl, Br, I, or CF_3 . In some embodiments, X is F, Cl, Br, or I. In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C_1 - C_6 alkyl. For example, in some embodiments, X is methyl. In some embodiments, X is ethyl. In some embodiments, X is C_1 - C_6 haloalkyl. For example, in some embodiments, X is CF_3 . In some embodiments, X is C_1 - C_6 alkylthio. For example, in some embodiments, X is $-S-CH_3$.

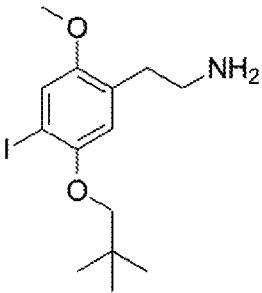
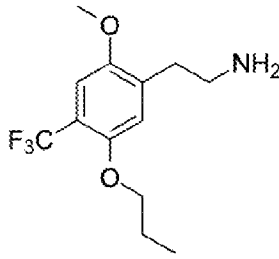
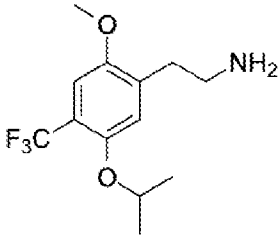
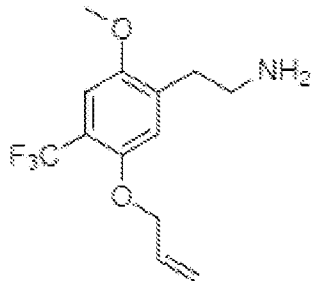
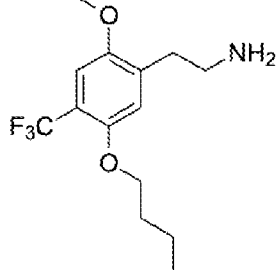
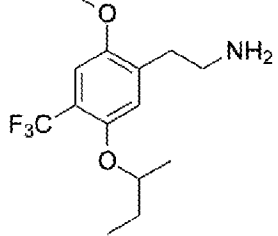
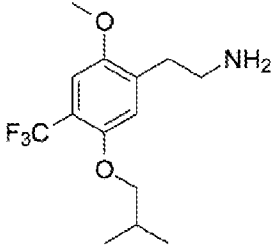
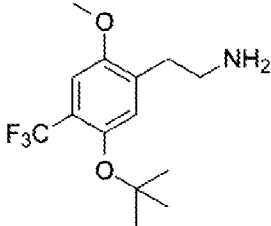
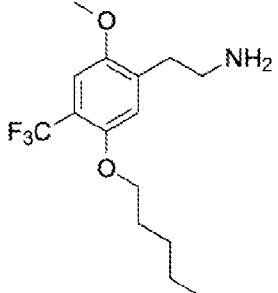
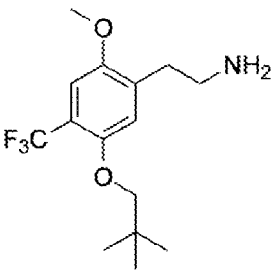
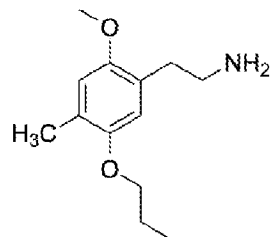
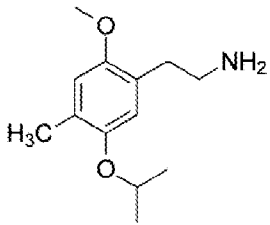
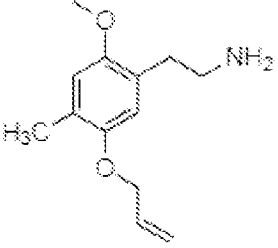
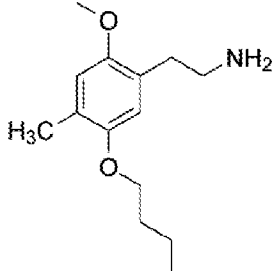
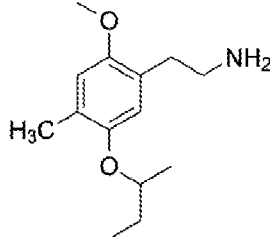
[111] In some embodiments, the compound is selected from **TABLE 1** or **TABLE 2**.

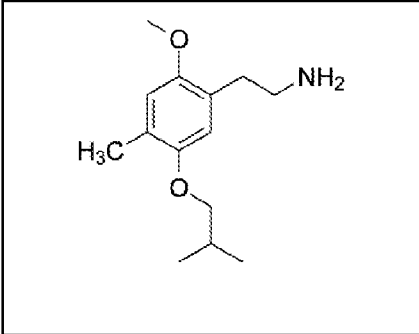
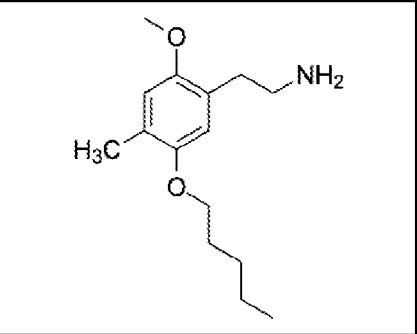
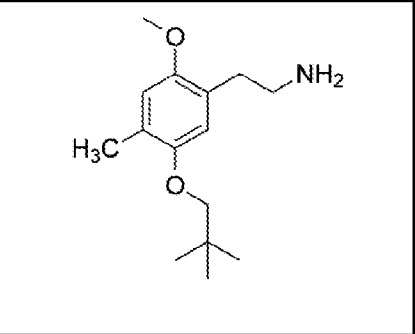
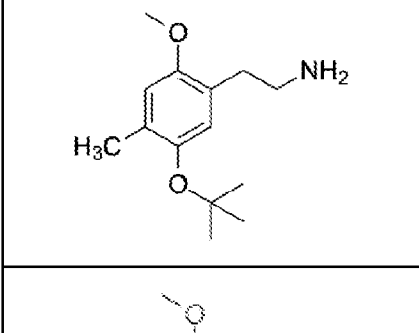
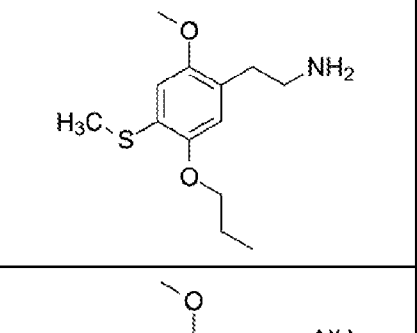
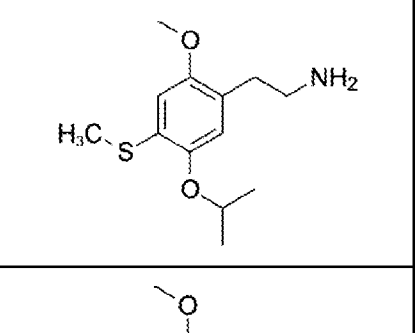
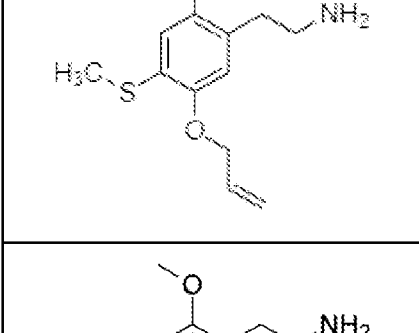
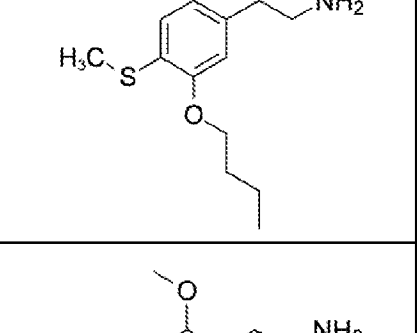
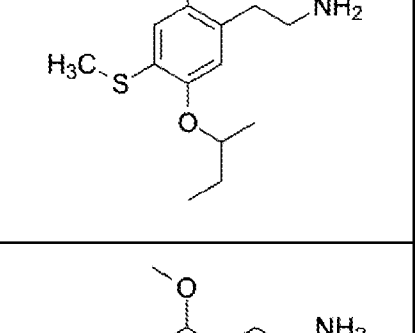
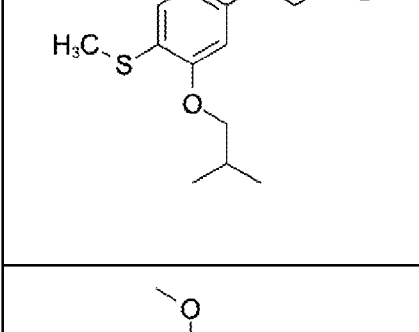
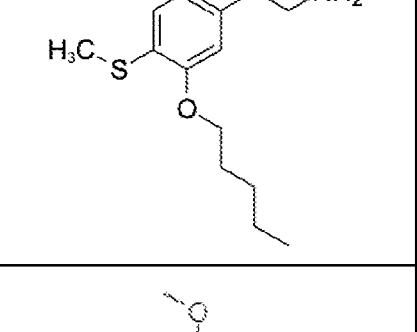
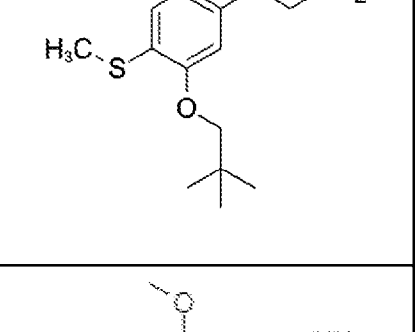
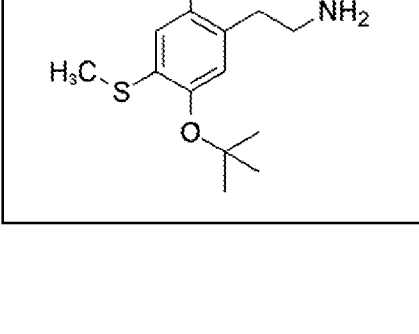
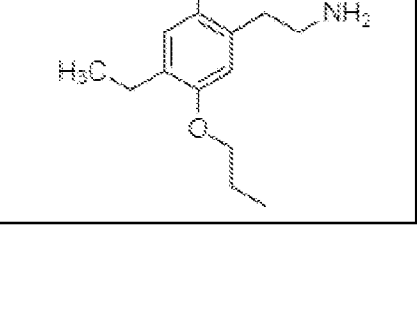
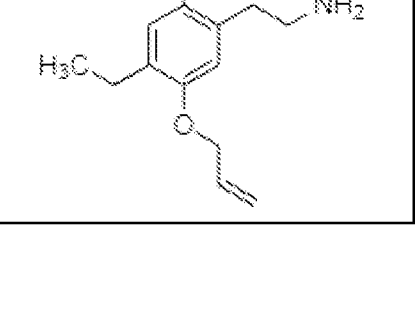
TABLE 1. Exemplary 2-methoxy-substituted compounds.

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 <chem>CCOC(c1ccc(NCC)c(OC)c1Br)CC</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1Br)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1Br)CC(C)(C)C</chem>
 <chem>CCOC(c1ccc(NCC)c(OC)c1Br)CCCCC</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1Br)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC</chem>
 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)C=C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC</chem>
 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC(C)(C)C</chem>
 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CCCCC</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1F)CC(C)C</chem>	 <chem>CCOC(c1ccc(NCC)c(OC)c1Cl)CC</chem>

 <chem>COc1cc(ccc1OCCN)ClOC(C)C</chem>	 <chem>COc1cc(ccc1OCCN)ClOCC=C</chem>	 <chem>COc1cc(ccc1OCCN)ClOCC</chem>
 <chem>COc1cc(ccc1OCCN)ClOC(C)CC</chem>	 <chem>COc1cc(ccc1OCCN)ClOC(C)C</chem>	 <chem>COc1cc(ccc1OCCN)ClOC(C)(C)C(C)C</chem>
 <chem>COc1cc(ccc1OCCN)ClOCC</chem>	 <chem>COc1cc(ccc1OCCN)ClOC(C)(C)C(C)C</chem>	 <chem>COc1cc(ccc1OCCN)IOCC</chem>
 <chem>COc1cc(ccc1OCCN)IOCC=C</chem>	 <chem>COc1cc(ccc1OCCN)IOCC</chem>	 <chem>COc1cc(ccc1OCCN)IOCC(C)C</chem>
 <chem>COc1cc(ccc1OCCN)IOCC(C)C</chem>	 <chem>COc1cc(ccc1OCCN)IOCC(C)(C)C(C)C</chem>	 <chem>COc1cc(ccc1OCCN)IOCC</chem>

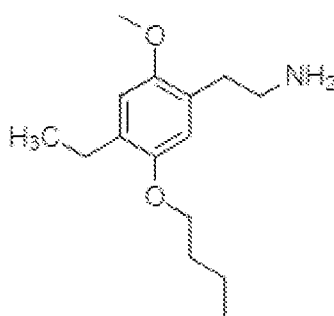
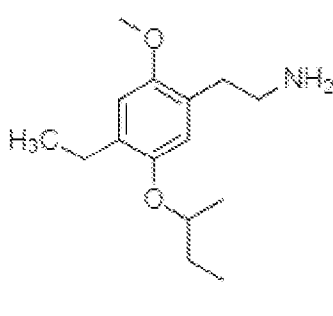
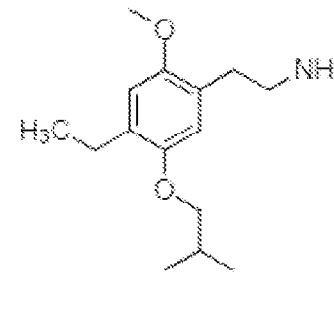
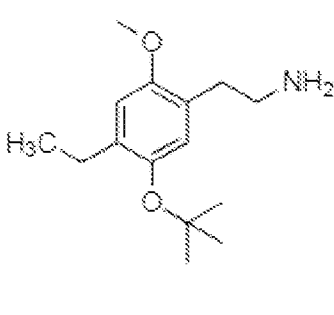
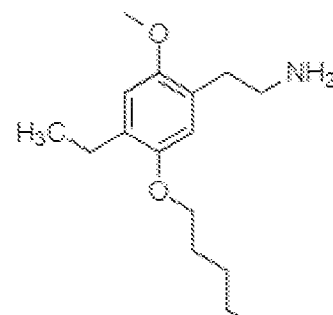
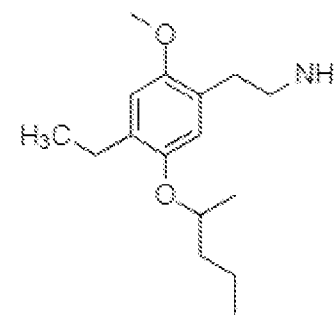
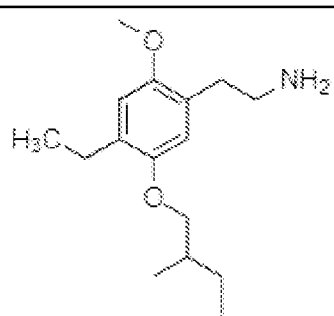
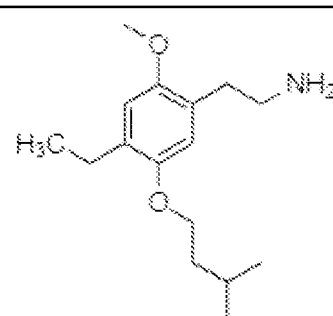
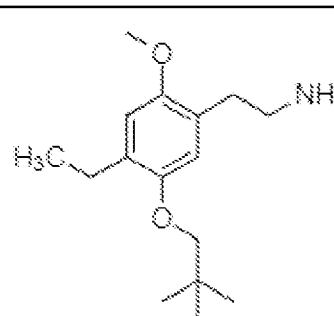
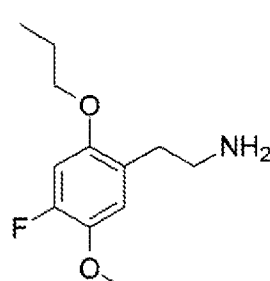
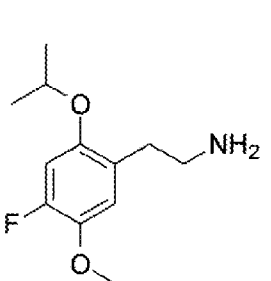
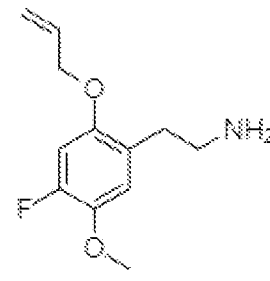
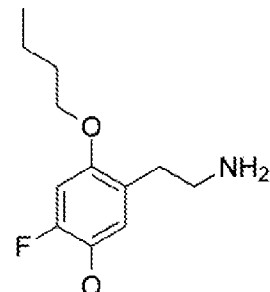
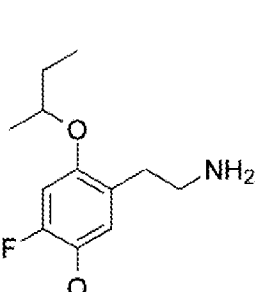
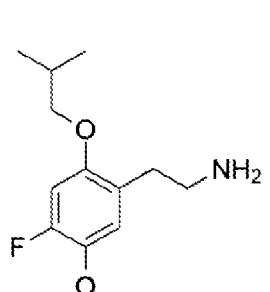
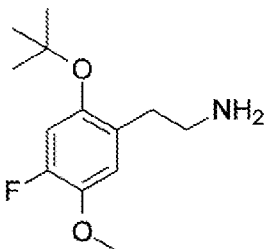
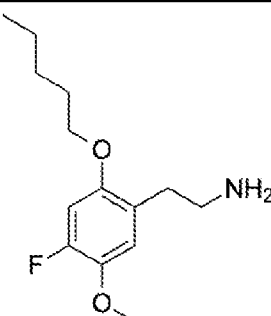
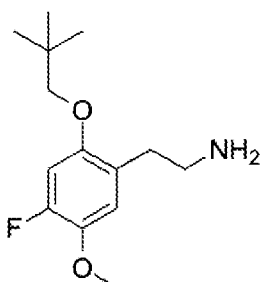
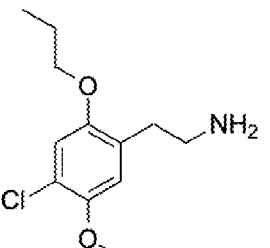
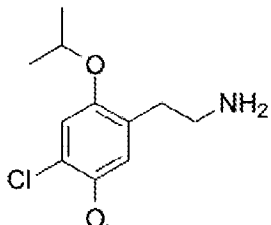
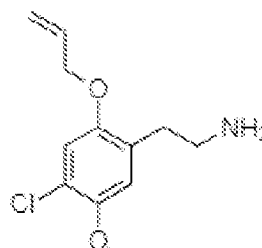
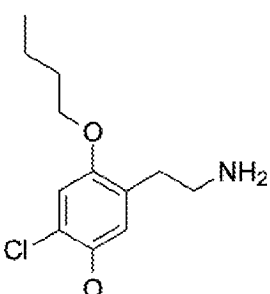
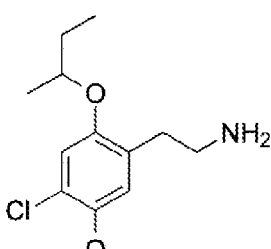
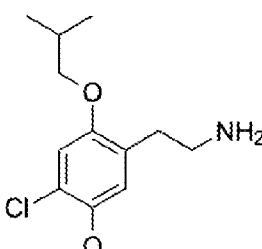
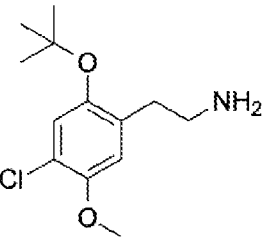
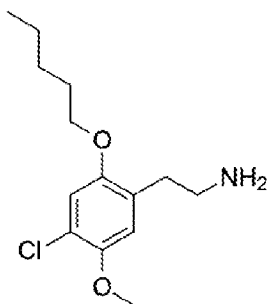
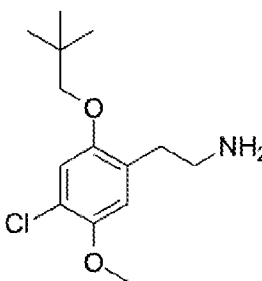
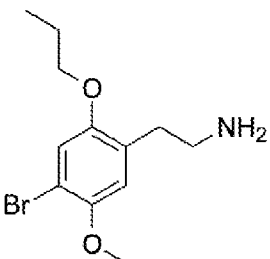
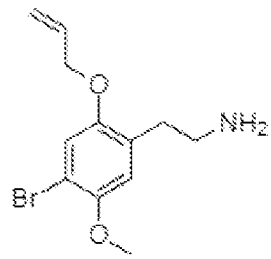
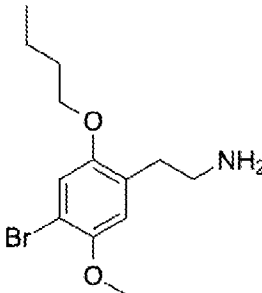
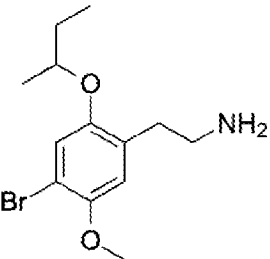
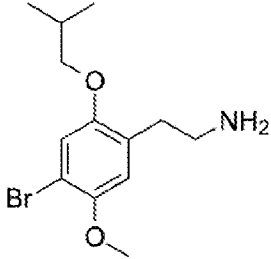
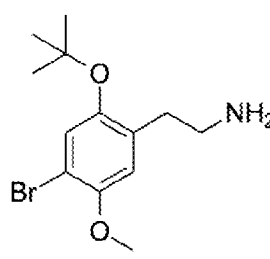
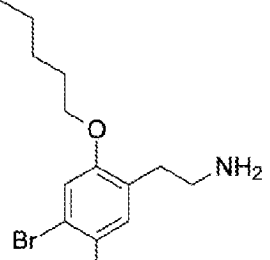
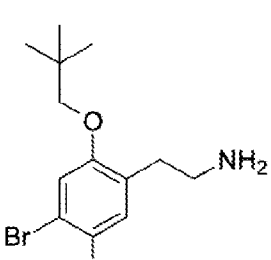
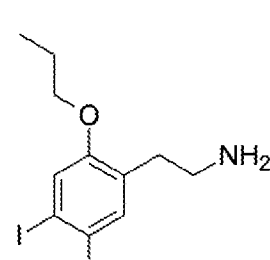
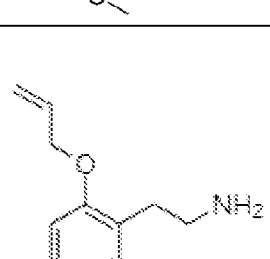
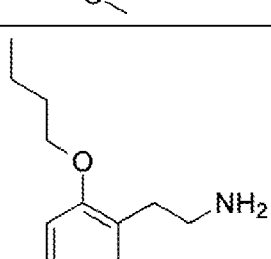
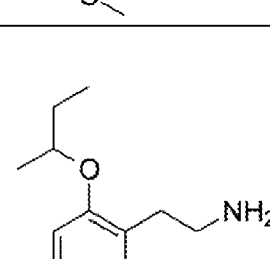
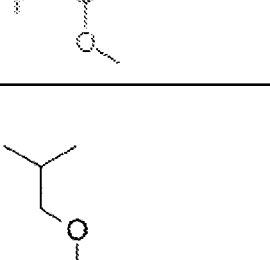
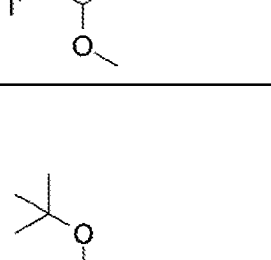
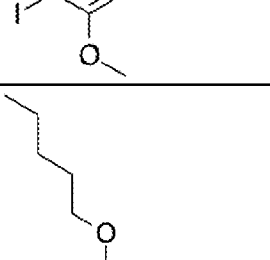
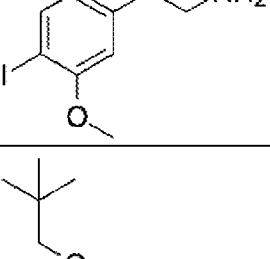
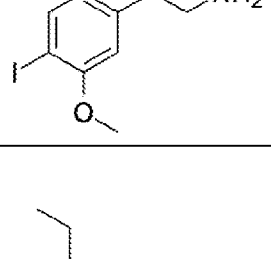
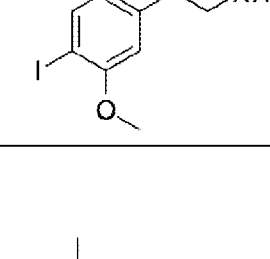
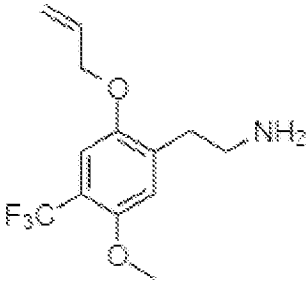
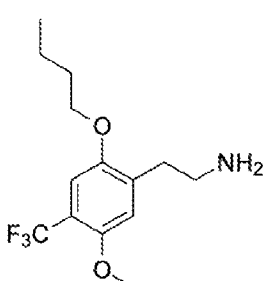
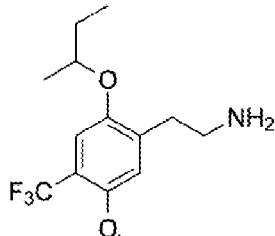
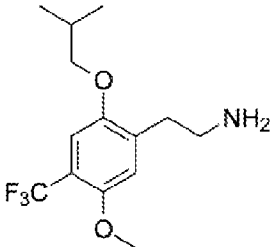
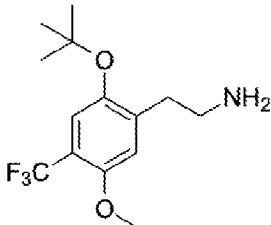
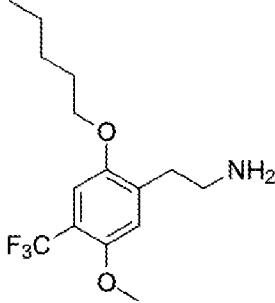
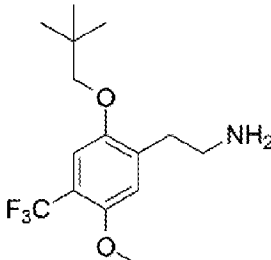
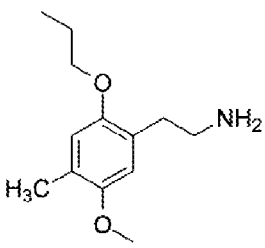
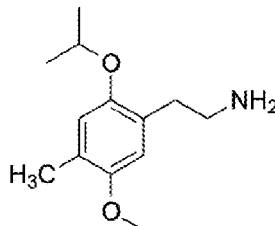
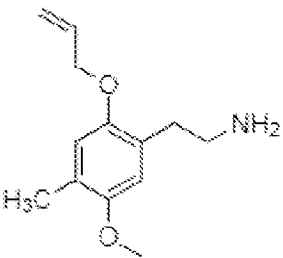
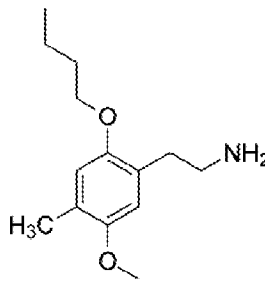
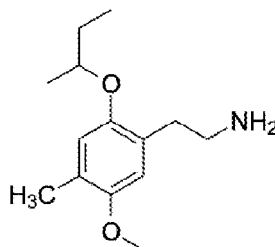
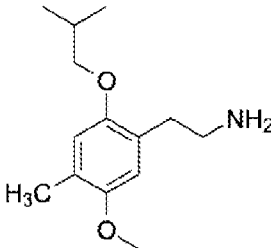
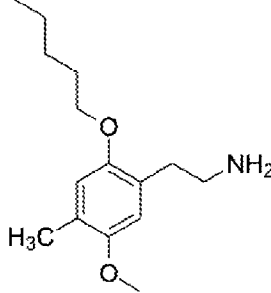
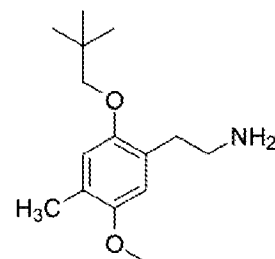
		
		
		

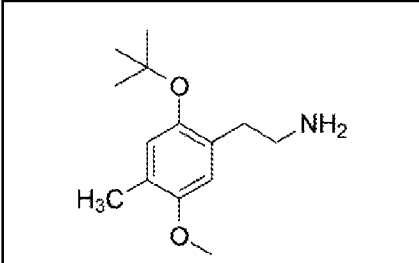
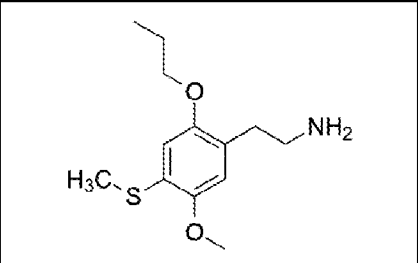
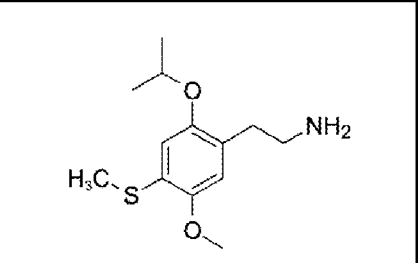
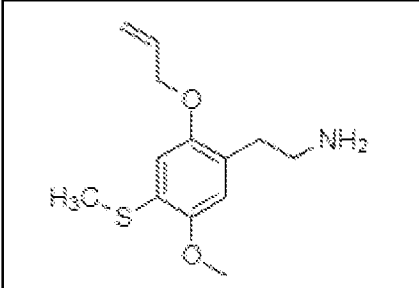
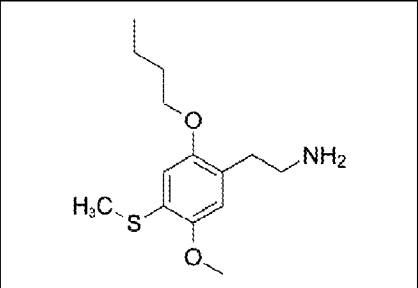
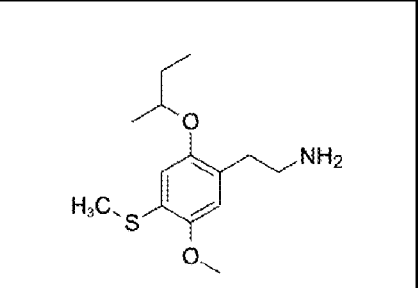
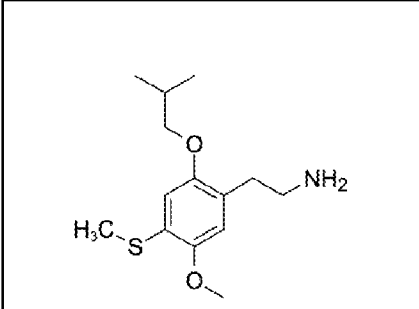
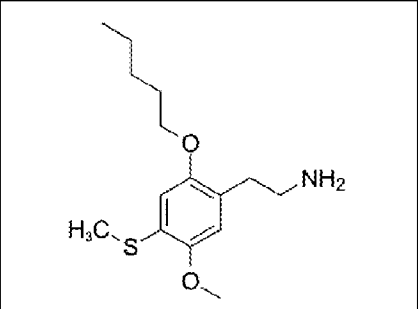
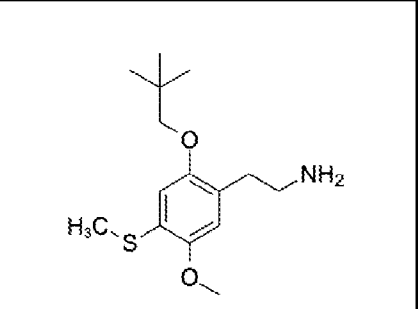
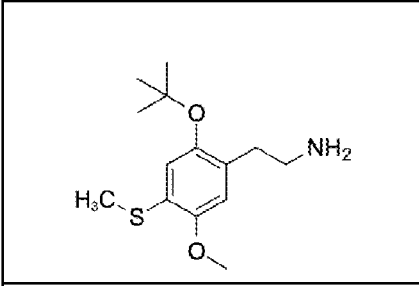
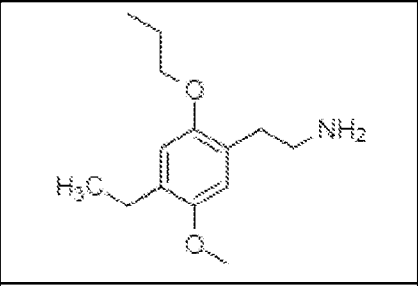
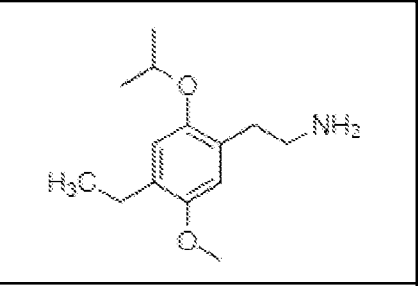
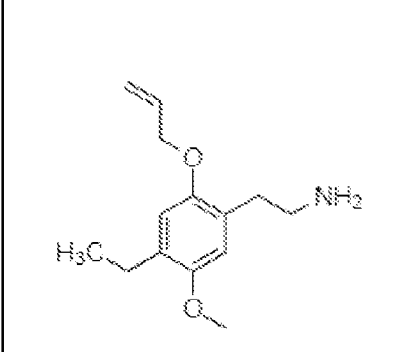
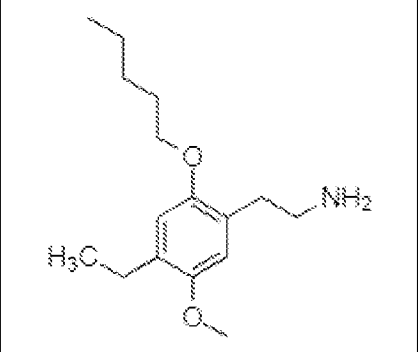
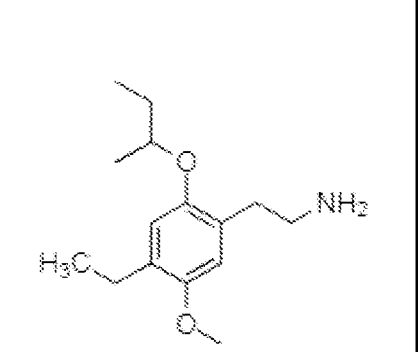
TABLE 2. Exemplary 5-methoxy-substituted compounds.

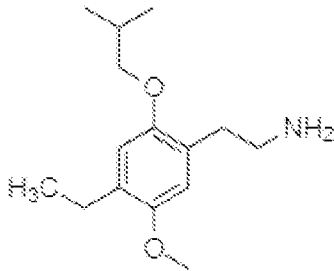
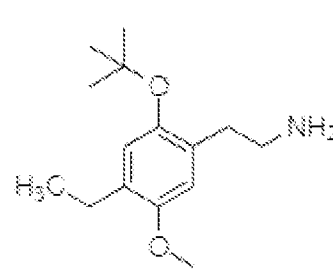
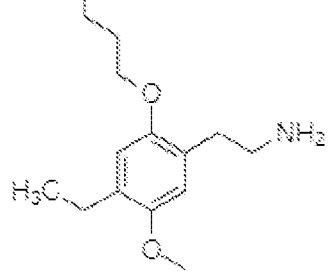
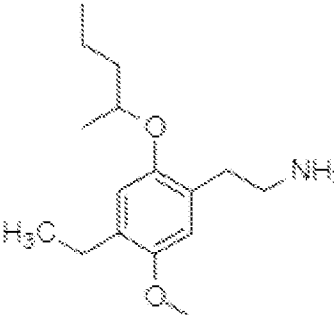
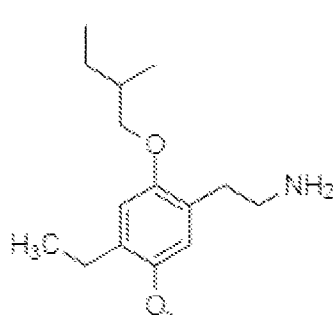
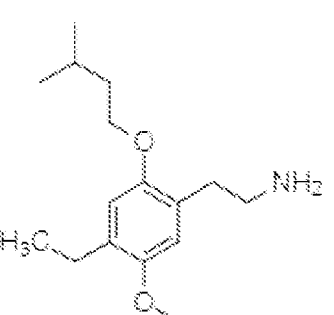
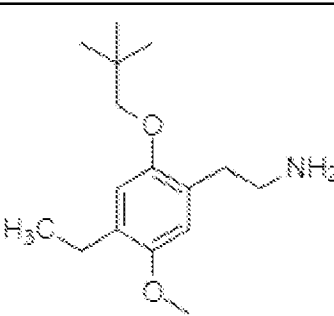
		
		

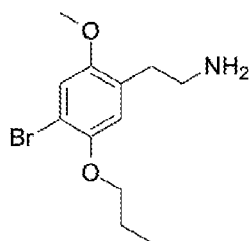
		
		
		
		
		

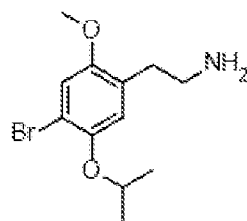
		
		
		
		
		



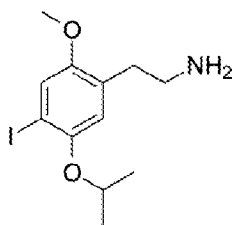
[112] In embodiments, the compound is salt, hydrate, solvate, or isotopic derivative thereof.

(ASR2001), or a pharmaceutically acceptable



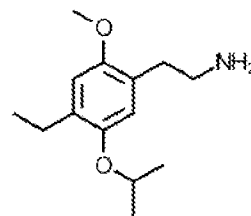
[113] In some embodiments, the compound is not

. In some embodiments, the

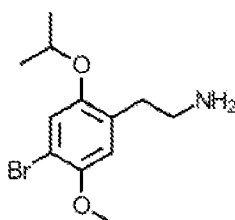


compound is not

. In some embodiments, the compound is not

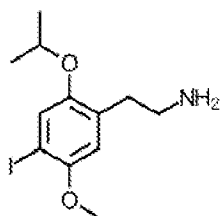


. In



some embodiments, the compound is not

. In some embodiments, the compound is not



[114] Herein, “a single compound of” will mean that the specified compound (e.g., by structural formula or description) is the only disclosed compound in the claimed embodiment, i.e., that a compound, composition, or method consists of, consists essentially of, or comprises no further disclosed compound(s) (i.e., compound(s) having a different structural formula or description). It does not mean that the embodiment has only a single molecule or single instance of the specified compound. For instance, embodiments “consisting of a single compound of Formula (I)” will include embodiments of “a compound of Formula (I),” or the use of “a compound of Formula (I),” and such embodiments, as well as embodiments of a composition “consisting essentially of a single compound of Formula (I),” each may comprise for example 5 mg, 10 mg, 20 mg, 40 mg, 50 mg, 100 mg, and other disclosed or known mass amounts or molar amounts of the compound of Formula (I).

[115] The individual compounds of disclosed compositions will also encompass pharmaceutically acceptable salts of such compounds. The term “pharmaceutically acceptable salt” refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases, and which may be synthesized by conventional chemical methods. Generally, such salts are prepared by reacting the free acid or base forms of these agents with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media (e.g., ether, ethyl acetate, ethanol, isopropanol, or acetonitrile) are preferred. For therapeutic use, salts of the compounds are those wherein the counter-ion is pharmaceutically acceptable.

[116] Exemplary salts include 2-hydroxyethanesulfonate, 2-naphthalenesulfonate, 2-napsylate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, 4-acetamidobenzoate, acefyllinate, acetate, aceturate, adipate,

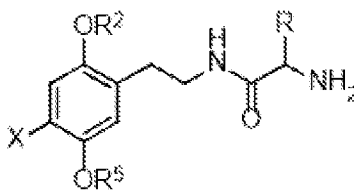
alginate, aminosalicylate, ammonium, amsonate, ascorbate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, butyrate, calcium edetate, calcium, camphocarbonate, camphorate, camphorsulfonate, camsylate, carbonate, cholate, citrate, clavuliate, cyclopentanepropionate, cypionate, d-aspartate, d-camsylate, d-lactate, decanoate, dichloroacetate, digluconate, dodecylsulfate, edentate, edetate, edisylate, estolate, esylate, ethanesulfonate, ethyl sulfate, fumarate, furate, fusidate, galactarate (mucate), galacturonate, gallate, gentisate, gluceptate, glucoheptanoate, gluconate, glucuronate, glutamate, glutarate, glycerophosphate, glycolate, glycolylarsanilate, hemisulfate, heptanoate (enanthate), heptanoate, hexafluorophosphate, hexanoate, hexylresorcinolate, hippurate, hybenzate, hydrabamine, hydrobromide, hydrobromide/bromide, hydrochloride, hydroiodide, hydroxide, hydroxybenzoate, hydroxynaphthoate, iodide, isethionate, isothionate, l-aspartate, l-camsylate, l-lactate, lactate, lactobionate, laurate, laurylsulphonate, lithium, magnesium, malate, maleate, malonate, mandelate, meso-tartrate, mesylate, methanesulfonate, methylbromide, methylnitrate, methylsulfate, mucate, myristate, N-methylglucamine ammonium salt, napadisilate, naphthylate, napsylate, nicotinate, nitrate, octanoate, oleate, orotate, oxalate, p-toluenesulfonate, palmitate, pamoate, pantothenate, pectinate, persulfate, phenylpropionate, phosphate, phosphateldiphosphate, picrate, pivalate, polygalacturonate, potassium, propionate, pyrophosphate, saccharate, salicylate, salicylsulfate, sodium, stearate, subacetate, succinate, sulfate, sulfosalicylate, sulfosalicylate, suramate, tannate, tartrate, teoclate, terephthalate, thiocyanate, thiosalicylate, tosylate, tribrophenate, triethiodide, undecanoate, undecylenate, valerate, valproate, xinafoate, zinc and the like. (See Berge et al. (1977) "Pharmaceutical Salts," J. Pharm. Sci. 66:1-19.)

[117] Prodrugs of the disclosed compounds also are within the scope of the disclosure. "Prodrug" refers to a precursor of a biologically active pharmaceutical agent, which may undergo a chemical or a metabolic conversion to become the biologically active agent. A prodrug can be converted *ex vivo* to the biologically active pharmaceutical agent by chemical transformative processes. *In vivo*, a prodrug is converted to the biologically active pharmaceutical agent by the action of a metabolic process, an enzymatic process or a degradative process that removes the prodrug moiety, such as a glycoside or acetyl group, to form the biologically active pharmaceutical agent. Other examples include addition of hydroxyl groups (Tsujikawa et al. 2011. *Xenobiotica*, 41(7), 578-584; Yamamoto et al. 1984. *Xenobiotica*, 14(11), 867-875), acyloxyalkoxycarbonyl derivatives, amino acids, vitamins, or peptides (Vig et al. 2013. *Advanced Drug Delivery Reviews*, 65(10), 1370-1385), which are generally added to the amine, and can be removed within the body by chemical reactions or enzymes, but other prodrugs and precursors, at the amine and other sites, should be understood to be within the scope of the disclosure (Simplicio, Clancy, & Gilmer. 2008. *Molecules*, 13(3), 519-547; Shah, Chauhan, Chauhan, & Mishra (Eds.). 2020. *Recent Advancement in Prodrugs*. CRC Press).

[118] Types of prodrugs within the scope of the disclosure therefore include compounds that are transformed in various organs or locations in the body (e.g., liver, kidney, G.I., lung, tissue) to release the active compound. For example, liver prodrugs will include active compounds conjugated with a polymer or chemical moiety that is not released until acted upon by liver cytochrome enzymes; CYP metabolism includes dealkylation, dehydrogenation, reduction, hydrolysis, oxidation, and the breakdown of aromatic rings. Kidney prodrugs will include active compounds conjugated to L-gamma-glutamyl or N-acetyl-L-gamma glutamic moieties so that they are metabolized by gamma-glutamyl transpeptidase before they are bioactive; alternatively, they may be conjugated to alkylglucoside moieties to create glycosylation-based prodrugs. Digestive or G.I. prodrugs will include those where an active compound is, e.g., formulated into microspheres or nanospheres that do not degrade until the spheres are subjected to an acidic pH; formulated with an amide that will resist biochemical degradation until colonic pH is achieved; or conjugated with a linear polysaccharide such as pectin that will delay activation until the combination reaches the bacteria in the colon. Besides these exemplary prodrug forms, many others will be known to those of ordinary skill.

[119] Typical examples of prodrugs also include compounds with biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Pat. Nos. 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a disclosed compound. The present disclosure includes within its scope, prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs" Ed. H. Bundgaard, Elsevier, 1985.

[120] In some embodiments, a prodrug comprising a disclosed compound is an amino acid prodrug. Amino acid refers to molecules comprising an amine group, a carboxylic acid group and a side-chain that varies among different amino acids. In some embodiments, one or more amino acids are directly conjugated to a disclosed compound to prepare a prodrug thereof. In some embodiments, a linker is used to conjugate a disclosed compound to the one or more amino acids to prepare a prodrug thereof. In some embodiments, amino acid prodrugs improve poor solubility, poor permeability, sustained release, intravenous delivery, drug targeting, and metabolic stability of the parent drug. See, e.g., Vig et al., *Advanced Drug Delivery Reviews*, 2013;65(10):1370-1385; Vale, et al., *Molecules*, 2018;23(9):2318. In some embodiments, provided are amino acid prodrugs of disclosed compounds, having the following structure:



wherein R is an amino acid side chain, such as hydrogen (in the case of glycine), methyl (in the case of alanine), or any other side chain known to those of skill in the art to correspond to a natural or unnatural amino acid.

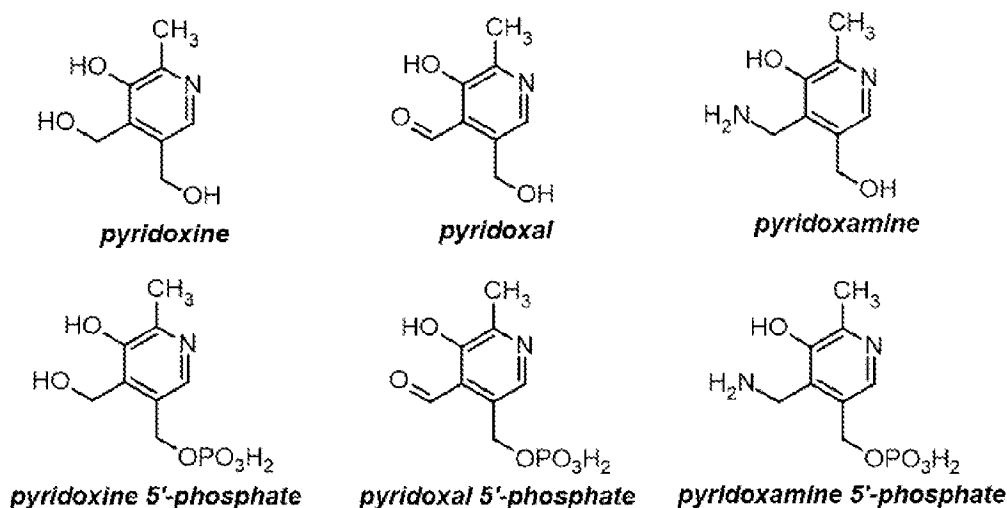
[121] Amino acid prodrugs can be synthesized according to conventional methods known to those of skill. For example, a disclosed compound (bearing a primary amine group) can be contacted with an amino acid in the presence of a suitable peptide coupling reagent (and optionally a suitable base).

[122] In some embodiments, the amino acid is a natural amino acid. In other embodiments, the amino acid is an unnatural amino acid. In embodiments, the amino acid is an L-amino acid. In embodiments, the amino acid is a D-amino acid. In embodiments, the amino acid is alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine. In embodiments, the amino acid is alanine. In embodiments, the amino acid is arginine. In embodiments, the amino acid is asparagine. In embodiments, the amino acid is aspartic acid. In embodiments, the amino acid is cysteine. In embodiments, the amino acid is glutamine. In embodiments, the amino acid is glutamic acid. In embodiments, the amino acid is glycine. In embodiments, the amino acid is histidine. In embodiments, the amino acid is isoleucine. In embodiments, the amino acid is leucine. In embodiments, the amino acid is lysine. In embodiments, the amino acid is methionine. In embodiments, the amino acid is phenylalanine. In embodiments, the amino acid is proline. In embodiments, the amino acid is serine. In embodiments, the amino acid is threonine. In embodiments, the amino acid is tryptophan. In embodiments, the amino acid is tyrosine. In embodiments, the amino acid is valine.

[123] In some embodiments, a disclosed compound is attached to a single amino acid which is either a naturally occurring amino acid or a synthetic amino acid. In embodiments, a disclosed compound is attached to a dipeptide or tripeptide, which could be any combination of naturally occurring amino acids and/or synthetic amino acids. In embodiments, the amino acids are selected from L-amino acids for digestion by proteases. In embodiments, a carrier peptide is attached to a disclosed compound through the carrier peptide's N-terminus, C-terminus, or side chain of an amino acid which may be either a single amino acid or part of a longer chain sequence (i.e., a dipeptide, tripeptide, oligopeptide, or polypeptide). The carrier peptide may also be (i) a homopolymer of a naturally occurring amino acid, (ii) a heteropolymer of two or more naturally occurring amino acids, (iii) a homopolymer of a synthetic amino acid, (iv) a heteropolymer of two or more synthetic amino acids,

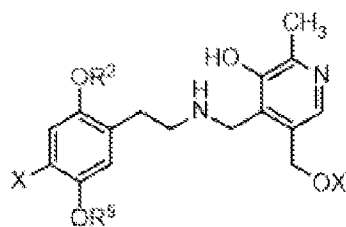
or (v) a heteropolymer of one or more naturally occurring amino acids and one or more synthetic amino acids. For example, carrier peptides may be homopolymers or heteropolymers of glutamic acid, aspartic acid, serine, lysine, cysteine, threonine, asparagine, arginine, tyrosine, and glutamine. Examples of peptides include, Lys, Ser, Phe, Gly-Gly-Gly, Leu-Ser, Leu-Glu, homopolymers of Glu and Leu, and heteropolymers of (Glu)_n-Leu-Ser.

[124] In some aspects, provided herein are prodrugs of disclosed compounds that incorporate a vitamin B6 moiety. Vitamin B6 has six chemically distinct forms, including pyridoxine, pyridoxal, pyridoxamine, and their respective phosphorylated derivatives:



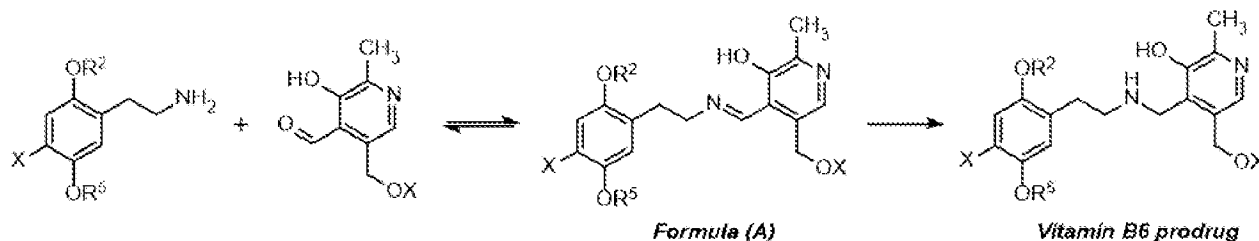
[125] Pyridoxal 5'-phosphate has the highest biological activity, but all of the other forms of vitamin B6 can be converted to pyridoxal 5'-phosphate *in vivo* (Bachmann, et al. *Molecules* 2018, 23(9), 2117). Humans cannot synthesize any forms of vitamin B6, and thus must obtain it by dietary means (Calderón-Ospina, et al. *CNS Neurosci. Ther.* 2020, 26(1), 5-13). As vitamin B6 plays an essential role in neurotransmitter production, it must be transported into the CNS (*Id.*). Transporters, such as SLC19A2 and SLC19A3, i.e., thiamine transporters (THTR) 1 and 2, are shown to transport pyridoxine (Yamashiro et al., *J Biol Chem.* 2020, 295(50), 16998-17008). Various vitamin B6 conjugates have been synthesized and evaluated for their ability to act as prodrugs by enabling the transport of a therapeutically active component across cellular membranes (see, e.g., Araujo de Oliveira, et al. *ACS Omega* 2022, 7(14), 11678-11687; Day, et al. *Mol Pharm.* 2011, 8(1), 297-301; Wu, et al. *FASEB J.* 2011, 25(7), 2109-2122; Zhang, et al. *Proc. Natl. Acad. Sci. USA* 1991, 88(23), 10407-10410).

[126] In embodiments, provided are vitamin B6 prodrugs of disclosed compounds, with the following structure:



, wherein X is H or PO_3H_2 .

[127] Vitamin B6 prodrugs are synthesized by first reacting a disclosed compound with a pyridoxal precursor. A condensation reaction between the primary amine ($-\text{NH}_2$) of the compound and the pyridoxal aldehyde ($-\text{COH}$) reversibly forms the imine compound of Formula (A), along with water (H_2O) as a reaction byproduct.



[128] The imine compound of Formula (A) may be isolated from the reaction mixture. In some embodiments, the compound of Formula (A) can be isolated, purified, and used as a prodrug as described in various embodiments herein. Alternatively, the compound of Formula (A) can be used as a synthetic intermediate (with or without being isolated from the reaction mixture) in the synthesis of vitamin B6 prodrugs of the disclosure. In some embodiments, the compound of Formula (A) is reduced with a suitable reducing agent (e.g., NaBH_4) to irreversibly form a vitamin B6 prodrug of the disclosure.

[129] Generally, the disclosed compounds are administered as part of a pharmaceutical composition or formulation, but are prepared for inclusion in such composition or formulation as isolated or purified compounds. The terms “isolated,” “purified,” or “substantially pure” herein refer to material that is substantially or essentially free from components that normally accompany the material when the material is synthesized, manufactured, or otherwise produced. An “isolated,” “purified,” or “substantially pure” preparation of a compound thus refers to a preparation having a chromatographic purity (of the desired compound) of greater than 90%, more preferably greater than 95%, more preferably greater than 96%, more preferably greater than 97%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, and most preferably greater than 99.9%, as determined by area normalization of an HPLC profile or other similar detection method.

[130] Preferably the substantially pure compound is substantially free of any other active compounds which are not intended to be administered to a subject. In this context “substantially free” can be taken to mean that no active compound(s) other than the active compound intended to be administered to a subject are detectable by HPLC or other similar detection method, or are below a desired threshold of detection such as defined

above.

[131] It should be understood that any reference to a disclosed compound or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, will include all amorphous and polymorphic forms. In the case of solid compositions, in particular, it is understood that the compounds used in the disclosed compositions and methods may exist in different forms. For example, the compounds may exist in stable and metastable crystalline forms, isotropic and amorphous forms, milled forms and nano-particulate forms, all of which are intended to be within the scope hereof. Further, disclosed compounds include crystalline forms, i.e., polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs may have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[132] The disclosed compounds now generally described will be more readily understood by reference to the following description and examples, which are included for the purposes of illustration of certain aspects of the embodiments of the present invention. The following is not intended to limit the invention, as one of skill in the art would recognize from the teachings and examples herein that other techniques and methods can satisfy the claims and be employed without departing from the scope of the invention. Indeed, while this invention has been particularly shown and described with reference to certain exemplary embodiments, it will be understood by those skilled in the art that various changes in form and details may be made without departing from the scope or spirit of the invention encompassed by the appended claims.

a. Deuterated and/or Fluorinated Compounds

[133] In some aspects the compounds have at least one desired isotopic substitution of an atom at an amount above the natural abundance of the isotope, i.e., are isotopically enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons.

[134] Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, and chlorine such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , and ^{36}Cl respectively. In one non-limiting embodiment, isotopically labeled compounds can be used in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of the

disclosure can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[135] By way of example and without limitation, isotopes of hydrogen including deuterium (^2H) and tritium (^3H) may be used anywhere in described structures that achieves the desired result. Alternatively or in addition, isotopes of carbon, e.g., ^{13}C and ^{14}C , may be used.

[136] Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is at least 60, 70, 80, 90, 95, or 99% or more enriched in an isotope at any location of interest. In one non-limiting embodiment, deuterium is 90, 95, or 99% enriched at a desired location.

[137] The term “isotopically-labeled” analog refers to an analog that is a “deuterated analog,” a “ ^{13}C -labeled analog,” or a “deuterated/ ^{13}C -labeled analog.” The term “deuterated analog” means a compound described herein, whereby a H-isotope, i.e., hydrogen/protium (^1H), is substituted by a H-isotope, i.e., deuterium (^2H). Deuterium substitution can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted by at least one deuterium. In certain embodiments, the isotope is at least 60, 70, 80, 90, 95, or 99% or more enriched in an isotope at any location of interest. In some embodiments it is deuterium that is 90, 95, or 99% enriched at a desired location. Unless indicated to the contrary, the deuteration is at least 80% at the selected location. Deuteration can occur at any replaceable hydrogen that provides the desired results.

[138] In some embodiments, the disclosed compounds are used as research tools, such as tools for scientific research. In embodiments, the disclosed compounds are used as analytical reagents. In embodiments, the disclosed compounds are used for spectroscopy, quality control, and forensic applications. In embodiments, disclosed compounds are useful in an imaging context, such as medical imaging. In embodiments, disclosed compounds may be used for tissue imaging.

[139] One example of use as a research tool is in the determination of the structure and function of a receptor in vitro, in vivo, or in silico. In embodiments, disclosed compounds are used in receptor, ion channel, enzyme, and transporter binding studies. In embodiments, disclosed compounds are used in mapping, and functional studies. In embodiments, disclosed compounds are used to identify binding sites. In embodiments, disclosed compounds for such uses are radiolabeled. In embodiments, disclosed compounds for such uses comprise an isotope of hydrogen and/or a radiohalogen. In embodiments, the isotope of hydrogen is protium, deuterium, or tritium. In embodiments, the radiohalogen is radioactive fluorine, chlorine, bromine, iodine, or astatine.

[140] In some embodiments, disclosed compounds may be used as research tools, such as receptor probes, for serotonin receptors, for example, HTR₁, HTR₂, and HTR₆ receptors, including subtypes thereof. In embodiments, disclosed compounds may be used as research tools for 5-HT_{2A} receptors. In embodiments, the research tool is a receptor probe, which may be used for determining downstream events of receptor-ligand interaction, e.g., calcium regulation, kinase, phosphatase and phospholipase activation, and lipid trafficking. In embodiments, the receptor is a recombinant receptor. In embodiments, the receptor is a wild-type receptor. In embodiments, the receptors are of mammalian origin. In embodiments, the receptors are of human origin.

[141] In some embodiments, a disclosed composition comprises a mixture of one or more deuterium-substituted compounds and corresponding non-substituted compounds in a fixed ratio, and will contain a ratio of deuterium-substituted to non-substituted compounds (as mole ratio or mass ratio), including a pharmaceutically acceptable salt, hydrate, or solvate thereof, of 1:1, at least 1:1, at least 1.1:1, at least 1.2:1, at least 1.3:1, at least 1.4:1, at least 1.5:1, at least 1.6:1, at least 1.7:1, at least 1.8:1, at least 1.9:1, at least 2.0:1, at least 2.5:1, at least 3.0:1, at least 4.0:1, at least 5.0:1, at least 6.0:1, at least 7.0:1, at least 8.0:1, at least 9.0:1, and at least 10:1, at least 11:1, at least 12:1, at least 13:1, at least 14:1, at least 15:1, at least 16:1, at least 17:1, at least 18:1, at least 19:1, at least 20:1, at least 25:1, at least 30:1, at least 40:1, at least 50:1, at least 60:1, at least 70:1, at least 80:1, at least 90:1, and at least 100:1, including these exact ratios themselves.

[142] In embodiments, a disclosed composition comprises a disclosed compound having fluorine substitution (e.g., a fluoroalkyl group) and corresponding non-substituted compounds in a fixed ratio, and contains a ratio of fluorine-substituted to non-substituted compounds (mole or mass ratio) of 1:1, at least 1:1, at least 1.1:1, at least 1.2:1, at least 1.3:1, at least 1.4:1, at least 1.5:1, at least 1.6:1, at least 1.7:1, at least 1.8:1, at least 1.9:1, at least 2.0:1, at least 2.5:1, at least 3.0:1, at least 4.0:1, at least 5.0:1, at least 6.0:1, at least 7.0:1, at least 8.0:1, at least 9.0:1, and at least 10:1, at least 11:1, at least 12:1, at least 13:1, at least 14:1, at least 15:1, at least 16:1, at least 17:1, at least 18:1, at least 19:1, at least 20:1, at least 25:1, at least 30:1, at least 40:1, at least 50:1, at least 60:1, at least 70:1, at least 80:1, at least 90:1, and at least 100:1, including these exact ratios.

b. Stereoisomers and Enantiomeric Mixtures

[143] The disclosed compounds may contain one or more asymmetric centers and give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)– or (S)–. The disclosure is meant to include all such possible isomers, as well as mixtures thereof, including racemic and optically pure forms.

[144] Optically active (R)– and (S)–, (–)– and (+)–, or (D)– and (L)–isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Various methods are known in the art

for preparing optically active forms and determining activity. Such methods include standard tests described herein and other similar tests known in the art. Examples of methods that can be used to obtain optical isomers of the compounds according to the disclosure include the following: i) physical separation of crystals whereby macroscopic crystals of the individual enantiomers are manually separated. This technique may particularly be used if crystals of the separate enantiomers exist (i.e., the material is a conglomerate), and the crystals are visually distinct; ii) simultaneous crystallization whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state; iii) enzymatic resolutions whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme; iv) enzymatic asymmetric synthesis, a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer; v) chemical asymmetric synthesis whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries; vi) diastereomer separations whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer; vii) first- and second-order asymmetric transformations whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually, in principle, all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomers; viii) kinetic resolutions comprising partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions; ix) enantiospecific synthesis from non-racemic precursors whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis; x) chiral liquid chromatography whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions; xi) chiral gas chromatography whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase; xii) extraction with chiral solvents whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a

particular chiral solvent; and xiii) transport across chiral membranes whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane, which allows only one enantiomer of the racemate to pass through.

[145] In embodiments, a disclosed compound may be provided in a composition that is not enantiomerically enriched (i.e., a composition comprising the disclosed compound(s) as a racemic mixture). In other embodiments, a disclosed compound may be provided in a composition that is enantiomerically enriched, such as a mixture of enantiomers in which one enantiomer is present in excess, in particular to the extent of at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, or at least 99.9%, and up to (and including) 100%.

[146] In embodiments, a compound is provided in a composition that is enantiomerically enriched with the R-isomer, comprising the R-isomer in enantiomeric excess of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%.

[147] In embodiments, a compound is provided in a composition that is enantiomerically enriched with the S-isomer, comprising the S-isomer in enantiomeric excess of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%.

[148] In embodiments, a disclosed compound is provided in a composition comprising the R-isomer and the S-isomer in a R:S ratio of about 20:1 to about 1:20. In some embodiments, the R:S ratio is greater than about 20:1, or about 20:1, 15:1, 12:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, or 2:1. In some embodiments, a disclosed compound is provided as the R-isomer in an enantiomerically pure composition. In some embodiments, the R:S ratio is about 1:1, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:15, 1:20, or greater than about 1:20. In some embodiments, a disclosed compound is provided as the S-isomer in an enantiomerically pure composition.

[149] When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, tautomeric forms are included.

C. Exemplary Features of Disclosed Compounds

[150] In some aspects, features of disclosed compounds provide various advantages. Such advantages may be related to modulation of neurotransmission, pharmacokinetics, such as properties related to absorption,

distribution, metabolism, and excretion of a disclosed compound, and subjective effects, such as upon administration to a subject. In some embodiments, such advantages are determined relative to a comparator. In some embodiments, the comparator is a 2,5-dimethoxyphenethylamine. In some embodiments, the comparator is a 4-halo-substituted 2,5-dimethoxyphenethylamine. In some embodiments, the comparator is 4-bromo-2,5-dimethoxyphenethylamine (2C-B).

[151] The 5-HT₂ receptor family consists of the three distinct receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. Among these, 5-HT_{2A} and 5-HT_{2C} receptors are more highly expressed in the brain, and 5-HT_{2B} receptors have lower brain expression but higher expression in the periphery. Activation of the 5-HT_{2A} receptor may provide therapeutic value through a variety of mechanisms, and is implicated in producing subjective hallucinogenic or psychedelic effect (López-Giménez & González-Maeso, Curr. Top. Behav. Neurosci. 2018, 36, 45-73). Due to high sequence homology among the three 5-HT₂ receptor subtypes, many compounds that activate the 5-HT_{2A} receptor are also agonists at the 5-HT_{2B} and 5-HT_{2C} receptors, which can result in side effects and/or reduced therapeutic efficacy (Nichols, Pharmacol. Rev., 2016, 68, 264-355). For example, activation of 5-HT_{2B} receptors in cardiac muscle tissue has been linked to heart valve disease (Hutcheson, et al., Pharmacol. Ther. 2011, 132(2): 146–157). Activation of 5-HT_{2B} receptors by classic psychedelics has raised concerns about potential long-term consequences of chronic psychedelic use, which may be necessary for treating chronic conditions like depression and anxiety.

[152] Because many of the therapeutic benefits of classical psychedelics may derive, at least in part, from activation of the 5-HT_{2A} receptor, next-generation compounds that selectively agonize the 5-HT_{2A} receptor may have increased therapeutic efficacy, improved safety profiles, and reduced side effects. Accordingly, in some embodiments, a disclosed compound has increased selectivity for the 5-HT_{2A} receptor over another serotonin receptor (e.g., the 5-HT_{2B} receptor, or the 5-HT_{2C} receptor) relative to a comparator. In some embodiments, a disclosed compound has increased selectivity for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor relative to a comparator. In some embodiments, a disclosed compound has increased selectivity for the 5-HT_{2A} receptor over the 5-HT_{2C} receptor relative to a comparator. In some embodiments, selectivity is defined by the ratio of the half-maximal effective concentration (EC₅₀) of a disclosed compound for the 5-HT_{2A} receptor as compared to another receptor (e.g., a serotonin receptor, such as the 5-HT_{2B} receptor, or the 5-HT_{2C} receptor).

[153] For example, **ASR2001** has a 5-HT_{2A} EC₅₀ of 0.0424 μM and a 5-HT_{2B} EC₅₀ of 3.9717 μM in an *in vitro* Ca flux model (see Example 2). As such, **ASR2001** has a ca. 94-fold selectivity for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor. In some embodiments, a disclosed compound has about a 2-fold, 5-fold, 10-fold, 20-fold, 30-fold, 50-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, or at least 200-fold selectivity for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor. In some embodiments, a disclosed compound has about a 90-fold selectivity

for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor. In some embodiments, a disclosed compound has at least a 2-fold, 5-fold, 10-fold, 20-fold, 30-fold, 50-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, or at least 200-fold selectivity for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor. In some embodiments, a disclosed compound has at least a 90-fold selectivity for the 5-HT_{2A} receptor over the 5-HT_{2B} receptor.

[154] In some embodiments, a disclosed compound has reduced adverse events relative to a comparator. Examples of adverse events include those related to neurotoxicity, cardiotoxicity, and renal toxicity, among others. In some embodiments, the reduction for at least one adverse event is at least a 5% reduction, at least a 10% reduction, at least a 15% reduction, at least a 25% reduction, at least a 50% reduction, at least a 75% reduction, at least a 90% reduction, at least a 95% reduction, at least a 99% reduction, or a reduction beyond the threshold of measurement, whether determined within-patient or across patients or patient groups, or in a rodent or other suitable animal model, or determined in vitro, in silico, or otherwise measured using a standard such as one known to those of ordinary skill for the determination or quantification of the adverse event(s) in question, such as relating to anxiety, cardiovascular effects such as blood pressure and heart rate, hyperthermia, hyperhidrosis, jaw tightness and bruxism, muscle tightness, psychostimulation, appetite, nausea, concentration, and balance, as well as markers for or correlated with potential neurotoxicity, and including such exemplary tests and procedures that are in silico (e.g., computer analysis or simulation, including by AI, machine learning, or deep learning), in vitro (e.g., biochemical assays, tissue culture), and in vivo (e.g., behavioral assessment; functional observational batteries; tests of motor activity, schedule-controlled operant behavior, neurological function, neurophysiological function, nerve-conduction, evoked-potential; neurochemical, neuroendocrine, or neuropathological measures; EEG; imaging), as well as the use of physiological biomarkers (body temperature; heart rate; respiratory rate; blood oxygenation; systolic blood pressure (SBP); diastolic blood pressure (DBP); mean arterial pressure (MAP); pulse pressure (PP); Continuous Beat-by-Beat Blood Pressure (CNIBP); heart rate variability (HRV); hemodynamic response (HR); glucose; cortisol; serotonin; dopamine; and brain derived neurotrophic factor (BDNF)), and patient assessments.

[155] In embodiments, a disclosed compound or composition thereof does not cause a neurotoxic effect, such as in an in vitro assay or upon administration to a subject. In some embodiments, a disclosed compound or composition thereof causes a reduced neurotoxic effect, such as in an in vitro assay or upon administration to a subject. In some embodiments, the reduction of a neurotoxic effect is at least a 5% reduction, at least a 10% reduction, at least a 15% reduction, at least a 25% reduction, at least a 50% reduction, at least a 75% reduction, at least a 90% reduction, or at least a 95% reduction, or at least a 99% reduction, relative to a comparator.

[156] In some embodiments, the neurotoxic effect is determined by measuring one or more of: a) oxidative stress and dopamine-based quinones; b) mitochondrial dysfunction; and c) activation of glial cells. In some embodiments, neurotoxicity or a reduction thereof is determined by evaluating mitochondrial dysfunction. Mitochondrial dysfunction may be evaluated by measuring one or more of mitochondrial membrane potential (MMP), mitochondrial swelling, mitochondrial outer membrane damage, the mitochondrial cytochrome c release, and ADP/ATP ratio. See, e.g., Taghizadeh et al., *Free Radic. Biol. Med.* 2016;99: 11–19, in which markers of mitochondrial dysfunction include a significant increase in ROS formation, collapse of MMP, mitochondrial swelling, outer membrane damage, cytochrome c release from the mitochondria, and increased ADP/ATP ratio.

[157] In some embodiments, neurotoxicity or a reduction thereof is determined by assessing the activation of glial cells. Activation of quiescent glial cells has been described, e.g., by Herndon et al., *Toxicological Sciences*, 2014;138(1):130–138. Reactive astrogliosis can be measured with glial fibrillary acidic protein (GFAP) staining, and microglia reactivity can be visualized by immunostaining complement type 3 receptor (CD11b). See, e.g., Frau et al., *J Neurochem.* 2013;124(1):69-78 and Frau et al., *Neurotoxicology.* 2016;56:127-138. In embodiments, neurotoxicity or a reduction thereof is determined in vitro. In embodiments, neurotoxicity or a reduction thereof is determined in vivo.

[158] In some embodiments, a subject administered a disclosed compound does not experience serotonin syndrome. In embodiments, a subject administered a disclosed compound experiences reduced incidence and/or severity of serotonin syndrome, e.g., relative to administration of a comparator compound. Co-administration of agents that increase serotonin levels, such as SERT inhibitors and MAOIs have been shown to potentiate serotonin neuromodulation, a potential complication of which is serotonin syndrome. See, e.g., Izumi et al., *Eur J Pharmacol.* 2006;532(3):258-64, Nakagawasai et al., *Neurotoxicol.* 2004;25(1-2):223-32, and Tadano et al., *J Pharmacol Exp Ther.* 1989;250(1):254-60. Serotonin syndrome ranges in severity from mild to fatal, and clinical presentations include autonomic dysfunction, neuromuscular excitation, and altered mental status, as described in, e.g., Boyer & Shannon, *N Engl J Med.* 2005;352(11):1112-20 and Wang et al., *Cleve Clin J Med.* 2016 Nov;83(11):810-817.

[159] In some embodiments, a subject administered a disclosed compound does not experience delirium. In embodiments, a subject administered a disclosed compound experiences reduced incidence and/or severity of delirium, e.g., relative to administration of a comparator compound. Signs of delirium, such as drug-induced delirium, include disturbances of consciousness, attention, cognition, and perception. The severity of delirium may be assessed using available tools, e.g., the Memorial Delirium Assessment Scale (MDAS) subitems and Karnofsky Performance Status scale (KPS). See, e.g., Boettger et al., *Journal of Geriatrics.* 2014:247042;

Carter et al. *Drug Saf.* 1996;15(4):291-301; Karlsson, *Dement Geriatr Cogn Disord.* 1999;10(5):412-5. Delirium has been described following ingestion of some psychedelics, such as the tryptamine 5-MeO-DALT, e.g., in Jovel et al., *J Forensic Sciences*, 59(3), 844–846.

[160] In some embodiments, disclosed compounds do not cause cardiotoxicity following administration to a subject. In some embodiments, reduced severity and/or incidence of cardiotoxicity is observed following administration of a disclosed compound to a subject, e.g., relative to administration of a comparator compound. In some embodiments, disclosed compounds do not cause irregular heartbeat, e.g., tachycardia. In some embodiments, disclosed compounds show reduced inhibition of a cardiac ion channel, such as by at least 5%, 10%, 25%, 50%, 75%, 100%, 150%, or 200% relative to a comparator. In some embodiments, disclosed compounds do not inhibit the function of, such as block, cardiac ion channels. In some embodiments, disclosed compounds do not block calcium channel CAV1.2. In some embodiments, disclosed compounds do not block potassium channel hERG. In some embodiments, disclosed compounds do not block sodium channel NAV1.5. In embodiments, a disclosed compound has an IC_{50} of greater than 10 μ M for any one or more of CAV1.2, hERG, and NAV1.5. In some embodiments, CAV1.2, hERG, and NAV1.5 are of human origin.

[161] In some embodiments, disclosed compounds do not cause rhabdomyolysis following administration to a subject. In some embodiments, reduced severity and/or incidence of rhabdomyolysis is observed following administration of a disclosed compound to a subject, e.g., relative to administration of a comparator compound. In some embodiments, disclosed compounds do not cause kidney injury, such as acute kidney injury, following administration to a subject. In some embodiments, reduced severity and/or incidence of kidney injury is observed following administration of a disclosed compound to a subject, e.g., relative to administration of a comparator compound. In embodiments, disclosed compounds do not elevate serum levels of rhabdomyolysis markers and/or kidney injury markers, e.g., muscular enzymes and creatinine phosphokinase. In embodiments, administration of a disclosed compound results in reduced markers of rhabdomyolysis and/or kidney injury, such as reductions by at least 5%, 10%, 25%, 50%, 75%, 100%, 150%, or 200%, relative to a comparator. In embodiments administration of disclosed compounds to a subject does not result in or results in a reduction of any one or more of renal vasoconstriction, intraluminal cast formation, and direct myoglobin toxicity.

[162] Adverse effects of certain psychedelics, such as the tryptamine 5-MeO-DALT, have been described and include, e.g., cardiac abnormalities, acute kidney injury and rhabdomyolysis. See, e.g., Dailey et al., *Toxicol. Clin. Toxicol.* 2003;41:742–743 and Jovel et al., *Journal of Forensic Sciences*, 59(3), 844–846. Rhabdomyolysis is a breakdown of skeletal muscle due to direct or indirect muscle injury that may lead to kidney injury, such as renal failure. See, e.g., Polderman, *Int J Artif Organs.* 2004;27(12):1030-3 and Lima et al., *Saudi J Kidney Dis Transpl.* 2008;19(5):721-9. Signs of rhabdomyolysis and kidney injury may be

determined according to known methods, including, e.g., measuring an elevation of muscular enzymes and creatinine phosphokinase, and identifying renal vasoconstriction, intraluminal cast formation, and direct myoglobin toxicity. Measurements and comparisons of toxicity can be made according to ordinary methods known to those in the art.

[163] In some embodiments, a disclosed compound has a reduced rate of metabolism, for example by O-demethylation or O-dealkylation, relative to a comparator, in an amount of at least a 5% reduction, at least a 10% reduction, at least a 15% reduction, at least a 25% reduction, at least a 50% reduction, at least a 75% reduction, at least a 90% reduction, at least a 95% reduction, or at least a 99% reduction.

[164] The permeability, such as apparent permeability, of a compound describes how effectively it can pass through a membrane. A medium permeability compound may have an in vitro apparent permeability of 50-150 nm/s, wherein the range is inclusive. A high permeability compound may have an in vitro apparent permeability in excess of 150 nm/s, wherein the range is inclusive. Measures of permeability, such as in vitro methods, are available to one of skill in the art and include, e.g., a Madin-Darby canine kidney cell line (MDCK) permeability assay and a parallel artificial membrane permeation assay (PAMPA). For example, PAMPA is an in vitro model of passive diffusion, which has shown a high degree of correlation with permeation across a variety of barriers, including Caco-2 cultures, the gastrointestinal tract, blood-brain barrier, and skin. See, e.g., Chavda & Shah, Chapter 25 - Self-emulsifying delivery systems: one step ahead in improving solubility of poorly soluble drugs, In Micro and Nano Technologies, Nanostructures for Cancer Therapy, Elsevier, 2017, pages 653-718.

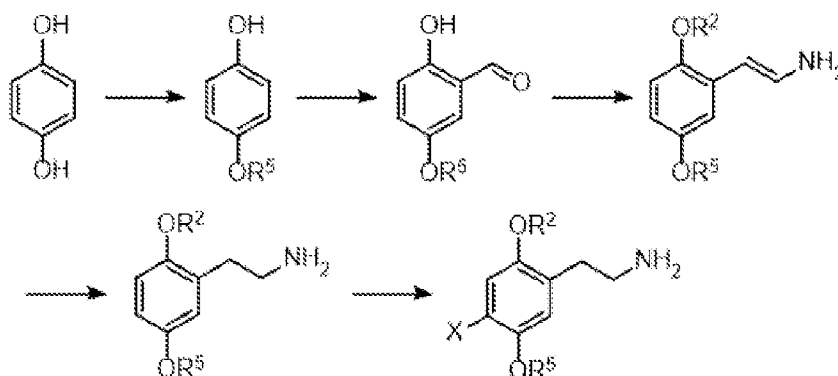
[165] In some embodiments, a disclosed compound has medium permeability. In embodiments, a disclosed compound has high permeability. In embodiments, a disclosed compound has increased permeability relative to a comparator. In embodiments, a disclosed compound has increased permeability relative to a comparator. In embodiments, permeability of a disclosed compound is increased by about or at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, or 200% relative to a comparator.

[166] In embodiments, disclosed compounds selectively inhibit the uptake activity of the serotonin transporter (SERT). Blocking the uptake activity of monoamine transporters, such as SERT, DAT, or NET, may result in an increase of circulating monoamines and in neurotransmission modulated thereby. In embodiments, the receptors and transporters are of mammalian origin. In embodiments, the receptors and transporters are of human origin.

C. Methods of Synthesis

[167] In some aspects, provided herein are methods of preparing the disclosed compounds.

[168] In embodiments, disclosed compounds are synthesized according to the general reaction sequence:



[169] Briefly, hydroquinone is monoalkylated to install R^5 , then oxidized to an aldehyde intermediate. The remaining phenol group is alkylated to install R^2 , then this dialkylated intermediate is converted to a nitrostyrene, which is reduced to a phenethylamine. Finally, X is installed. Each of these reactions can be performed according to methods known to one of skill in the art, for example those disclosed in WO2023/049480. See also Example 1, which provides an exemplary synthesis of 2-(4-bromo-5-propoxy-2-methoxyphenyl)ethan-1-amine.

[170] Other methods for synthesis of disclosed compounds, and any necessary starting materials, are either described in the art or will be readily apparent to the skilled artisan in view of general references well-known in the art (see, e.g., Green et al., "Protective Groups in Organic Chemistry," (Wiley, 2nd ed. 1991); Harrison et al., "Compendium of Synthetic Organic Methods," Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser et al., "Reagents for Organic Synthesis," Volumes 1-17, Wiley Interscience; Trost et al., "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," John Wiley & Sons, 1995) and may be used to synthesize the disclosed compounds.

[171] In general, the approaches used for similar compounds (Shulgin & Shulgin. 1992. PiHKAL. A chemical love story, Transform Press, Berkeley CA; Glennon et al. 1986. J. Med. Chem., 29(2), 194-199; Nichols et al. 1991. J. Med. Chem., 34(1), 276-281; Kedrowski et al. 2007. Organic Letters, 9(17), 3205-3207; Heravi & Zadsirjan. 2016. Current Organic Synthesis, 13(6), 780-833; Keri et al. 2017. European J. Med. Chem., 138, 1002-1033; Pérez-Silanes et al. 2001. J. Heterocyclic Chem, 38(5), 1025-1030; and references therein), such adaptation being that known and understood to those of ordinary skill.

D. Pharmaceutical Compositions

[172] In some aspects, provided herein are compositions, such as pharmaceutical compositions, comprising a disclosed compound, such as a compound of any disclosed Formulae or subformula thereof. "Pharmaceutical

compositions” are compositions comprising disclosed compound(s) together in an amount (for example, in a unit dosage form) with a pharmaceutically acceptable carrier, diluent, or excipient. Some embodiments will not have a single carrier, diluent, or excipient alone, but will include multiple carriers, diluents, and/or excipients. Compositions can be prepared by standard pharmaceutical formulation techniques as disclosed in, e.g., Remington: The Science & Practice of Pharmacy (2020) 23th ed., Acad. Press., Cambridge, Mass.; The Merck Index (1996) 12th ed., Merck Pub. Grp., Whitehouse, N.J.; Pharm. Principles Solid Dosage Forms (1993), Tech. Pub. Co., Inc., Lancaster, Pa.; Ansel & Stoklosa, Pharm. Calculations (2001) 11th ed., Lippincott Williams & Wilkins, B'more, Md.; & Poznansky et al. Drug Delivery Sys. (1980), R.L. Juliano, ed., Oxford, N.Y., pp. 253-315).

[173] “Pharmaceutically acceptable” used in connection with an excipient, carrier, diluent, or other ingredient means the ingredient is generally safe and, within the scope of sound medical judgment, suitable for use in contact with cells of humans and animals without undue toxicity, irritation, allergic response, or complication, commensurate with a reasonable risk/benefit ratio.

[174] In some embodiments, pharmaceutical compositions comprising a disclosed compound can be administered by a variety of routes including oral, mucosal (e.g., buccal, sublingual), rectal, transdermal, subcutaneous, intravenous, intramuscular, inhaled, and intranasal. In some embodiments, the compounds employed in the methods of this disclosure are effective as oral, mucosal (e.g., buccal, sublingual), rectal, transdermal, subcutaneous, intravenous, intramuscular, inhaled, and intranasal compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound (see, e.g., Remington, 2020).

[175] The disclosed compositions can be formulated in a unit dosage form, each dosage containing a therapeutically effective amount of the active ingredients, for example in the dosage amounts disclosed below. The term “unit dosage form” refers to a physically discrete unit suited as unitary dosages for the subject to be treated, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect(s), in association with a suitable pharmaceutical carrier, diluent, or excipient. Unit dosage forms are often used for ease of administration and uniformity of dosage. Unit dosage forms can contain a single or individual dose or unit, a sub-dose, or an appropriate fraction thereof (e.g., one half a “full” dose for a “booster” dose as described below), of the pharmaceutical composition administered.

[176] Unit dosage forms include capsules, troches, cachets, lozenges, tablets, ampules and vials, which may include a composition in a freeze-dried or lyophilized state; a sterile liquid carrier, for example, can be added prior to administration or delivery in vivo. Unit dosage forms include ampules and vials with liquid compositions disposed therein. Unit dosage forms further include compounds for transdermal administration, such as

“patches” that contact the epidermis (including the mucosa) of a subject for an extended or brief period of time.

[177] In embodiments, disclosed compositions are formulated in a pharmaceutically acceptable oral dosage form. Oral dosage forms include oral liquid dosage forms (e.g., tinctures, drops, emulsions, syrups, elixirs, suspensions, solutions, and the like) and oral solid dosage forms. Disclosed pharmaceutical compositions also may be prepared as formulations suitable for intramuscular, subcutaneous, intraperitoneal, or intravenous injection, comprising physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, liposomes, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

[178] In some embodiments, a disclosed composition is formulated as an oral solid dosage form. Oral solid dosage forms may include but are not limited to, lozenges, troches, tablets, capsules, caplets, powders, pellets, multiparticulates, beads, spheres, and/or any combinations thereof. Oral solid dosage forms may be formulated as immediate release, controlled release, sustained release, extended release, or modified release formulations. Accordingly, in some embodiments, the disclosed oral solid dosage forms may be in the form of a tablet (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder), a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or “sprinkle capsules”), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In embodiments, the pharmaceutical formulation is in the form of a powder. In embodiments, the pharmaceutical formulation is in the form of a tablet, including a fast-melt tablet. Additionally, pharmaceutical formulations may be administered as a single capsule or in multiple capsule dosage form. In embodiments, the pharmaceutical formulation is administered in two, three, four, or more capsules or tablets.

[179] Oral solid dosage forms may contain pharmaceutically acceptable excipients such as fillers, diluents, lubricants, surfactants, glidants, binders, dispersing agents, suspending agents, disintegrants, viscosity-increasing agents, film-forming agents, granulation aid, flavoring agents, sweetener, coating agents, solubilizing agents, and combinations thereof. Oral solid dosage forms also can comprise one or more pharmaceutically acceptable additives such as a compatible carrier, complexing agent, ionic dispersion modulator, disintegrating agent, surfactant, lubricant, colorant, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, alone or in combination, as well as supplementary active compound(s).

[180] Supplementary active compounds include preservatives, antioxidants, antimicrobial agents including biocides and biostats such as antibacterial, antiviral and antifungal agents. Preservatives can be used to inhibit

microbial growth or increase stability of the active ingredient thereby prolonging the shelf life of the formulation. Suitable preservatives are known in the art and include EDTA, EGTA, benzalkonium chloride or benzoic acid or benzoates, such as sodium benzoate. Antioxidants include vitamin A, vitamin C (ascorbic acid), vitamin E, tocopherols, other vitamins or provitamins, and compounds such as alpha lipoic acid.

[181] In embodiments, a disclosed composition is formulated as an oral liquid dosage form. Oral liquid dosage forms include tinctures, drops, emulsions, syrups, elixirs, suspensions, and solutions, and the like. Oral liquid dosage forms may be formulated with any pharmaceutically acceptable excipient known to those of skill for the preparation of liquid dosage forms, and with solvents, diluents, carriers, excipients, and the like chosen as appropriate to the solubility and other properties of the active agents and other ingredients. Solvents may be, for example, water, glycerin, simple syrup, alcohol, medium chain triglycerides (MCT), and combinations thereof.

[182] Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as but not limited to, an oil, water, an alcohol, and combinations of these pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration. Liquid formulations also may be prepared as single dose or multi-dose beverages. Suspensions may include oils. Such oils include peanut oil, sesame oil, cottonseed oil, corn oil, and olive oil. Suitable oils also include carrier oils such as MCT and long chain triglyceride (LCT) oils. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides, and acetylated fatty acid glycerides. Suspension formulations may include alcohols, (such as ethanol, isopropyl alcohol, hexadecyl alcohol), glycerol, and propylene glycol. Ethers, such as poly(ethylene glycol), petroleum hydrocarbons such as mineral oil and petrolatum, and water may also be used in suspension formulations. Suspension can thus include an aqueous liquid or a non-aqueous liquid, an oil-in-water liquid emulsion, or a water-in-oil emulsion.

[183] In some embodiments, formulations are provided comprising the disclosed compositions and at least one dispersing agent or suspending agent for oral administration to a subject. The formulation may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained. The aqueous dispersion can comprise amorphous and non-amorphous particles consisting of multiple effective particle sizes such that a drug is absorbed in a controlled manner over time.

[184] Dosage forms for oral administration can be aqueous suspensions selected from the group including pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, and syrups. See, e.g., Singh et al., *Encyclopedia of Pharm. Tech.*, 2nd Ed., 754-757 (2002). In addition to the disclosed compounds, the liquid

dosage forms may comprise additives, such as one or more (a) disintegrating agents, (b) dispersing agents, (c) wetting agents, (d) preservatives, (e) viscosity enhancing agents, (f) sweetening agents, or (g) flavoring agents.

[185] Disclosed compositions may be prepared as formulations suitable for intramuscular, subcutaneous, intraperitoneal, or intravenous injection, comprising physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, liposomes, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

[186] In embodiments, disclosed pharmaceutical compositions may be formulated into a topical dosage form. Topical dosage forms include transmucosal and transdermal formulations, such as aerosols, emulsions, sprays, ointments, salves, gels, pastes, lotions, liniments, oils, and creams. For such formulations, penetrants and carriers can be included in the pharmaceutical composition. Penetrants are known in the art, and include, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. For transdermal administration, carriers can include Vaseline®, lanolin, PEG, alcohols, transdermal enhancers, and combinations thereof.

E. Pharmaceutical Combinations

[187] It should be readily appreciated that the disclosed compositions are not limited to combinations of a single compound, or (when formulated as a pharmaceutical composition) limited to a single carrier, diluent, and/or excipient alone, but may also include combinations of multiple compounds (including additional active compounds), and/or multiple carriers, diluents, and excipients. Pharmaceutical compositions of this disclosure thus may comprise a disclosed compound together with one or more other active agents (or their derivatives and analogs) in combination, together with one or more pharmaceutically-acceptable carriers, diluents, and/or excipients, and additionally with one or more other active compounds.

[188] In embodiments, a disclosed formulation is prepared to increase an existing therapeutic effect, provide an additional therapeutic effect, increase a desired property such as stability or shelf-life, decrease an unwanted effect or property, alter a property in a desirable way (such as pharmacokinetics or pharmacodynamics), modulate a desired system or pathway (e.g., a neurotransmitter system), or provide synergistic effects.

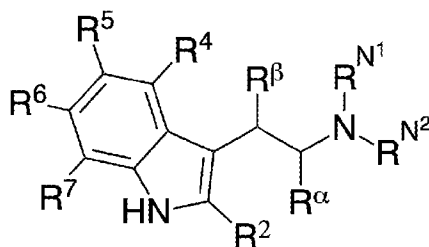
[189] "Therapeutic effects" that may be increased or added in embodiments of the disclosure include, but are not limited to, antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, and stimulant effects.

[190] "Synergistic effects" should be understood to include increases in potency, bioactivity, bioaccessibility, bioavailability, or therapeutic effect, that are greater than the additive contributions of the components acting

alone. Numerous methods known to those of skill in the art exist to determine whether there is synergy as to a particular effect, i.e., whether, when two or more components are mixed together, the effect is greater than the sum of the effects of the individual components applied alone, thereby producing “1+1 > 2.” Suitable methods include isobologram (or contour) analysis (Huang, *Front Pharmacol.* 2019; 10:1222), or the equation of Loewe additivity (Loewe & Muischnek, *Arch Exp Pathol Pharmacol.* 1926;114: 313-326). A synergistic effect also may be calculated using methods such as the Sigmoid-Emax equation (Holford & Scheiner, *Clin Pharmacokinet.* 1981;6: 429-453) and the median-effect equation (Chou & Talalay, *Adv Enzyme Regul.* 1984;22:27-55). The corresponding graphs associated with the equations referred to above are the concentration-effect curve and combination index curve, respectively. Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination.

[191] In some embodiments, a disclosed pharmaceutical composition comprises an additional active compound. In some embodiments, the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, plasticity-inducing agents (e.g., psychoplastogens), monoamine oxidase inhibitors, tryptamines, terpenes, phenylalkylamines, sedatives, stimulants, serotonergic agents, and vitamins. In some embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, increase plasticity (e.g., neural plasticity), or alter pharmacokinetics or pharmacodynamics. In some embodiments, the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.

[192] In embodiments, an additional active compound is a tryptamine. As will be understood by those in the art, tryptamines are compounds having the general structure below, wherein R^{N1} , R^{N2} , R^a , R^b , R^2 , R^4 , R^5 , R^6 , and R^7 are as defined herein and as generally understood in the art:



[193] In some embodiments, R^{N1} , R^{N2} , R^α , R^β , R^2 , R^4 , R^5 , R^6 , and R^7 are each independently hydrogen, deuterium, halogen (F, Cl, Br, or I), OH, phosphoryloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. Additionally, any two of R^{N1} , R^{N2} , R^α , R^β , R^2 , R^4 , R^5 , R^6 , and R^7 and the intervening atoms can be taken together to form an optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. In embodiments, the tryptamine is a quaternary salt, in which an additional R^{N3} is connected to the nitrogen to which R^{N1} and R^{N2} are bound; wherein R^{N3} is optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl.

[194] In some embodiments, the additional active compound is a tryptamine selected from the group consisting of O-Phosphoryl-4-hydroxy-N,N-dimethyltryptamine (psilocybin), 6-allyl-N,N-diethyl-norlysergamide (AL-LAD), N,N-dibutyltryptamine (DBT), N,N-diethyltryptamine (DET), N,N-diisopropyl-tryptamine (DiPT), 5-methoxy- α -methyltryptamine (α ,O-DMS), N,N-dimethyl-tryptamine (DMT), 2, α -dimethyltryptamine (2, α -DMT), α ,N-dimethyltryptamine (α ,N-DMT), N,N-dipropyltryptamine (DPT), N-ethyl-N-isopropyltryptamine (EiPT), α -ethyltryptamine (AET), 6,N,N-triethylnorlysergamide (ETH-LAD), 3,4-dihydro-7-methoxy-1-methylcarboline (Harmaline), 7-methoxy-1-methylcarboline (Harmine), N,N-dibutyl-4-hydroxy-tryptamine (4-HO-DBT), N,N-diethyl-4-hydroxytryptamine (4-HO-DET), N,N-diisopropyl-4-hydroxytryptamine (4-HO-DiPT), 4-hydroxy-N,N,N-trimethyltryptamine (4-HO-TMT), N,N-dimethyl-4-hydroxytryptamine (4-HO-DMT), N,N-dimethyl-5-hydroxytryptamine (5-HO-DMT, bufotenine), N,N-dipropyl-4-hydroxytryptamine (4-HO-DPT), N-ethyl-4-hydroxy-N-methyltryptamine (4-HO-MET), 4-hydroxy-N-isopropyl-N-methyltryptamine (4-HO-MiPT), 4-hydroxy-N-methyl-N-propyl-tryptamine (4-HO-MPT), 4-hydroxy-N,N-tetramethylene-tryptamine (4-HO-pyr-T), 12-methoxy-ibogamine (ibogaine), N-butyl-N-methyltryptamine (MBT), N,N-diisopropyl-4,5-methylenedioxytryptamine (4,5-MDO-DiPT), N,N-diisopropyl-5,6-methylenedioxytryptamine (5,6-MDO-DiPT), N,N-dimethyl-4,5-methylene-dioxytryptamine (4,5-MDO-DMT), N,N-dimethyl-5,6-methylenedioxytryptamine (5,6-MDO-DMT), N-isopropyl-

N-methyl-5,6-methylenedioxytryptamine (5,6-MDO-MIPT), N,N-diethyl-2-methyltryptamine (2-Me-DET), 2,N,N-trimethyltryptamine (2-Me-DMT), N-acetyl-5-methoxytryptamine (melatonin), N,N-diethyl- 5-methoxytryptamine (5-MeO-DET), N,N-diisopropyl-5-methoxy-tryptamine (5-MeO-DiPT), N,N,diallyl-5-methoxytryptamine (5-MeO-DALT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), N-isopropyl- 4-methoxy-N-methyltryptamine (4-MeO-MIPT), N-isopropyl-5-methoxy-N-methyltryptamine (5-MeO-MIPT), 5,6-dimethoxy-N-isopropyl-N-methyl- tryptamine (5,6-MeO-MIPT), 5-methoxy-N-methyl-tryptamine (5-MeO-NMT), 5-methoxy-N,N-tetramethylene- tryptamine (5-MeO-pyr-T), 6-methoxy-1-methyl-1,2,3,4-tetrahydrocarboline (6-MeO-THH), 5-methoxy-2,N,N- trimethyltryptamine (5-MeO-TMT), N,N-dimethyl- 5-methylthiotryptamine (5-MeS-DMT), N-isopropyl-N-methyl- tryptamine (MiPT), α -methyltryptamine (α -MT), N-ethyltryptamine (NET), N-methyltryptamine (NMT), 6-propyl- norlysergamide (PRO-LAD), N,N-tetra- methylenetryptamine (pyr-T), tryptamine (T), 7-methoxy-1-methyl-1,2,3,4-tetrahydrocarboline (THH), or α ,N-dimethyl-5-methoxytryptamine (α ,N,O-TMS), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a combination thereof.

[195] In embodiments, an additional tryptamine will be a “complex tryptamine” or other indolamine such as, e.g., iboga alkaloids such as ibogaine, and their analogs, metabolites, and derivatives, and beta-carbolines.

[196] In embodiments, the additional active compound is a phenylalkylamine. In embodiments, and as will be understood by those in the art, a phenylalkylamine may be a phenylalkylamine having the structure of Formula (A), wherein R^{N1} , R^{N2} , R^α , R^β , and each of R^2 - R^6 are as defined herein and as generally understood in the art.

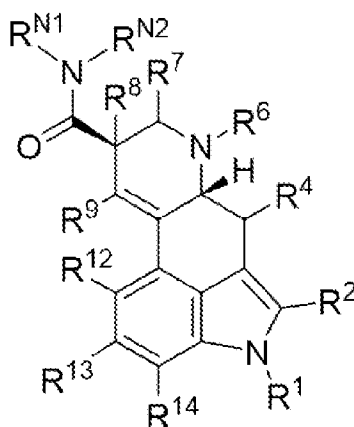
[197] In some embodiments, the additional active compound is a phenylalkylamine selected from the group consisting of α -ethyl-3,4,5-trimethoxy-phenethylamine (AEM), 4-allyloxy-3,5-dimethoxy- phenethylamine (AL), 2,5-dimethoxy-4-methylthioamphetamine (ALEPH), 2,5-dimethoxy-4-ethylthioamphetamine (ALEPH-2), 2,5-dimethoxy-4-isopropylthioamphetamine (ALEPH-4), 2,5-dimethoxy-4-phenylthioamphetamine (ALEPH-6), 2,5-dimethoxy-4-propylthioamphetamine (ALEPH-7), 2,5-dimethoxy- α -ethyl-4-methylphenethylamine (ARIADNE), 3,4-diethoxy-5-methoxy-phenethylamine (ASB), 4-butoxy-3,5- dimethoxyphenethylamine (B), 2,5-dimethoxy-4,N-dimethylamphetamine (BEATRICE), 2,5-bismethylthio-4- methylamphetamine (BIS-TOM), 4-bromo-2,5, β -trimethoxyphenethylamine (BOB), 2,5, β -trimethoxy-4- methylphenethylamine (BOD), β -methoxy-3,4-methylenedioxyphenethylamine (BOH), 2,5-dimethoxy- β - hydroxy-4-methylphenethylamine (BOHD), 3,4,5, β -tetramethoxyphenethylamine (BOM), 4-bromo-3,5- dimethoxyamphetamine (4-Br-3,5-DMA), 2-bromo-4,5-methylenedioxyamphetamine (2-Br-4,5-MDA), 3,4-methylenedioxy-N-ethylamphetamine (MDEA), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-benzyloxy-3,5-dimethoxy- amphetamine (3C-BZ), 4-chloro-2,5-dimethoxyphenethylamine (2C-C), 2,5-dimethoxy- 4-methyl-phenethylamine (2C-D), 2,5-dimethoxy-4-ethyl-phenethylamine (2C-E), 3,5-dimethoxy-4-ethoxyamphetamine (3C-E),

2,5-dimethoxy-4-fluorophenethylamine (2C-F), 2,5-dimethoxy-3,4-dimethylphenethylamine (2C-G), 2,5-dimethoxy-3,4-trimethylene-phenethylamine (2C-G-3), 2,5-dimethoxy-3,4-tetramethylenephethylamine (2C-G-4), 3,4-norbornyl-2,5-dimethoxy-phenethylamine (2C-G-5), 1,4-dimethoxynaphthyl-2-ethylamine (2C-G-N), 2,5-dimethoxyphenethylamine (2C-H), 4-iodo-2,5-dimethoxyphenethylamine (2C-I), 2,5-dimethoxy-4-nitro-phenethylamine (2C-N), 2,5-dimethoxy-4-isopropoxyphenethylamine (2C-O-4), 2,5-dimethoxy-4-propylphenethylamine (2C-P), 4-cyclopropylmethoxy-3,5-dimethoxyphenethylamine (CPM), 2,5-dimethoxy-4-methylselenophenethylamine (2C-SE), 2,5-dimethoxy-4-methylthiophenethylamine (2C-T), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), 2,5-dimethoxy-4-isopropylthiophenethylamine (2C-T-4), 2,6-dimethoxy-4-isopropylthiophenethylamine (psi-2C-T-4), 2,5-dimethoxy-4-propylthiophenethylamine (2C-T-7), 4-cyclopropylmethylthio-2,5-dimethoxyphenethylamine (2C-T-8), 4-(t)-butylthio-2,5-dimethoxyphenethylamine (2C-T-9), 2,5-dimethoxy-4-(2-methoxyethylthio)phenethylamine (2C-T-13), 4-cyclopropylthio-2,5-dimethoxy-phenethylamine (2C-T-15), 4-(s)-butylthio-2,5-dimethoxyphenethylamine (2C-T-17), 2,5-dimethoxy-4-(2-fluoro-ethylthio)phenethylamine (2C-T-21), 3,5-dimethoxy-4-trideuteromethylphenethylamine (4-D), β,β -dideutero-3,4,5-trimethoxyphenethylamine (β -D), 3,5-dimethoxy-4-methylphenethylamine (DESOXY), 2,4-dimethoxy-amphetamine (2,4-DMA), 2,5-dimethoxyamphetamine (2,5-DMA), 3,4-dimethoxyamphetamine (3,4-DMA), 2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine (DMCPA), 3,4-dimethoxy- β -hydroxyphenethylamine (DME), 2,5-dimethoxy-3,4-methylenedioxyamphetamine (DMMDA), 2,3-dimethoxy-4,5-methylenedioxyamphetamine (DMMDA-2), 3,4-dimethoxyphenethylamine (DMPEA), 4-amyl-2,5-dimethoxyamphetamine (DOAM), 4-bromo-2,5-dimethoxyamphetamine (DOB), 4-butyl-2,5-dimethoxyamphetamine (DOBU), 4-chloro-2,5-dimethoxy-amphetamine (DOC), 2,5-dimethoxy-4-(2-fluoroethyl)amphetamine (DOEF), 2,5-dimethoxy-4-ethylamphetamine (DOET), 4-iodo-2,5-dimethoxyamphetamine (DOI), 2,5-dimethoxy-4-methylamphetamine (DOM (STP)), 2,6-dimethoxy-4-methylamphetamine (psi-DOM), 2,5-dimethoxy-4-nitroamphetamine (DON), 2,5-dimethoxy-4-propylamphetamine (DOPR), 3,5-dimethoxy-4-ethoxyphenethylamine (E), 2,4,5-triethoxyamphetamine (EEE), 2,4-diethoxy-5-methoxyamphetamine (EEM), 2,5-diethoxy-4-methoxyamphetamine (EME), 4,5-dimethoxy-2-ethoxyamphetamine (EMM), 2-ethylamino-1-(3,4-methylenedioxyphenyl)butane (ETHYL-J), 2-ethylamino-1-(3,4-methylenedioxyphenyl)pentane (ETHYL-K), 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran (F-2), 6-(2-aminopropyl)-2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran (F-22), N-hydroxy-N-methyl-3,4-methylenedioxyamphetamine (FLEA), 2,5-dimethoxy-3,4-(trimethylene)amphetamine (G-3), 2,5-dimethoxy-3,4-(tetramethylene)amphetamine (G-4), 3,6-dimethoxy-4-(2-aminopropyl)benzonorbornane (G-5), 2,5-dimethoxy-3,4-dimethyl-amphetamine (GANESHA), 1,4-dimethoxynaphthyl-2-isopropylamine (G-N), 2,5-dimethoxy-4-ethylthio-N-hydroxyphenethylamine (HOT-2),

2,5-dimethoxy-N-hydroxy-4-(n)-propylthio-phenethylamine (HOT-7),
 4-(s)-butylthio-2,5-dimethoxy-N-hydroxyphenethylamine (HOT-17), 2,5-dimethoxy-
 N,N-dimethyl-4-iodoamphetamine (IDNNA), 2,3,4-trimethoxyphenethylamine (IM), 3,5-dimethoxy-4-isopropoxy-
 phenethylamine (IP), 5-ethoxy-2-methoxy-4-methyl- amphetamine (IRIS), 2-amino-1-(3,4-methylenedioxy-
 phenyl)butane (J, BDB), 3-methoxy-4,5-methylene- dioxyphenethylamine (LOPHOPHINE), 3,4,5-trimethoxy-
 phenethylamine (M), 4-methoxyamphetamine (4-MA, PMA), 2,N-dimethyl-4,5-methylenedioxyamphetamine
 (MADAM-6), 3,5-dimethoxy-4-methallyloxy- phenethylamine (MAL), 3,4-methylenedioxyamphetamine (MDA),
 N-allyl-3,4-methylenedioxyamphetamine (MDAL), N-butyl-3,4-methylenedioxyamphetamine (MDBU),
 N-benzyl-3,4-methylenedioxy- amphetamine (MDBZ), N-cyclopropylmethyl-3,4-methylenedioxyamphetamine
 (MDCPM), N,N-dimethyl-3,4-methylene- dioxyamphetamine (MDDM),
 N-ethyl-3,4-methylenedioxy- amphetamine (MDE), N-(2-hydroxyethyl)-3,4-methylenedioxyamphetamine
 (MDHOET), N-isopropyl-3,4-methylenedioxy- amphetamine (MDIP),
 N-methyl-3,4-methylenedioxyamphetamine (MDMA), 3,4-ethylenedioxy-N-methyl- amphetamine (MDMC),
 N-methoxy-3,4-methylenedioxyamphetamine (MDMEO), N-(2-methoxyethyl)-3,4- methylenedioxyamphetamine
 (MDMEOET), 3,4-methylenedioxy- α,α -N-trimethylphenethylamine (MDMP), N-hydroxy-3,4-
 methylenedioxyamphetamine (MDOH), 3,4-methylenedioxyphenethylamine (MDPEA),
 α,α -dimethyl-3,4-methylenedioxyphenethylamine (MDPH), 3,4-methylenedioxy-N-propargyl- amphetamine
 (MDPL), 3,4-methylenedioxy-N-propyl- amphetamine (MDPR), 3,4-dimethoxy- 5-ethoxyphenethylamine (ME),
 4,5-ethylenedioxy-3-methoxyamphetamine (MEDA), 4,5-diethoxy-2-methoxyamphetamine (MEE),
 2,5-dimethoxy-4-ethoxyamphetamine (MEM), 4-ethoxy-3-methoxyphenethylamine (MEPEA),
 5-bromo-2,4-dimethoxyamphetamine (META-DOB), 2,4-dimethoxy-5-methylthioamphetamine (META-DOT),
 2,5-dimethoxy- N-methylamphetamine (METHYL-DMA), 4-bromo-2,5-dimethoxy-N-methylamphetamine
 (METHYL-DOB), 2-methylamino-1-(3,4-methylenedioxyphenyl)butane (METHYL-J, MBDB),
 2-methylamino-1-(3,4-methylenedioxyphenyl)pentane (METHYL-K), 4-methoxy-N-methyl- amphetamine
 (METHYL-MA, PMMA), 2-methoxy-N-methyl-4,5-methylenedioxyamphetamine (METHYL-MMDA-2),
 3-methoxy-4,5-methylenedioxyamphetamine (MMDA), 2-methoxy- 4,5-methylenedioxyamphetamine
 (MMDA-2), 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a), 4-methoxy-2,3-methylenedioxy-
 amphetamine (MMDA-3b), 2,4-dimethoxy-5-ethoxyamphetamine (MME), 3,4-dimethoxy-5-(n)-
 propoxyphenethylamine (MP), 2,5-dimethoxy-4-(n)-propoxyamphetamine (MPM), 4,5-dimethoxy-2-
 methylthioamphetamine (ORTHO-DOT), 3,5-dimethoxy-4-propoxyphenethylamine (P), 3,5-dimethoxy-4-
 phenethyloxyphenethylamine (PE), phenethylamine (PEA), 3,5-dimethoxy-4-(2-propynyloxy) phenethylamine
 (PROPYNYL), 3,5-diethoxy-4-methoxyphenethylamine (SB), 2,3,4,5-tetra-methoxyamphetamine (TA),

4-ethoxy-3-ethylthio- 5-methoxyphenethylamine (3-TASB), 3-ethoxy-4-ethylthio-5-methoxyphenethylamine (4-TASB), 3,4-diethoxy-5-methylthio-phenethylamine (5-TASB), 4-(n)-butylthio-3,5-dimethoxyphenethylamine (TB), 4-ethoxy-5-methoxy-3-methylthio- phenethylamine (3-TE), 3,5-dimethoxy-4-ethylthiophenethylamine (TE, 4-TE), 3,4-dimethoxy-2-methylthiophenethylamine (2-TIM), 2,4-dimethoxy-3-methylthio-phenethylamine (3-TIM), 2,3-dimethoxy-4-methylthiophenethylamine (4-TIM), 3,4-dimethoxy-5-methylthiophenethylamine (3-TM), 3,5-dimethoxy-4-methylthiophenethylamine (4-TM), 3,4,5-trimethoxyamphetamine (TMA), 2,4,5-trimethoxy- amphetamine (TMA-2), 2,3,4-trimethoxyamphetamine (TMA-3), 2,3,5-trimethoxyamphetamine (TMA-4), 2,3,6-trimethoxyamphetamine (TMA-5), 2,4,6-trimethoxyamphetamine (TMA-6), 4,5-dimethoxy-3-ethylthio- phenethylamine (3-TME), 3-ethoxy-5-methoxy-4-methylthiophenethylamine (4-TME), 3-ethoxy-4-methoxy- 5-methylthiophenethylamine (5-TME), 3,4-methylenedioxy-2-methylthioamphetamine (2T-MMDA-3a), 2-methoxy-4,5-methylenethiooxyamphetamine (4T-MMDA-2), 2,4,5-trimethoxyphenethylamine (TMPEA), 4-ethyl-5-methoxy-2-methylthioamphetamine (2-TOET), 4-ethyl-2-methoxy-5-methylthio- amphetamine (5-TOET), 5-methoxy-4-methyl-2-methylthioamphetamine (2-TOM), 2-methoxy-4-methyl-5-methylthio- amphetamine (5-TOM), 2-methoxy-4-methyl-5-methylsulfinylamphetamine (TOMSO), 3,5-dimethoxy-4- propylthiophenethylamine (TP), 3,4,5-triethoxyphenethylamine (TRIS), 3-ethoxy-5-ethylthio-4-methoxy- phenethylamine (3-TSB), 3,5-diethoxy-4-methylthiophenethylamine (4-TSB), 3,4-diethoxy-5-ethylthio- phenethylamine (3-T-TRIS), 3,5-diethoxy-4-ethylthiophenethylamine (4-T-TRIS), (R)-2,5-dimethoxy-4-iodo- amphetamine (R-DOI), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, or a combination thereof.

[198] In some embodiments, the additional active compound is an ergoline. In embodiments, the additional active compound is an ergot alkaloid. In embodiments, the additional active compound is a lysergamide. As will be understood by those in the art, lysergamides are compounds having the general structure below, wherein R^{N1} , R^{N2} , R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{12} , R^{13} , and R^{14} are as defined herein and as generally understood in the art:



[199] In some embodiments, R^{N1} , R^{N2} , R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{12} , R^{13} , and R^{14} are each independently hydrogen, deuterium, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. Additionally, any two of R^{N1} , R^{N2} , R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{12} , R^{13} , and R^{14} and the intervening atoms can be taken together to form an optionally substituted optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. In embodiments, the lysergamide is a quaternary salt, in which an additional R^{6A} is connected to the nitrogen to which R^6 is bound; wherein R^{6A} is optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl.

[200] In some embodiments, the additional active compound is a lysergamide selected from the group consisting of lysergic acid diethylamide (i.e., LSD, LSD-25, LAD, Delysid), 6-ethyl-6-*nor*-lysergic acid diethylamide (ETH-LAD), 6-propynyl-6-*nor*-lysergic acid diethylamide (PARGY-LAD), 6-allyl-6-*nor*-lysergic acid diethylamide (AL-LAD), 6-propyl-6-*nor*-lysergic acid diethylamide (PRO-LAD), 6-isopropyl-6-*nor*-lysergic acid diethylamide (IP-LAD), 6-cyclopropyl-6-*nor*-lysergic acid diethylamide (CIP-LAD), 6-butyl-6-*nor*-lysergic acid diethylamide (BU-LAD), 6-(2-fluoroethyl)-6-*nor*-lysergic acid diethylamide (FLUOROETH-LAD), 1-acetyl-lysergic acid diethylamide (i.e., ALD, ALD-52, N-acetyl-LSD), 1-propionyl-lysergic acid diethylamide (1P-LSD), 1-butyryl-lysergic acid diethylamide (1B-LSD), 1-valeryl-lysergic acid diethylamide (1V-LSD), 1-(cyclopropyl- methanoyl)-lysergic acid diethylamide (1cP-LSD), 1-(1,2-dimethylcyclobutane-1-carbonyl)-lysergic acid diethylamide (1D-LSD), 1-propionyl-6-allyl-6-*nor*-lysergic acid diethylamide (1P-AL-LAD), 1-(cyclopropyl- methanoyl)-6-allyl-6-*nor*-lysergic acid diethylamide (1cP-AL-LAD), 1-propionyl-6-ethyl-6-*nor*-lysergic acid diethylamide (1P-ETH-LAD), lysergic acid 2,4-dimethylazetidine (i.e., LA-SS-Az, LSZ), lysergic acid piperidine (LSD-Pip), and lysergic acid methylisopropyl amide (MIPLA).

[201] Other tryptamines, phenylalkylamines, and lysergamides useful as additional active compounds for purposes of the disclosure and thus contemplated for inclusion therein will be as generally known in the art (see, e.g., Shulgin and Shulgin, PiHKAL: A Chemical Love Story, Transform Press (1991); Shulgin and Shulgin, TiHKAL: The Continuation, Transform Press (1997); Grob & Grigsby, Handbook of Medical Hallucinogens, 2021; Luethi & Liechti, Arch Toxicol. 2020; 94, 1085-1133; Nichols, Pharmacol Reviews, 2016;68(2):264-355; Glennon, Pharmacol Biochem & Behav. 1999;64:251-256; all are incorporated by reference as if fully set forth herein).

F. Dose and Dosage

[202] In some embodiments, pharmaceutical compositions comprise a therapeutically effective amount or an

effective amount of a disclosed compound, such as for administration to a subject. Administration of pharmaceutical compositions in a “therapeutically effective amount,” or an “effective amount” to a subject means administration of an amount of composition sufficient to achieve the desired effect. When an “effective amount” means an amount effective in treating the stated disorder or symptoms in a subject, “therapeutic effect” would be understood to mean the responses(s) in a subject after treatment that are judged to be desirable and beneficial. Hence, depending on the mental health disorder to be treated, or improvement in mental health or functioning sought, and depending on the particular constituent(s) in the disclosed compositions under consideration, those responses shall differ, but would be readily understood by those of ordinary skill, through an understanding of the disclosure herein and the general knowledge of the art (e.g., by reference to the symptoms listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for the stated disorder).

[203] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (in a milligram dosage amount calculated based on the kilogram weight of the patient), e.g., 0.25 mg/kg or less (including a dose of 0.10 mg/kg or less, 0.05 mg/kg or less, 0.01 mg/kg or less, and 0.005 mg/kg or less), at least 0.50 mg/kg, at least 0.55 mg/kg, at least 0.60 mg/kg, at least 0.65 mg/kg, at least 0.70 mg/kg, at least 0.75 mg/kg, at least 0.80 mg/kg, at least 0.85 mg/kg, at least 0.90 mg/kg, at least 0.95 mg/kg, at least 1.0 mg/kg, at least 1.1 mg/kg, at least 1.2 mg/kg, at least 1.3 mg/kg, or at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2.0 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, or at least 3.0 mg/kg, as well as amounts within these ranges.

[204] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (in a milligram dosage amount calculated based on the kilogram weight of the patient) between about 0.01 mg/kg and 0.1 mg/kg, such as about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg about 0.08 mg/kg about 0.09 mg/kg, and about 0.1 mg/kg, as well as ranges between these values. In some embodiments, a single dose is between about 0.1 mg/kg and 1.0 mg/kg, such as about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg about 0.8 mg/kg about 0.9 mg/kg, and about 1.0 mg/kg, as well as ranges between these values.

[205] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (whether or not such dose is present in a unit dosage form), e.g., 25 mg or less (including a dose of 10 mg or less, 5 mg or less, 1 mg or less, and 0.5 mg or less), at least 25

mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 105 mg, at least 110 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185 mg, at least 190 mg, at least 195 mg, at least 200 mg, at least 225 mg, or at least 250 mg, as well as amounts within these ranges.

[206] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (whether or not such dose is present in a unit dosage form) between about 0.1 mg and 1.0 mg, such as about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, and about 1.0 mg, as well as ranges between these values. In embodiments, a single dose is between about 1 mg and 10 mg, such as about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, and about 10 mg, as well as ranges between these values. In embodiments, a single dose is between about 10 mg and 100 mg.

[207] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (in a microgram dosage amount calculated based on the kilogram weight of the patient), e.g., 0.25 µg/kg or less (including a dose of 0.10 µg/kg or less, 0.05 µg/kg or less, and 0.01 µg/kg or less), at least 0.50 µg/kg, at least 0.55 µg/kg, at least 0.60 µg/kg, at least 0.65 µg/kg, at least 0.70 µg/kg, at least 0.75 µg/kg, at least 0.80 µg/kg, at least 0.85 µg/kg, at least 0.90 µg/kg, at least 0.95 µg/kg, at least 1.0 µg/kg, at least 1.1 µg/kg, at least 1.2 µg/kg, at least 1.3 µg/kg, at least 1.4 µg/kg, at least 1.5 µg/kg, at least 1.6 µg/kg, at least 1.7 µg/kg, at least 1.8 µg/kg, at least 1.9 µg/kg, at least 2.0 µg/kg, at least 2.1 µg/kg, at least 2.2 µg/kg, at least 2.3 µg/kg, at least 2.4 µg/kg, at least 2.5 µg/kg, at least 2.6 µg/kg, at least 2.7 µg/kg, at least 2.8 µg/kg, at least 2.9 µg/kg, or at least 3.0 µg/kg, as well as amounts within these ranges.

[208] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (in a microgram dosage amount calculated based on the kilogram weight of the patient) between about 0.01 µg/kg and 0.1 µg/kg, such as about 0.01 µg/kg, about 0.02 µg/kg, about 0.03 µg/kg, about 0.04 µg/kg, about 0.05 µg/kg, about 0.06 µg/kg, about 0.07 µg/kg about 0.08 µg/kg about 0.09 µg/kg, and about 0.1 µg/kg, as well as ranges between these values. In some embodiments, a single dose is between about 0.1 µg/kg and 3.0 µg/kg, such as about 0.1 µg/kg, about 0.2 µg/kg, about 0.3 µg/kg, about 0.4 µg/kg, about 0.5 µg/kg, about 0.6 µg/kg, about 0.7 µg/kg about 0.8 µg/kg about 0.9 µg/kg, about 1.0 µg/kg, about 1.2 µg/kg, about 1.4 µg/kg, about 1.6 µg/kg, about 1.8 µg/kg, about 2.0 µg/kg, about 2.2 µg/kg, about 2.4 µg/kg, about 2.6 µg/kg, about 2.8 µg/kg, about 3.0 µg/kg, as well as ranges between

these values.

[209] In some embodiments, where a pharmaceutical composition includes a disclosed compound, it may be present in an amount so that a single dose is (whether or not it is present in a unit dosage form), e.g., 25 µg or less (including a dose of 10 µg or less, 5 µg or less, and 1 µg or less), from about 25 to 1000 µg, 50 to 1000 µg, 100 to 1000 µg, 200 to 1000 µg, 300 to 1000 µg, 400 to 1000 µg, 500 to 1000 µg, or greater than 1000 µg.

[210] In some embodiments, where a pharmaceutical composition includes an additional active compound, for instance where the additional active compound is a phenylalkylamine or tryptamine, it may be present in an amount so that a single dose is (in a mg dosage amount based on the kg weight of the patient), e.g., 0.25 mg/kg or less (including a dose of 0.10 mg/kg or less, 0.05 mg/kg or less, 0.01 mg/kg or less, and 0.005 mg/kg or less), at least 0.50 mg/kg, at least 0.55 mg/kg, at least 0.60 mg/kg, at least 0.65 mg/kg, at least 0.70 mg/kg, at least 0.75 mg/kg, at least 0.80 mg/kg, at least 0.85 mg/kg, at least 0.90 mg/kg, at least 0.95 mg/kg, at least 1.0 mg/kg, at least 1.1 mg/kg, at least 1.2 mg/kg, at least 1.3 mg/kg, or at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2.0 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, or at least 3.0 mg/kg, as well as amounts within these ranges.

[211] In some embodiments, where a pharmaceutical composition includes an additional active compound, for instance where the additional active compound is a phenylalkylamine or a tryptamine, it may be present in an amount so that a single dose is (whether or not such dose is present in a unit dosage form), e.g., 25 mg or less (including a dose of 10 mg or less, 5 mg or less, 1 mg or less, and 0.5 mg or less), at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 105 mg, at least 110 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185 mg, at least 190 mg, at least 195 mg, at least 200 mg, at least 225 mg, or at least 250 mg, as well as amounts within these ranges.

[212] In some embodiments, a dose of a disclosed compound is from about 1 mg to about 100 mg. For example, the dose may be about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg. In some embodiments, a dose of a disclosed compound is between about 0.1 mg to about 100 mg, about 1 mg to about 50 mg, about 10 mg to about 50 mg, about 20 mg to about 50 mg, or about 5 mg to about 30 mg. In some

embodiments, a dose of a disclosed compound is about 1 mg, about 10 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg. In some embodiments, a dose of a disclosed compound is from about 0.001 mg to about 1 g. In some embodiments, a dose of a disclosed compound is from about 1 mg to about 100 mg. In some embodiments, a dose of a disclosed compound is from about 100 mg to about 250 mg. In some embodiments, a dose of a disclosed compound is from about 1 mg to about 50 mg. In some embodiments, a dose of a disclosed compound is from about 20 mg to about 50 mg. In some embodiments, a dose of a disclosed compound is about 20 mg. In some embodiments, a dose of a disclosed compound is about 25 mg. In some embodiments, a dose of a disclosed compound is about 50 mg.

[213] In some embodiments, a disclosed compound is administered daily. In embodiments, a disclosed compound is administered twice a day. In embodiments, a disclosed compound is administered three times a day. In embodiments, a disclosed compound is administered every other day. In embodiments, a disclosed compound is administered every third day. In embodiments, a disclosed compound is administered every fourth day. In embodiments, a disclosed compound is administered every fifth day. In embodiments, a disclosed compound is administered weekly. In embodiments, a disclosed compound is administered every other week. In embodiments, a disclosed compound is administered every third week. In embodiments, a disclosed compound is administered monthly.

[214] In some embodiments, about 20 mg of a disclosed compound is administered daily. In embodiments, about 20 mg of a disclosed compound is administered twice a day. In embodiments, about 20 mg of a disclosed compound is administered three times a day. In embodiments, about 20 mg of a disclosed compound is administered every other day. In embodiments, about 20 mg of a disclosed compound is administered every third day. In embodiments, about 20 mg of a disclosed compound is administered every fourth day. In embodiments, about 20 mg of a disclosed compound is administered every fifth day. In embodiments, about 20 mg of a disclosed compound is administered weekly. In embodiments, about 20 mg of a disclosed compound is administered every other week. In embodiments, about 20 mg of a disclosed compound is administered every third week. In embodiments, about 20 mg of a disclosed compound is administered monthly.

[215] In some embodiments, about 50 mg of a disclosed compound is administered daily. In embodiments, about 50 mg of a disclosed compound is administered twice a day. In embodiments, about 50 mg of a disclosed compound is administered three times a day. In embodiments, about 50 mg of a disclosed compound is administered every other day. In embodiments, about 50 mg of a disclosed compound is administered every third day. In embodiments, about 50 mg of a disclosed compound is administered every fourth day. In embodiments, about 50 mg of a disclosed compound is administered every fifth day. In embodiments, about 50 mg of a disclosed compound is administered weekly. In embodiments, about 50 mg of a disclosed compound is

administered every other week. In embodiments, about 50 mg of a disclosed compound is administered every third week. In embodiments, about 50 mg of a disclosed compound is administered monthly.

[216] In embodiments, about 100 mg of a disclosed compound is administered daily. In embodiments, about 100 mg of a disclosed compound is administered twice a day. In embodiments, about 100 mg of a disclosed compound is administered three times a day. In embodiments, about 100 mg of a disclosed compound is administered every other day. In embodiments, about 100 mg of a disclosed compound is administered every third day. In embodiments, about 100 mg of a disclosed compound is administered every fourth day. In embodiments, about 100 mg of a disclosed compound is administered every fifth day. In embodiments, about 100 mg of a disclosed compound is administered weekly. In embodiments, about 100 mg of a disclosed compound is administered every other week. In embodiments, about 100 mg of a disclosed compound is administered every third week. In embodiments, about 100 mg of a disclosed compound is administered monthly.

[217] In embodiments, about 150 mg of a disclosed compound is administered daily. In embodiments, about 150 mg of a disclosed compound is administered twice a day. In embodiments, about 150 mg of a disclosed compound is administered three times a day. In embodiments, about 150 mg of a disclosed compound is administered every other day. In embodiments, about 150 mg of a disclosed compound is administered every third day. In embodiments, about 150 mg of a disclosed compound is administered every fourth day. In embodiments, about 150 mg of a disclosed compound is administered every fifth day. In embodiments, about 150 mg of a disclosed compound is administered weekly. In embodiments, about 150 mg of a disclosed compound is administered every other week. In embodiments, about 150 mg of a disclosed compound is administered every third week. In embodiments, about 150 mg of a disclosed compound is administered monthly.

[218] In embodiments, about 200 mg of a disclosed compound is administered daily. In embodiments, about 200 mg of a disclosed compound is administered twice a day. In embodiments, about 200 mg of a disclosed compound is administered three times a day. In embodiments, about 200 mg of a disclosed compound is administered every other day. In embodiments, about 200 mg of a disclosed compound is administered every third day. In embodiments, about 200 mg of a disclosed compound is administered every fourth day. In embodiments, about 200 mg of a disclosed compound is administered every fifth day. In embodiments, about 200 mg of a disclosed compound is administered weekly. In embodiments, about 200 mg of a disclosed compound is administered every other week. In embodiments, about 200 mg of a disclosed compound is administered every third week. In embodiments, about 200 mg of a disclosed compound is administered monthly.

[219] In embodiments, about 250 mg of a disclosed compound is administered daily. In embodiments, about 250 mg of a disclosed compound is administered twice a day. In embodiments, about 250 mg of a disclosed compound is administered three times a day. In embodiments, about 250 mg of a disclosed compound is administered every other day. In embodiments, about 250 mg of a disclosed compound is administered every third day. In embodiments, about 250 mg of a disclosed compound is administered every fourth day. In embodiments, about 250 mg of a disclosed compound is administered every fifth day. In embodiments, about 250 mg of a disclosed compound is administered daily. In embodiments, about 250 mg of a disclosed compound is administered weekly. In embodiments, about 250 mg of a disclosed compound is administered every other week. In embodiments, about 250 mg of a disclosed compound is administered every third week. In embodiments, about 250 mg of a disclosed compound is administered monthly.

[220] In embodiments, an initial dose of a disclosed compound is administered, which is then boosted 30 minutes-4 hours later by administering a second dose of the disclosed compound. In embodiments, the boosted dose is administered about 30 min after the initial dose. In embodiments, the boosted dose is administered about 60 min after the initial dose. In embodiments, the boosted dose is administered about 90 min after the initial dose. In embodiments, the boosted dose is administered about 120 min after the initial dose. In embodiments, the boosted dose is administered about 150 min after the initial dose. In embodiments, the boosted dose is administered about 180 min after the initial dose. In embodiments, the boosted dose is administered about 210 min after the initial dose. In embodiments, the boosted dose is administered about 240 min after the initial dose.

[221] In embodiments, the boosted dose is from about 10% to 100% of the amount of the initial dose. In embodiments, the boosted dose is the same amount as the initial dose. In embodiments, the boosted dose is about half of the amount of the initial dose. In embodiments, this dosing schedule is performed daily. In embodiments, this dosing schedule is performed twice a day. In embodiments, this dosing schedule is performed three times a day. In embodiments, this dosing schedule is performed every other day. In embodiments, this dosing schedule is performed every third day. In embodiments, this dosing schedule is performed every fourth day. In embodiments, this dosing schedule is performed every fifth day. In embodiments, this dosing schedule is performed weekly. In embodiments, this dosing schedule is performed every other week. In embodiments, this dosing schedule is performed every third week. In embodiments, this dosing schedule is performed monthly.

[222] In some embodiments, a dose of a disclosed compound may be in the range of about 1 mg/kg to about 100 mg/kg. For example, the dose may be about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50

mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg. In some embodiments, the dose of a disclosed compound is between about 0.1 mg/kg to about 100 mg/kg, about 1 mg/kg to about 50 mg/kg, or about 5 mg/kg to about 30 mg/kg. In some embodiments, the dose of a disclosed compound is about 1 mg/kg, about 10 mg/kg, or about 25 mg/kg. In some embodiments, the dose of a disclosed compound is from about 0.001 mg/kg to about 1 g/kg. In some embodiments, the dose of a disclosed compound is from about 100 mg/kg to about 250 mg/kg. In some embodiments, the dose of a disclosed compound is about 25 mg/kg.

[223] In some embodiments, a disclosed compound is administered, e.g., as a single dose or one or more times per week (up to twice daily or even three times a days). In some embodiments, a disclosed compound is administered according to a dosing schedule provided herein. In some embodiments, a disclosed compound is administered as an extended release or sustained release formulation, for example, to achieve a dosing regimen disclosed herein and releasing 50 mg to 1 g on a set schedule to patients according to the indication(s) being treated in those patients.

[224] It will be readily appreciated that dosages may vary depending upon whether the treatment is therapeutic or prophylactic, the onset, progression, severity, frequency, duration, probability of or susceptibility of the symptom to which treatment is directed, clinical endpoint desired, previous, simultaneous or subsequent treatments, general health, age, gender, and race of the subject, bioavailability, potential adverse systemic, regional or local side effects, the presence of other disorders or diseases in the subject, and other factors that will be appreciated by the skilled artisan (e.g., medical or familial history).

[225] Dose amount, frequency or duration may be increased or reduced, as indicated by the clinical outcome desired, status of the pathology or symptom, any adverse side effects of the treatment or therapy, or concomitant medications. The skilled artisan with the teaching of this disclosure in hand will appreciate the factors that may influence the dosage, frequency, and timing required to provide an amount sufficient or effective for providing a therapeutic effect or benefit, and to do so depending on the type of therapeutic effect desired, as well as to avoid or minimize adverse effects.

[226] It will be understood that, in some embodiments, the dose actually administered will be determined by a physician, in light of the relevant circumstances, including the disorder to be treated, the chosen route of administration, the actual composition or formulation administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore any dosage ranges disclosed herein are not intended to limit the scope of the disclosure. In some instances, dosage levels below the lower limit of a disclosed range may be more than adequate, while in other cases doses above a range may be employed without causing any harmful side effects, provided for instance that such larger doses also may be

divided into several smaller doses for administration, either taken together or separately.

[227] In embodiments, especially where a formulation is prepared in single unit dosage form, such as a capsule, tablet, or lozenge, suggested dosage amounts may be known by reference to the format of the preparation itself. In embodiments, where a formulation is prepared in multiple dosage form, for instance liquid suspensions and topical preparations, suggested dosage amounts may be known by reference to the means of administration or by reference to the packaging and labeling, package insert(s), marketing materials, training materials, or other information and knowledge available to one of skill or the public.

[228] Accordingly, another aspect of this disclosure provides pharmaceutical kits containing a pharmaceutical composition or formulation of the disclosure, suggested administration guidelines or prescribing information therefore, and a suitable container. Individual unit dosage forms can be included in multi-dose kits or containers. pharmaceutical formulations also can be packaged in single or multiple unit dosage forms for uniformity of dosage and ease of administration.

G. Kits

[229] Provided in another aspect are pharmaceutical kits containing a disclosed pharmaceutical composition or formulation, suggested administration guidelines or prescribing information therefore, and a suitable container. Individual unit dosage forms can be included in multi-dose kits or containers. pharmaceutical formulations also can be packaged in single or multiple unit dosage forms for uniformity of dosage and ease of administration.

[230] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub- unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

[231] Preferably, information pertaining to dosing and proper administration (if needed) is printed onto a multi-dose kit directly (e.g., on a blister pack or other interior packaging holding the disclosed compositions or formulations); however, disclosed kits can further contain package inserts and other printed instructions (e.g., on exterior packaging) for administering the disclosed compositions and for their appropriate therapeutic use.

H. Methods of Use

[232] In some aspects, provided herein are methods of using the disclosed compounds. In embodiments, disclosed compounds are used to modulate neurotransmission. In embodiments, disclosed compounds are used to treat a condition, such as a disease or a disorder. In embodiments, disclosed compounds are used in the manufacture of a medicament for the therapeutic and/or the prophylactic treatment of a condition, such as a disease or a disorder. In embodiments, disclosed compounds are administered as part of psychedelic-assisted therapy. In embodiments, disclosed compounds are administered in a therapeutically effective amount to a subject having a condition, such as a disease or a disorder. In embodiments, the condition is a mental health disorder. In embodiments, the condition is a neurodegenerative disorder. In embodiments, the condition is an inflammatory disorder. In embodiments, the condition is pain and/or inflammation. In embodiments, disclosed compounds are administered to a subject that is healthy.

[233] As used herein, the terms “subject,” “user,” “patient,” and “individual” are used interchangeably, and refer to any mammal, including murines, simians, mammalian farm animals, mammalian sport animals, and mammalian pets, such as canines and felines, although preferably humans. Such terms will be understood to include one who has an indication for which a compound, composition, or method described herein may be efficacious, or who otherwise may benefit by the invention. In general, all of the compounds, compositions, and disclosed methods will be appreciated to work for all individuals, although individual variation is to be expected, and will be understood. The disclosed methods of treatment also can be modified to treat multiple patients at once, including couples or families. Hence, these terms will be understood to also mean two or more individuals.

[234] In embodiments, disclosed compounds or compositions thereof are orally, mucosally, rectally, subcutaneously, intravenously, intramuscularly, intranasally, by inhalation or transdermally administered to a subject. In some embodiments, when administered through one or more such routes, the disclosed compounds and the disclosed compositions and formulations comprising them are useful in methods for treating a patient in need of such treatment.

3. Modulating Neurotransmission and Neuroplasticity

[235] In some embodiments, administration of a disclosed compound modulates neurotransmission in a subject, such as following administration of a pharmacologically effective amount to said subject. In some embodiments, modulating neurotransmission comprises regulating levels of monoamines in, for example, the CNS and peripheral tissues. In some embodiments, modulating neurotransmission comprises increasing levels of monoamines in, for example, the CNS and peripheral tissues of a subject to whom a disclosed compound has been administered. In some embodiments, modulating neurotransmission comprises decreasing levels of

monoamines in, for example, the CNS and peripheral tissues of a subject to whom a disclosed compound has been administered. In some embodiments, modulating neurotransmission by administering a disclosed compound to a subject treats a disease or disorder in the subject.

[236] In some embodiments, administration of a disclosed compound or composition thereof results in inhibiting the reuptake of one or more neurotransmitters. In some embodiments, administration of a disclosed compound or composition thereof results in increasing the extracellular concentration of one or more neurotransmitters, including the amount of extracellular serotonin, dopamine, or norepinephrine.

[237] In some embodiments, the disclosed compounds are used to modulate neurotransmission, such as neurotransmission in a subject. In some methods herein, the disclosed compositions, when administered in a pharmacologically effective amount, thus affect monoaminergic neurotransmission, including serotonergic, dopaminergic, and noradrenergic neurotransmission. Accordingly, in some embodiments, the disclosed compositions, when administered in a pharmacologically effective amount, are used to treat a medical condition linked to dysregulation or inadequate functioning of neurotransmission, and in specific embodiments, are used to treat a medical condition linked to monoaminergic neurotransmission.

[238] In embodiments, administration of a disclosed compound or composition thereof results in modulation of one or more monoamine receptors, such as a serotonin receptor, a dopamine receptor, or a norepinephrine receptor. In embodiments, administration of a disclosed compound or composition thereof results in agonism or partial agonism of a monoamine receptor, including any one or more of a serotonin receptor, a dopamine receptor, and a norepinephrine receptor.

[239] In embodiments, administration of a disclosed compound or composition thereof results in activation of a serotonin receptor. In some embodiments, administration of a disclosed compound or composition thereof results in agonism and/or antagonism of a serotonin receptor (HTR). In some embodiments, administration of a disclosed compound or composition thereof results in agonism or partial agonism of an HTR, such as any one or more of an HTR₁, such as HTR_{1A} and HTR_{1B}, an HTR₂, such as HTR_{2A}, HTR_{2B}, and HTR_{2C}, and HTR₆.

[240] In some embodiments, a disclosed compound has an in vitro EC₅₀ (agonist mode) for any one or more of HTR_{1A}, HTR_{1B}, HTR_{2A}, HTR_{2B}, and HTR₆ that is less than 10 μM, less than 5 μM, less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In embodiments, a disclosed compound has an in vitro EC₅₀ (agonist mode) for HTR_{2A} that is less than 1 μM, less than 0.5 μM, less than 0.1 μM, less than 0.05 μM, less than 0.01 μM, less than 0.005 μM, or less than 0.001 μM.

[241] In embodiments, administration of a disclosed compound or composition results in increased agonism of HTR_{2A} relative to other HTRs. In some embodiments, administration of a disclosed compound or composition thereof results in increased agonism of HTR_{2A} relative to any one or more of an HTR₁, such as HTR_{1A} and

HTR_{1B}, another HTR₂, such as HTR_{2B} and HTR_{2C}, an HTR₅, e.g., HTR_{5A}, HTR₆, and an HTR₇, e.g., HTR_{7D}.

[242] In some embodiments, a disclosed compound modulates the activity of a dopamine receptor (DR), such as any one or more of DRD1, DRD2, DRD3, DRD4, and DRD5. In some embodiments, a disclosed compound agonizes or partially agonizes a dopamine receptor. In some embodiments, a disclosed compound agonizes or partially agonizes DRD2. In some embodiments, a disclosed compound agonizes or partially agonizes the DRD2 short isoform (DRD2S). In embodiments, a disclosed compound has an in vitro EC₅₀ for DRD2S that is less than 10 μ M, less than 5 μ M, less than 1 μ M, less than 0.5 μ M, or less than 0.1 μ M.

[243] Determining agonism and antagonism, and measuring EC₅₀ and IC₅₀, respectively, may be determined according to methods available to one of skill. In one example, measuring Gq-mediated calcium flux is a known method for assessing modulation, e.g., activation, of HTR_{2A}, a widely recognized target of psychedelic compounds. See, e.g., Klein et al., ACS Pharmacol Transl Sci. 2020 14;4(2):533-542; Flanagan et al., ACS Pharmacol Transl Sci. 2020;4(2):488-502; Toro-Sazo et al., PLoS One. 2019;14(1):e0209804; Halberstadt et al., Psychopharmacology (Berl). 2019;236(2):799-808. As will be recognized, a partial agonist shows reduced maximum efficacy (E_{MAX}) relative to a full agonist (E_{MAX} = 100%), e.g., serotonin in the example of an HTR.

[244] In some embodiments, disclosed compounds or compositions thereof, when administered in a pharmacologically effective amount, result in modulation of one or more membrane monoamine transporters, including any one or more of a serotonin membrane transporter (SERT), a dopamine membrane transporter (DAT), a norepinephrine membrane transporter (NET), and a vesicular monoamine transporter. In some embodiments, a disclosed compound blocks the uptake activity of monoamine transporters. In some embodiments, a disclosed compound blocks the uptake activity of one or more of a serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET).

[245] In some embodiments, a disclosed compound inhibits the uptake activity of any one or more of SERT, DAT, and NET. In some embodiments, a disclosed compound inhibits the uptake activity of SERT, DAT, and NET. In embodiments, a disclosed compound has an in vitro IC₅₀ of less than 10 μ M for any one or more of SERT, DAT, and NET. In embodiments, a disclosed compound does not inhibit the uptake activity of SERT. In embodiments, a disclosed compound has an in vitro IC₅₀ of less than 10 μ M for SERT. In embodiments, a disclosed compound selectively inhibits the uptake activity of SERT. In embodiments, a disclosed compound shows greater potency for inhibiting the uptake activity of SERT relative to DAT and NET.

[246] Determining whether a disclosed compound results in inhibition of the uptake activity of a monoamine transporter, or whether such activity is lacking, may be determined according to available methods, which may include live-cell fluorescent assays or radioactive assays. In some examples, inhibition of monoamine uptake may be determined in rat synaptosomes or human platelets. See, e.g., Segonzac et al., J Neurochem.

1985;44(2):349-56; Cozzi et al., J Neural Transm (Vienna). 2009;116(12):1591-9. In some examples, inhibitory activity may be compared to uptake inhibitors having low nM potency, e.g., DAT inhibitor GBR 12909, NET inhibitor desipramine, and SERT inhibitor clomipramine.

[247] In some embodiments, administration of a disclosed compound or composition according to the methods herein results in an improved pharmacological profile, such as a relative increase in agonism of serotonin receptors compared to dopamine and/or norepinephrine receptors, compared to a corresponding composition, which may be an increase of 5% or more, 10% or more, 25% or more, or 50% or more, and including amounts in between. Measurements of agonism of a receptor will be as understood by those in the art or by reference to the general knowledge in the art.

[248] In some embodiments, an improved pharmacological profile of a disclosed compound or composition will be a relative increase in extracellular concentration of serotonin compared to dopamine and/or norepinephrine, compared to a corresponding non-substituted composition, which may be an increase of 5% or more, 10% or more, 25% or more, or 50% or more, and including amounts in between. Measurements of extracellular concentration of a neurotransmitter will be as understood by those in the art or by reference to the general knowledge in the art.

[249] Detecting a change in monoamine levels in a subject, such as an increase or a decrease, can be achieved according to methods known in the art, for example, brain microdialysis (Chefer et al., Curr Protoc Neurosci. 2009; Chapter: Unit 7.1; Darvesh et al., Expert Opin Drug Discov. 2011;6(2):109–127) and brain imaging, for example, positron emission tomography (PET) and single photon emission computed tomography (SPECT) (e.g., Wong & Gjedde, Encyclopedia Neurosci, 2009; 939-952 and Takano, Front Psych. 2018; 9:228).

[250] In some embodiments, a disclosed compound is used to increase neuroplasticity. Neuroplasticity, also known as neural plasticity or brain plasticity, refers to the brain's ability to change and adapt in response to experiences, learning, and environmental factors. Neuroplasticity occurs through several mechanisms, including synaptic plasticity, which involves the strengthening or weakening of connections (synapses) between neurons. Synaptic plasticity is often associated with learning and memory processes. Another form of plasticity is called structural plasticity, which involves changes in the physical structure of neurons, such as the growth of new dendritic branches or the formation of new synapses. In some embodiments, increasing neuroplasticity contributes to the therapeutic effects of a disclosed compound in a subject. In some embodiments, increasing neuroplasticity by administering a disclosed compound to a subject treats a disease or disorder in the subject.

[251] Neuroplasticity can be defined in terms of neuritogenesis, spinogenesis, and synaptogenesis in neurons. Neuritogenesis refers to the process by which neurons generate and extend their neurites (i.e., to

form axons and dendrites). Neuritogenesis is a critical step in neural development and the formation of neuronal circuits. Spinogenesis refers to the formation of dendritic spines, which are small protrusions on the dendrites of neurons. Dendritic spines are crucial for synaptic connections and play a vital role in synaptic transmission and plasticity. Synaptogenesis refers to the formation of synapses, which is crucial for the establishment and refinement of neural circuits, and is a fundamental process underlying learning, memory, and information processing in the brain.

[252] In some embodiments, administration of a disclosed compound or composition thereof increases neuritogenesis. Neuritogenesis can be measured in terms of total neurite length, maximum neurite length, number of neurite nodes, and/or number of neurite extremities. In embodiments, administration of a disclosed compound or composition thereof increases total neurite length. In embodiments, administration of a disclosed compound or composition thereof increases maximum neurite length. In embodiments, administration of a disclosed compound or composition thereof increases the number of neurite nodes. In embodiments, administration of a disclosed compound or composition thereof increases the number of neurite extremities.

[253] In some embodiments, administration of a disclosed compound or composition thereof to a subject results in an increase in the number of dendritic branches, the number of dendritic crossings, the density of dendritic spines, the density of synapses (i.e., number of synapses per neuron), or total dendritic length. These factors can be measured using a Sholl analysis and other techniques known to those of skill in the art (Ly et al. *ACS Pharmacol Transl Sci.* 2020;4(2):452-460).

b. Treatment

[254] In some embodiments, a disclosed compound is used to treat a medical condition, such as a disease or disorder. In embodiments, a disclosed compound is used in the manufacture of a medicament to treat a condition, such as a disease or disorder. Also provided are methods of administering disclosed compounds to a subject having a condition, such as a disease or disorder, thereby treating said condition.

[255] In some embodiments, a disclosed compound or pharmaceutical composition comprising the disclosed compounds are administered to a subject by one or more routes of administration, including, e.g., oral, mucosal, rectal, subcutaneous, intravenous, intramuscular, intranasal, inhaled, ocular, intraocular, topical, and transdermal routes. When administered through one or more of such routes, the disclosed compounds and the disclosed compositions comprising them are useful in methods for treating a patient in need of such treatment.

[256] In some embodiments are provided methods of treating and/or preventing a condition in a subject, the method comprising administering to the mammal a therapeutically effective amount of a disclosed compound or pharmaceutical composition. In some embodiments, “treating” or “treatment” refers to treating a disease or disorder in a subject, and preferably in a human, and includes causing a desired biological or pharmacological

effect, such as: (a) preventing a disorder from occurring in a subject who may be predisposed to the disorder but has not yet been diagnosed with it; (b) inhibiting a disorder, i.e. arresting its development; (c) relieving a disorder, i.e., causing regression thereof; (d) protecting from or relieving a symptom or pathology caused by or related to a disorder; (e) reducing, decreasing, inhibiting, ameliorating, or preventing the onset, severity, duration, progression, frequency or probability of one or more symptoms or pathologies associated with a disorder; and (f) preventing or inhibiting of a worsening or progression of symptoms or pathologies associated with a disorder or comorbid with a disorder. In embodiments, treatment includes prevention. In other embodiments, treatment does not include prevention. Other such measurements, benefits, and surrogate or clinical endpoints, alone or in combination, will be understood to one of skill in view of the teachings herein and the knowledge in the art.

[257] In embodiments, a disclosed compound is used to treat a central nervous system (CNS) disorder. Broadly, CNS disorders include diseases of the nervous system (e.g., movement disorders, neurodegenerative disorders) as well as mental, behavioral, and neurodevelopmental disorders, such as those in the DSM-5, Merck Manual, ICD-11, or other such diagnostic resources known to one of skill.

i. Mental, Behavioral, or Neurodevelopmental Disorders

[258] In some embodiments, a disclosed compound is used to treat a mental, behavioral, or neurodevelopmental disorder. In some embodiments, disclosed compounds are administered, such as in a therapeutically effective amount, to a subject having a mental, behavioral, or neurodevelopmental disorder, thereby treating said mental, behavioral, or neurodevelopmental disorder. In some methods herein, a disclosed composition, when administered in a therapeutically effective amount, provides one or more therapeutic effects for the treatment of a mental, behavioral, or neurodevelopmental disorder.

[259] The ICD-11, which is incorporated by reference herein in its entirety, defines “mental, behavioral, or neurodevelopmental disorders” as syndromes characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioral functioning. Such disorders include, but are not limited to, neurodevelopmental disorders, schizophrenia or other primary psychotic disorders, catatonia, mood disorders, anxiety or fear-related disorders, obsessive-compulsive or related disorders, disorders specifically associated with stress, dissociative disorders, feeding (or eating) disorders, elimination disorders, disorders of bodily distress or bodily experience, disorders due to substance use or addictive behaviors, impulse control disorders, disruptive behavior or dissocial disorders, personality disorders (and related traits), paraphilic disorders, factitious disorders, neurocognitive disorders, mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, sleep-wake disorders, sexual dysfunctions,

and gender incongruence.

[260] A mental, behavioral, or neurodevelopmental disorder where otherwise undefined, will be understood to refer to the disorder as defined in the ICD-11. Within the category of mental, behavioral, or neurodevelopmental disorders, the term mental disorder (or “mental health disorder”) generally refers to a disease condition that involves negative changes in emotion, mood, thinking, and/or behavior. In general, mental health disorders are characterized by clinically significant disturbances in an individual's cognition, emotion, behavior, or a combination thereof, resulting in impaired functioning, distress, or increased risk of suffering. Although the terms “mental disorder” and “mental health disorder,” as well as terms that define specific diseases and disorders, generally shall refer to the criteria in the ICD-11, or a patient with a diagnosis based thereon, it will be appreciated that disclosed methods are equally applicable to patients having an equivalent underlying disorder, whether that disorder is diagnosed based on the criteria in ICD-11, ICD-10, DSM-5, or DSM-IV (each of which is incorporated by reference herein in its entirety) whether the diagnosis is based on other clinically acceptable criteria, or whether the patient has not yet had a formal clinical diagnosis.

[261] In some embodiments, a disclosed compound is used to treat a mental health disorder. In some embodiments, disclosed compounds are administered, such as in a therapeutically effective amount, to a subject having a mental health disorder, thereby treating said mental health disorder. In some methods herein, a disclosed composition, when administered in a therapeutically effective amount, provides one or more therapeutic effects for the treatment of a mental health disorder. In some embodiments, a compound or composition of the disclosure is used to reduce the symptoms of a mental health disorder. The symptoms of the mental health disorder to be treated shall be able to be determined by one of skill in the art, by reference to the general understanding of the art regarding that disorder.

[262] In some embodiments, measures of therapeutic efficacy include reports by a subject or an observer. In some embodiments, measures of therapeutic efficacy include responses to a questionnaire. Non-limiting representative examples of applicable measures of symptom improvement include the Generalized Anxiety Disorder Scale-7 (GAD-7), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF) Scale, Clinical Global Impression (CGI), Substance Abuse Questionnaire (SAQ), Mini International Neuropsychiatric Interview 5 (MINI 5), Columbia Suicide Severity Rating Scale (C-SSRS), Patient Health Questionnaire (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), Interpersonal Reactivity Index (IRI), Short Form (36) Health Survey (SF-36), Self-Compassion Scale (SCS), Trauma History Questionnaire (THQ), Beck Depression Index (BDI), and related subject- or observer-reported measures.

[263] In some embodiments, a disclosed compound is used to treat a neurodevelopmental disorder. In some embodiments, a “neurodevelopmental disorder” is a neurological and/or cognitive disorder that arises during

the developmental period that involves significant difficulties in the acquisition and execution of specific neurological functions (e.g., intellectual, motor, language, or social functions). In some embodiments, the neurodevelopmental disorder is a disorder of intellectual development, a developmental speech or language disorder, autism spectrum disorder, a developmental learning disorder, a developmental motor coordination disorder, attention deficit hyperactivity disorder, or stereotypic movement disorder.

[264] In some embodiments, a disclosed compound is used to treat schizophrenia or another primary psychotic disorder. In general, these disorders are characterized by significant impairments in reality and alterations in behavior manifest in positive symptoms like persistent delusions, persistent hallucinations, disorganized thinking and speech, grossly disorganized behavior, as well as experience of negative symptoms such as blunted or flat affect and avolition and psychomotor disturbances. In some embodiments, a disclosed compound is used to treat schizophrenia, schizoaffective disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, or a substance-induced psychotic disorder.

[265] In some embodiments, a disclosed compound is used to treat catatonia. In some embodiments, "catatonia" refers to a category of syndromes characterized by the co-occurrence of several symptoms of decreased, increased, or abnormal psychomotor activity. In some embodiments, the catatonia is associated with another mental disorder. In some embodiments, the catatonia is induced by substances or medications.

[266] In some embodiments, a disclosed compound is used to treat a mood disorder. As defined in the ICD-11, mood disorders are categorized according to the specific type(s) of mood episodes, and their pattern over time. The primary types of mood episodes are depressive episodes, manic episodes, mixed episodes, and hypomanic episodes. In some embodiments, the mood disorder is a bipolar or related disorder (e.g., bipolar type I disorder, bipolar type II disorder, cyclothymic disorder), a depressive disorder, or a substance-induced mood disorder. In some embodiments, the mood disorder is a depressive disorder. In embodiments, the depressive disorder is single-episode depressive disorder, major depressive episode disorder, persistent depressive disorder (formally known as dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, postpartum depression, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, seasonal affective disorder, mixed depressive and anxiety disorder, or an unspecified depressive disorder. In embodiments, depression is assessed through the Patient Health Questionnaire-9 (PHQ-9) screening tool, Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale, Beck Depression Inventory (BDI-II), Zung Self-Rating Depression Scales (SDS), Major Depression Inventory (MDI), Center for Epidemiologic Studies Depression Scale (CED-D), Rome Depression Inventory (RDI), Hamilton Rating Scale for Depression (HRSD), and Carroll Rating Scale (CRS).

[267] In some embodiments, a disclosed compound is used to treat an anxiety or fear-related disorder. An

“anxiety disorder” refers to a class of mental disorders that induce excessive or abnormal fear, dread, or worry. In some embodiments, the anxiety disorder is selected from the group consisting of generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism, or a substance-induced anxiety disorder.

[268] In some embodiments, a disclosed compound is used to treat an obsessive-compulsive or related disorder. In general, these disorders are characterized by repetitive thoughts and behaviors, such as cognitive phenomena (obsessions, intrusive thoughts and preoccupations). In some embodiments, the disorder is characterized by a compulsive need to accumulate possessions and distress related to discarding them (i.e., hoarding disorder). In some embodiments, the disorder is body-focused and can be characterized by recurrent and habitual actions (hair-pulling, skin-picking). In some embodiments, the disorder is obsessive-compulsive disorder, body dysmorphic disorder, olfactory reference disorder, hypochondriasis, hoarding disorder, a body-focused repetitive behavior disorder, or a substance-induced obsessive-compulsive disorder.

[269] In some embodiments, a disclosed compound is used to treat a disorder associated with stress. In some embodiments, the disorder associated with stress has an identifiable stressor that is a causal factor, like exposure to a stressful or traumatic event, or a series of such events or adverse experiences. Stressors may be within the normal range of life experiences (e.g., divorce, socioeconomic problems), or from a threatening or traumatizing experience. In general, the nature and duration of the symptoms that arise in response to the stressor can distinguish the disorder from everyday stress. In embodiments, a disclosed compound is used to treat post-traumatic stress disorder, complex post-traumatic stress disorder, prolonged grief disorder, adjustment disorder, reactive attachment disorder, or disinhibited social engagement disorder.

[270] In some embodiments, a disclosed compound is used to treat a dissociative disorder. Dissociative disorders can be characterized by involuntary disruption or discontinuity in the normal integration of one or more of the following: identity, sensations, perceptions, affects, thoughts, memories, control over body movements, or behavior. In some subjects, dissociative disorder symptoms can be severe, and may result in impairment in personal, social, educational, occupational or other areas of functioning. In some embodiments, a disclosed compound is used to treat dissociative neurological symptom disorder, dissociative amnesia (including amnesia with dissociative fugue and without dissociative fugue), trance disorder, possession trance disorder, dissociative identity disorder, partial dissociative identity disorder, or depersonalization- derealization disorder.

[271] In some embodiments, a disclosed compound is used to treat a feeding or eating disorder. Feeding or eating disorders generally involve abnormal eating or feeding behaviors that are not explained by another health condition, and are not developmentally appropriate or culturally sanctioned. These disorders can involve

preoccupation with food as well as body weight and shape concerns. In embodiments, a disclosed compound is used to treat anorexia nervosa (including anorexia with significantly low body weight, anorexia with dangerously low body weight, or anorexia in recovery with normal body weight), bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, or rumination-regurgitation disorder.

[272] In some embodiments, a disclosed compound is used to treat an elimination disorder. Elimination disorders include, for example, the repeated voiding of urine into clothes or bed, and the repeated passage of feces in inappropriate places once the individual has reached a developmental age when continence is ordinarily expected. In embodiments, a disclosed compound is used to treat enuresis (including nocturnal enuresis, diurnal enuresis, and nocturnal and diurnal enuresis) or encopresis (including both with encopresis constipation or overflow incontinence, and encopresis without constipation or overflow incontinence).

[273] In some embodiments, a disclosed compound is used to treat a disorder of bodily distress or bodily experience. Disorders of bodily stress typically involve bodily symptoms that the subject finds distressing and to which the subject devotes excessive attention. Bodily integrity dysphoria typically involves a disturbance in the person's experience of the body manifested by persistent discomfort or intense feelings of body configuration. In some embodiments, a disclosed compound is used to treat a bodily distress disorder (including mild, moderate, and severe bodily distress disorder) or body integrity dysphoria.

[274] In some embodiments, a disclosed compound is used to treat a disorder due to substance use or addictive behaviors. Disorders due to substance use or addictive behaviors are mental and/or behavioral disorders that develop predominantly as a result of the use of psychoactive substances (including medications and illegal or illicit substances), or specific repetitive rewarding and reinforcing behaviors. In embodiments, a disclosed compound is used to treat disorders due to substance use (i.e., a substance use disorder, or SUD). In embodiments, the substance use disorder is associated with alcohol, cannabis, synthetic cannabinoids, opioids, sedatives, hypnotics or anxiolytics, cocaine, stimulants (e.g., amphetamines, methamphetamines, methcathinone, synthetic cathinones, caffeine), hallucinogens, nicotine, volatile inhalants, MDMA or MDA, dissociative drugs like ketamine and phencyclidine, or another substance (including medications and non-psychoactive substances). In embodiments, the substance use disorder is selected from alcohol use disorder, cannabis use disorder, caffeine use disorder, phencyclidine use disorder, inhalants use disorder, opioids use disorder, sedatives use disorder, hypnotics use disorder, anxiolytics use disorder, stimulants use disorder, and tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder. In embodiments, the substance use disorder is cannabis use disorder. In embodiments, the substance use disorder is caffeine use disorder. In embodiments, the substance use disorder is phencyclidine use disorder. In embodiments, the substance use disorder is inhalant use disorder. In embodiments, the substance use disorder

is opioids use disorder. In embodiments, the substance use disorder is sedatives use disorder. In embodiments, the substance use disorder is hypnotics use disorder. In embodiments, the substance use disorder is anxiolytics use disorder. In embodiments, the substance use disorder is stimulants use disorder. In embodiments, the substance use disorder is tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder, wherein said alcohol use disorder is selected from alcohol abuse, alcohol dependence, and alcoholism. In embodiments, the disorder is associated with another addictive behavior (e.g., gambling disorders, gaming disorder). In embodiments, a substance use disorder can be screened using a Screening to Brief Intervention (S2BI), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD), Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS), the Opioid Risk Tool - OUD (ORT-OUD) Chart, Drug Abuse Screen Test (DAST-10), and Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS).

[275] In some embodiments, a disclosed compound is used to treat an impulse control disorder. In general, impulse control disorders are characterized by the repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the subject despite negative long-term consequences, such as harm to the subject or a significant impairment in important areas of the subject's functioning. In embodiments, impulse control behaviors include fire-setting, stealing, inappropriate sexual behavior, and explosive outbursts. In embodiments, a disclosed compound is used to treat pyromania, kleptomania, compulsive sexual behavior disorder, or intermittent explosive disorder.

[276] In some embodiments, a disclosed compound is used to treat a disruptive behavior disorder or a dissocial disorder. Such disorders may be broadly characterized by persistent behavior problems that range from persistently defiant, disobedient, provocative or spiteful behaviors to behaviors that violate the rights of others or norms, rules, or laws. In embodiments, a disclosed compound is used to treat oppositional defiant disorder (including oppositional defiant disorder with chronic irritability-anger and oppositional defiant disorder without chronic irritability-anger) or conduct-dissocial disorder (including childhood-onset conduct-dissocial disorder and adolescent-onset conduct-dissocial disorder).

[277] In some embodiments, a disclosed compound is used to treat a personality disorder. Personality disorders may be generally characterized by problems in perceiving one's identity, self-worth, accuracy of self-view, and self-discretion that is manifest in patterns of cognition, emotional experience, emotional expression, and maladaptive behavior. In embodiments, a disclosed compound is used to treat a mild, moderate, or severe personality disorders. In embodiments, a disclosed compound is used to treat a prominent personality trait or patterns (e.g., negative affectivity, detachment, dissociality, disinhibition, anankastia, borderline pattern). In embodiments, the personality disorder is antisocial personality disorder, avoidant

personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, masochistic or sadistic behavior, narcissistic personality disorder, obsessive-compulsive personality disorder, paranoid personality disorder, psychopathy, sociopathy, schizoid personality disorder, or schizotypal personality disorder.

[278] In some embodiments, a disclosed compound is used to treat a paraphilic disorder. Paraphilic disorders can be characterized by persistent and intense patterns of atypical sexual arousal, the focus of which involves others whose age or status renders them unwilling or unable to consent. In embodiments, a disclosed compound is used to treat exhibitionistic disorder, voyeuristic disorder, pedophilic disorder, coercive sexual sadism disorder, frotteuristic disorder, other paraphilic disorders involving non-consenting individuals, or paraphilic disorders involving solitary behavior or consenting individuals.

[279] In some embodiments, a disclosed compound is used to treat a factitious disorder. In general, factitious disorders may be characterized by intentionally feigning, falsifying, inducing or aggravating medical, psychological, or behavior signs and symptoms or injury to oneself or another person. Subjects with factitious disorders may seek treatment or otherwise present themselves or another person as ill, injured, or impaired. In embodiments, a disclosed compound is used to treat factitious disorder imposed on self or a factitious disorder imposed on another.

[280] In some embodiments, a disclosed compound is used to treat a neurocognitive disorder. Neurocognitive disorders may be characterized by primary clinical defects in cognitive functioning that are acquired (rather than developmental), and therefore the subject experiences a decline from a previously attained level of functioning. In embodiments, a disclosed compound is used to treat delirium. In embodiments, the delirium is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed compound is used to treat mild neurocognitive disorder. In embodiments, a disclosed compound is used to treat an amnesic disorder. In embodiments, the amnesic disorder is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed compound is used to treat dementia. In embodiments, the dementia is associated with Alzheimer's disease, Parkinson's disease, cerebrovascular disease, Lewy body disease, a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed compound is used to treat a behavioral or psychological disturbance associated with dementia. In embodiments, dementia is assessed using a Functional Activities Questionnaire (FAQ), Ascertain Dementia 8 (AD8), Mini-Cog, Mini-Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA), and the Neuropsychiatric Inventory Questionnaire (NPI-Q).

[281] In some embodiments, a disclosed compound is used to treat a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium. In embodiments, the syndrome associated with pregnancy or the puerperium involves significant mental and behavioral features, including a depressive symptom. In embodiments, the disorder includes psychotic symptoms. In embodiments, a disclosed compound is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, with psychotic symptoms. In embodiments, a disclosed compound is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, without psychotic symptoms.

[282] In embodiments, a disclosed compound is used to treat a sleep-wake disorder. In general, sleep-wake disorders are associated with difficulty initiating or maintaining sleep (e.g., insomnia), excessive sleepiness (e.g., hypersomnolence disorders), respiratory disturbance during sleep (e.g., sleep-related breathing disorders (SRBDs), such as obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation disorders, sleep-related hypoxemia disorder, snoring, catathrenia, Cheyne-Stokes breathing, and sleep-disordered breathing), disorders of the sleep-wake schedule (e.g., circadian rhythm sleep-wake disorders), abnormal movements during sleep, or problematic behavioral or psychological events that occur while falling asleep, during sleep, or upon arousal from sleep (e.g., parasomnia disorders). In embodiments, a disclosed compound is used to treat an insomnia disorder, a hypersomnolence disorder, a sleep-related breathing disorder, a circadian rhythm sleep-wake disorder, or a parasomnia disorder.

[283] In some embodiments, a disclosed compound is used to treat sexual dysfunction. Sexual dysfunctions can be defined as syndromes wherein a subject may have difficulty experiencing personally satisfying, non-coercive sexual activities. In embodiments, a disclosed compound is used to treat hypoactive sexual desire dysfunction, sexual arousal dysfunction, orgasmic dysfunction, ejaculatory dysfunction, or sexual dysfunction associated with pelvic organ prolapse.

[284] In some embodiments, a disclosed compound or composition is administered together with psychotherapy, such as psychosocial or behavioral therapy, including any of (or adapted from any of) cognitive behavioral therapy (e.g., as described in Arch Gen Psychiatry. 1999;56:493-502), interpersonal therapy (e.g., as described in Psychol Addict Behav. 2009;23(1):168-174), contingency management based therapy (e.g., as described in Psychol Addict Behav. 2009;23(1):168-174; in J Consul Clin Psychol. 2005;73(2):354-59; or in Case Reports in Psychiatry. Vol. 2012, Article ID 731638), motivational interviewing based therapy (e.g., as described in J Consul Clin Psychol 2001; 69(5): 858-62), meditation based therapy, such as transcendental meditation based therapy (e.g., as described in J Consul Clin Psychol. 2000;68(3):515-52), or the therapeutic approach used by MAPS to treat patients with PTSD (e.g., as in Mithoefer, M (2017). Manual for MDMA-Assisted Psychotherapy in the Treatment of PTSD).

[285] In some embodiments, a disclosed compound or composition may be administered in conjunction with or as an adjunct to psychotherapy. In other embodiments, psychotherapy is neither necessitated nor desired, or no specific type of psychotherapy is necessitated or desired, however any of the disclosed methods can be used in combination with one or more psychotherapy sessions. The flexibility to participate in specific therapies, as well as to choose between any such therapies (or to decide to forgo any specific therapy), while still receiving clinically significant therapeutic effects, is among the advantages of the invention. Furthermore, a patient can participate in numerous other therapeutically beneficial activities, where such participation follows or is in conjunction with the administration of the composition, including breathing exercises, meditation and concentration practices, focusing on an object or mantra, listening to music, physical exercise, stretching or bodywork, journaling, grounding techniques, positive self-talk, or engaging with a pet or animal, and it should be understood that such participation can occur with or without the participation or guidance of a therapist.

[286] In some embodiments, “psychotherapy” is specifically “psychedelic-assisted psychotherapy.” Psychedelic-assisted psychotherapy, broadly, includes a range of related approaches that involve at least one session where the patient ingests a psychedelic and is monitored, supported, or otherwise engaged by one or more trained mental health professionals while under the effects of the psychedelic (see, e.g., Schenberg 2018). Protocols have been developed for the standardization of procedures which emphasize a high degree of care (see, e.g., Johnson 2008), such as the therapeutic approach used by MAPS to treat patients with PTSD using MDMA (e.g., as described in Mithoefer 2017).

[287] In some embodiments, the psychotherapy conducted with a disclosed compound is conducted in widely spaced sessions. These sessions can be as frequently as weekly but are more often approximately monthly or less frequently. In most cases, a small number of sessions, on the order of one to three, is needed for a patient to experience significant clinical progress, as indicated, for example, by a reduction in the symptoms of the mental health disorder being treated. In embodiments, psychotherapy comprises multiple sessions, during some of which a disclosed compound is administered (“drug-assisted psychotherapy”); in others, the patient participates in psychosocial or behavioral therapy without concomitant administration of a drug, or without administration of a disclosed compound.

[288] In some embodiments, a disclosed compound or composition is administered together with standardized psychological treatment or support, which refers to any accepted modality of standard psychotherapy or counseling sessions, whether once a week, twice a week, or as needed; whether in person or virtual (e.g., over telemedicine or by means of a web program or mobile app); and whether with a human therapist or a virtual or AI “therapist.” As used herein, “therapist” refers to a person who treats a patient using the disclosed compositions and methods, whether that person is a psychiatrist, clinical psychologist, clinical

therapist, registered therapist, psychotherapist, or other trained clinician, counselor, facilitator, or guide, although it will be understood that certain requirements will be appropriate to certain aspects of the drug-assisted therapy (e.g., prescribing, dispensing, or administering a drug, offering psychotherapeutic support). In embodiments, a “person” be an AI.

[289] In some embodiments, a patient will participate in a treatment protocol or a disclosed method, or be administered a disclosed composition as part of such a method, if the patient meets certain specified inclusion criteria, does not meet certain specified exclusion criteria, does not meet any specified withdrawal criteria during the course of treatment, and otherwise satisfies the requirements of the disclosed embodiment.

[290] In some embodiments, administration of a disclosed compound or composition occurs without or with reduced risk of side effects that would require physician supervision, and therefore allows for treatment at home or otherwise outside of a clinic and without the need for such supervision, and/or additionally without the requirement of adjunctive psychotherapy, psychological support, or other patient monitoring.

[291] In some embodiments, a disclosed compound or composition may be administered in conjunction with or as an adjunct to psychotherapy. In other embodiments, psychotherapy is neither necessitated nor desired, or no specific type of psychotherapy is necessitated or desired, however any of the disclosed methods can be used in combination with one or more psychotherapy sessions. The flexibility to participate in specific therapies, as well as to choose between any such therapies (or to decide to forgo any specific therapy), while still receiving clinically significant therapeutic effects, is among the advantages of the invention. Furthermore, a patient can participate in numerous other therapeutically beneficial activities, where such participation follows or is in conjunction with the administration of the composition, including breathing exercises, meditation and concentration practices, focusing on an object or mantra, listening to music, physical exercise, stretching or bodywork, journaling, grounding techniques, positive self-talk, or engaging with a pet or animal, and it should be understood that such participation can occur with or without the participation or guidance of a therapist.

[292] In some instances, certain personalized approaches (i.e., “personalized” or “precision” medicine) may be utilized, based on individual characteristics, including drug metabolism (e.g., CYP2D6 or CYP3A4) or individual genetic variation. The term “genetic variation” refers to a change in a gene sequence relative to a reference sequence (e.g., a commonly-found and/or wild-type sequence). Genetic variation may be recombination events or mutations such as substitution/deletion/insertion events like point and splice site mutations. In embodiments, the genetic variation is a genetic variation in one or more cytochrome P450 (CYP or CYP450) enzymes that affects drug metabolism, including metabolism of a disclosed composition, and including CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4 and CYP3A5. Other examples of CYP enzymes include CYP1A1, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2E1, CYP2G1,

CYP2J2, CYP2R1, CYP2S1, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[293] In some embodiments, a disclosed compound or composition is taken together with a compound that is metabolized by the same CYP enzyme(s) as the disclosed compound, so as to permit a lower dose to be taken, increase the effective bioavailability of one or both, or otherwise affect drug metabolism or pharmacokinetics. In some embodiments, the dose of a disclosed composition is adjusted, such as reduced, when administered to a subject known to be a poor metabolizer of an active compound in the composition (e.g., having a genetic variation in CYP2D6 and/or CYP3A4), or increased when administered to a subject known to be a rapid metabolizer. In some embodiments, a patient is tested using ordinary means known to those of skill to determine if the patient is a poor or rapid metabolizer for one or more such CYP enzymes.

[294] In some embodiments, the genetic variation is a genetic variation in metabotropic glutamate receptor type 5 (mGluR5), which has been implicated in mood and anxiety symptoms in humans. In another embodiment, the genetic variation is one or more single nucleotide polymorphisms (SNPs) in the FKBP5 gene that are associated with elevated levels of FKBP51 protein relative to persons lacking such SNPs. The FKBP5 gene has been implicated in responses to stress and trauma, and such SNPs are correlated with susceptibility to certain depression, PTSD, and anxiety disorders. In some embodiments, a genetic variation is an inclusion criteria for the administration of a disclosed compound. In some embodiments, a genetic variation is an exclusion criteria for the administration of a disclosed compound.

[295] In some embodiments, the mammal being treated has altered epigenetic regulation of a gene, the expression of which is associated with a mental health condition or susceptibility to a mental health treatment, such as the SIGMAR1 gene for the non-opioid sigma-1 receptor.

ii. Neurodegenerative Disorders

[296] In some embodiments, a disclosed compound is used to treat a neurodegenerative disorder. In embodiments, disclosed compounds are administered, such as in a therapeutically effective amount, to a subject having a neurodegenerative disorder. In embodiments, a disclosed composition, when administered in a therapeutically effective amount, provides one or more therapeutic effects for the treatment of a neurodegenerative disorder.

[297] The term “neurodegenerative disorder” refers to a class of progressive, chronic, and debilitating conditions characterized by the gradual loss of structure and function of neurons within the central nervous system (CNS) or peripheral nervous system (PNS). These disorders involve the degeneration, impairment, or

death of neuronal cells, leading to a decline in cognitive, motor, and/or sensory abilities.

[298] Neurodegenerative disorders can be classified according to primary clinical features, e.g., dementia, parkinsonism, or motor neuron disease, anatomic distribution of neurodegeneration, e.g., frontotemporal degenerations, extrapyramidal disorders, or spinocerebellar degenerations, or principal molecular abnormality (Dugger B, Dickson DW. Pathology of Neurodegenerative Diseases. Cold Spring Harbor Perspectives in Biology. 2017;9(7):a028035). These disorders may involve various etiologies, including but not limited to, presence of pathogenic proteins, age, environmental stressors, and genetic predisposition (Armstrong R. Folia Neuropathologica. 2020;58(2):93-112).

[299] In embodiments, the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis or Charcot's disease, chronic traumatic encephalopathy, corticobasal degeneration, dementias including vascular dementia, Huntington's disease, Lytico-Bodig disease, mild cognitive impairment, multiple sclerosis, a motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson's disease or Parkinsonisms, prion diseases, progressive supranuclear palsy, and traumatic brain injury.

iii. Pain and Inflammation

[300] In some embodiments, a disclosed compound is used to treat pain and/or inflammation, such as a pain disorder and/or an inflammatory disorder. In some embodiments, a disclosed compound is administered, such as in a pharmacologically effective amount, to a subject having pain and/or inflammation, thereby treating said pain and/or inflammation. In some methods, a disclosed composition, when administered in a pharmacologically effective amount, provides one or more therapeutic effects for the treatment of pain and/or inflammation.

[301] In some embodiments, a disclosed compound is used to treat a pain disorder. In embodiments, the pain disorder is any of arthritis, allodynia, atypical trigeminal neuralgia, trigeminal neuralgia, somatoform disorder, hypoesthesia, hyperalgesia, neuralgia, neuritis, neurogenic pain, phantom limb pain, analgesia, anesthesia dolorosa, causalgia, sciatic nerve pain disorder, degenerative joint disorder, fibromyalgia, visceral disease, chronic pain disorders, headache disorders, migraine headaches, chronic cluster headaches, concussion headache, short-lasting unilateral neuralgiform headache attacks, chronic fatigue syndrome, complex regional pain syndrome, neurodystrophy, plantar fasciitis, or pain associated with cancer.

[302] In some embodiments, a disclosed compound is used to treat an inflammatory disorder. In some embodiments, the inflammatory disorder is characterized by inflammation of an organ or tissue. In embodiments, the inflammatory disorder comprises any one or more of skin inflammation, muscle inflammation, tendon inflammation, ligament inflammation, bone inflammation, cartilage inflammation, lung inflammation,

heart inflammation, liver inflammation, pancreatic inflammation, kidney inflammation, bladder inflammation, gastric inflammation, intestinal inflammation, neuroinflammation, and brain inflammation. In embodiments, the inflammatory disorder is a disorder that causes acute inflammation, or that exhibits chronic inflammation as a symptom. In some embodiments, the inflammatory disorder comprises chronic inflammation.

[303] In embodiments, a disclosed compound is used to reduce inflammation. In embodiments, a disclosed compound is used in the manufacture of a medicament to reduce inflammation. In embodiments, a disclosed compound, e.g., in a therapeutically effective amount, is administered to a subject to reduce inflammation.

[304] The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Although the mechanism for serotonin modulators, such as 5-HT_{2A} agonists and 5-HT_{2A} antagonists, to ameliorate pain remains unclear, the synaptic plasticity associated with such compounds may alter pathologic changes in neural connections seen in chronic pain states, potentially resulting in a reduced pain intensity and duration (Castellanos et al., *Reg Anesth Pain Med.* 2020;45(7):486-494). Additionally, 5-HT_{2AR} activation has been shown to promote anti-inflammatory effects, e.g., a reduction of TNF- α -induced inflammation. See, e.g., Pelletier & Siegel, *Mol Interv.* 2009;9(6):299-301, Flanagan et al., *Sci Rep.* 2019;9(1):13444, Nichols et al., *Clin Pharmacol Ther.* 2017;101(2):209-219; *Int Rev Psychiatry.* 2018;30(4):363-375, Okamoto et al., *Neurosci.* 2005;130(2):465-74.

[305] Pain, such as chronic pain, and improvements thereof, such as a reduction of symptoms, may be measured according to known methods, e.g., by subject reporting, pain diaries, pain scales, applicable questionnaires (assessments of chronic pain and its impact on physical, emotional and social functions), ecological momentary assessments and computerized versions thereof. See, e.g., Salaffi et al., *Best Practice & Research Clinic Rheumatol.* 2015;29(1):164-186 and Hawker et al., *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S240-52. Exemplary questionnaires include the Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP), Migraine Diagnosis Questionnaire, the Migraine-Screen Questionnaire (MS-Q), the Fibromyalgia Survey Questionnaire (FSQ).

[306] A reduction in inflammation, such as chronic systemic inflammation, may be measured according to various methods available to one of skill. Inflammatory biomarkers may be detected from biological specimens, for example, a subject's blood, such as plasma or serum, or saliva. In one example, inflammation may be detected by measuring high-sensitivity C-reactive protein (CRP) and white blood cell count from a blood test. CRP may also be detected in a saliva sample. Salivary CRP is not synthesized locally in the mouth and may

reflect more systemic levels of inflammation compared to other inflammatory biomarkers, such as cytokines (Szabo & Slavish, *Psychoneuroendocrinol.* 202;124:105069). Additionally clinical pathology data, e.g., hematology data on erythrocyte parameters, platelet count, total number of leukocytes, and leukocyte differentials and morphology, coagulation data on clotting times and fibrinogen, and clinical chemistry data on total protein, albumin and globulin, liver enzymes, renal parameters, electrolytes, and bilirubin can provide an initial indication of the presence and potentially the location of inflammation, in the absence of specific data on immune tissues. See, e.g., Germolec et al., *Methods Mol Biol.* 2018;1803:57-79 and Luo et al., *Clin Lab.* 2019 1;65(3).

iv. Ischemic Injury

[307] In some embodiments, a disclosed compound is used to treat an ischemic injury. In some embodiments, a disclosed compound is administered, such as in a pharmacologically effective amount, to a subject having an ischemic injury, thereby treating said ischemic injury. In some methods, a disclosed composition, when administered in a pharmacologically effective amount, provides one or more therapeutic effects for the treatment of an ischemic injury.

[308] In some embodiments, the ischemic injury is a stroke. As used herein, “stroke” is a general term that refers to conditions caused by the occlusion or hemorrhage of one or more blood vessels supplying the brain, leading to cell death. “Ischemic stroke”, as used herein, refers to stroke caused by an occlusion of one or more blood vessels supplying the brain. Types of ischemic stroke include, e.g., embolic stroke, cardioembolic stroke, thrombotic stroke, large vessel thrombosis, lacunar infarction, artery-artery stroke and cryptogenic stroke. “Hemorrhagic stroke”, as used herein, refers to stroke caused by hemorrhage of one or more blood vessels supplying the brain. Types of hemorrhagic stroke include, e.g., subdural stroke, intraparenchymal stroke, epidural stroke and subarachnoid stroke. In some embodiments, the stroke is a hemorrhagic stroke, ischemic stroke, or a transient ischemic attack (TIA). In some embodiments, the ischemic injury is an ischemia-reperfusion injury (IRI; also known as reoxygenation injury). In some embodiments, the ischemic injury is tissue damage that occurs when blood flow returns to an organ after a period of ischemia or lack of oxygen.

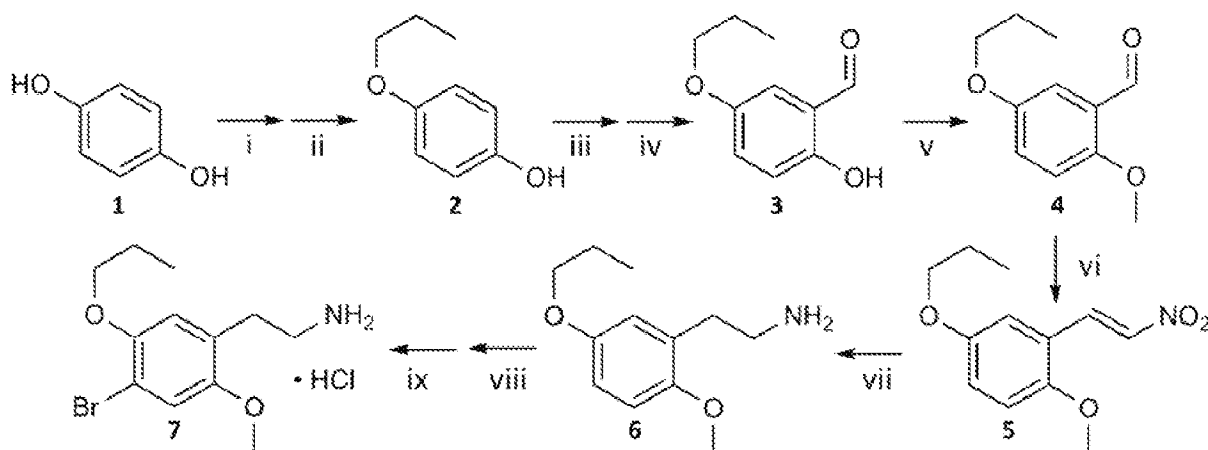
[309] In some embodiments, treating an ischemic injury with a disclosed compound results in an improvement measured using an assessment scale. Assessment scales include, for example, the Berg Balance Scale, the Modified Rankin Scale, the Stroke Impact Scale (SIS), the Stroke Specific Quality of Life Measure (SS-QOL), the American Heart Association Stroke Outcome Classification (AHA SOC), the Barthel Index, the Functional Independence Measurement (FIM™), the Glasgow Outcome Scale (GOS), and the Health Survey SF36™ & SF12™. Other diagnostic and screening tests include the Action Research Arm Test,

the Blessed-Dementia Scale, the Blessed-Dementia Information-Memory-Concentration Test, the DSM-IV criteria for the diagnosis of vascular dementia, the Hachinski Ischaemia Score, the Hamilton Rating Scale for Depression, the NINDS-AIREN criteria for the diagnosis of vascular dementia, the Orpington Prognostic Score, the Short Orientation-Memory-Concentration Test, the Thrombosis In Myocardial Infarction grading scheme, MRI imaging, diffusion-weighted (DWI) MRI techniques, and PET imaging.

I. Examples

[310] The examples are included for illustrative purposes only and should not limit the scope of the invention.

Example 1: Synthesis of 2-(4-bromo-5-propoxy-2-methoxyphenyl)ethan-1-amine (ASR2001)



- i. hydroquinone, NaNO_2 , n-propanol; ii. H_2SO_4 ; iii. NaOH ; iv. CHCl_3 ; v. K_2CO_3 , CH_3I ; vi. CH_3NO_2 , $\text{NH}_4\text{CH}_3\text{CO}_2$; vii. LAH/THF; viii. Br_2 , HOAC; ix. IPA/HCl

[311] 4-propoxyphenol (2):

[312] Hydroquinone (1; 110.1 g), sodium nitrite (3.45 g), and n-propanol (500 mL) were combined and stirred at room temperature. Concentrated H_2SO_4 (53.3 mL) was added dropwise over approximately 30 minutes, keeping the temperature stable. The reaction was monitored by GC-MS for the appearance of 2 and the disappearance of 1. After 1 h, the reaction mixture was poured into 1 L distilled H_2O , and extracted with CH_2Cl_2 . Excess CH_2Cl_2 and n-propanol were removed under reduced pressure to yield 103.7 g of 4-propoxyphenol (2).

[313] 2-hydroxy-5-propoxybenzaldehyde (3):

[314] 2 (38 g) was dissolved in 35% aqueous NaOH and stirred. A condenser was attached to the flask and the reaction was placed under N_2 atmosphere. CHCl_3 (350 mL) was added dropwise over approximately 1 h, and the reaction was then brought to reflux. After 2 h, TLC indicated no further change, and the reaction mixture was cooled with an ice bath to 10 °C. The pH was adjusted to < 2 with aqueous HCl, and the reaction was extracted with ethyl acetate. The ethyl acetate extract was dried over sodium sulfate, and the solvent was removed under reduced pressure to yield 43 g of crude 2-hydroxy-5-propoxybenzaldehyde (3). Purification by silica gel chromatography (4% ethyl acetate in heptane) yielded 7.2 g of crystalline

2-hydroxy-5-propoxybenzaldehyde (**3**).

[315] 2-methoxy-5-propoxybenzaldehyde (**4**):

[316] K_2CO_3 (17.86 g) was added to a stirring solution of acetone and **3** (7.2 g). Methyl iodide (6.22 mL) was added. The flask and condenser were flushed with N_2 and the reaction mixture was brought to reflux using a water bath. After confirming the reaction was complete by GC-MS, the mixture was cooled in an ice bath, poured into 200 mL of distilled water, and extracted with ethyl acetate. The organic layer was separated and dried over Na_2SO_4 . The solvent was removed under reduced pressure to yield 7.4 g of 2-MeO-5-propoxybenzaldehyde (**4**).

[317] (*E*)-1-methoxy-2-(2-nitrovinyl)-4-propoxybenzene (**5**):

[318] **4** (7 g), nitromethane (11.9 mL), and ammonium acetate (770 mg) were combined and stirred at room temperature for 2 h. Excess nitromethane was removed under vacuum to yield 9.3 g of crude (*E*)-1-methoxy-2-(2-nitrovinyl)-4-propoxybenzene (**5**), which was dissolved in isopropyl alcohol and allowed to stand. Crystallization produced 2.3 g of **5** as a free-flowing bright orange powder.

[319] 2-(2-methoxy-5-propoxyphenyl)ethan-1-amine (**6**):

[320] Under N_2 atmosphere, **5** (1.8 g) was transferred to a condenser-fitted flask containing stirred tetrahydrofuran (THF). Lithium aluminum hydride in THF (2 M) was then added dropwise to the refluxing reaction mixture. After approximately 1.5 h, the reaction mixture was returned to room temperature and neutralized with isopropyl alcohol and NaOH. The solvent was removed under reduced pressure to yield 1.38 g of 2-(2-methoxy-5-propoxyphenyl)ethan-1-amine (**6**) as a tan oil.

[321] 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine hydrochloride (**ASR2001**; **7**)

[322] Bromine/acetic acid solution was added dropwise to equimolar **6** and acetic acid. The reaction took on a dark orange-brown oily appearance. The reaction mixture was then combined with 25 mL of aqueous NaOH and extracted with CH_2Cl_2 . The combined CH_2Cl_2 layers were dried over sodium sulfate, and the solvent was removed under reduced pressure to yield 1.9 g of freebase 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine as a tan oil. This oil was dissolved in isopropyl alcohol, and hydrochloric acid to a slightly acidic pH, causing spontaneous crystallization of 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine hydrochloride (**ASR2001**; **7**). The crystalline product was harvested by suction filtration, and further purified by trituration in ether, filtration, and recrystallization from acetone, to yield 1.06 g of **7** as a crystalline solid consisting of bright white, shiny needles.

Example 2: In Vitro Receptor and Transporter Interactions

[323] Purpose: A comprehensive study was conducted to profile the interactions of disclosed compounds with various receptors, transporters, and ion channels. Comparisons may then be made regarding the

pharmacological activity of a disclosed compound and a comparator. Among other targets, activity was assessed at serotonin receptors (HTR_{1A}, HTR_{1B}, HTR_{2A}, HTR_{2B}, HTR_{5A}, HTR₆, HTR_{7D}), monoamine transporters (DAT, NET, and SERT), and the nicotinic acetylcholine receptor nAChR (α4/β2).

[324] Methods - Arrestin: Activation of HTR_{5A} and HTR₆, was determined using the PathHunter® β-Arrestin assay. The assay monitors restoration of β-galactosidase (β-Gal) as a marker of GPCR activation and recruitment of β-Arrestin to the receptor.

[325] To determine agonistic activity, cells were expanded from freezer stocks, seeded into multi-well plates, and incubated at 37 °C prior to addition of a test compound. 3.5 μL of concentrated sample was added to cells and incubated at 37 °C or room temperature for 90 to 180 minutes. Vehicle concentration was 1%.

[326] Assay signal was generated through a single addition of 50% v/v of PathHunter Detection reagent cocktail, followed by a one hour incubation at room temperature. Microplates were read following signal generation with a plate reader set to detect chemiluminescent signals. Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA).

[327] Percentage activity was calculated using the following formula:

[328] % Activity = $100\% \times (\text{mean RLU of test sample} - \text{mean RLU of vehicle control}) / (\text{mean MAX control ligand} - \text{mean RLU of vehicle control})$.

[329] Methods - cAMP: Activation of HTR_{1B} and GRM2, among other targets, was determined using the Hit Hunter® cAMP assay. The assay monitors the activation of a GPCR via Gi and Gs secondary messenger signaling, using β-Gal as a functional reporter.

[330] To determine agonistic activity at Gi/Gs, cells were expanded from freezer stocks, seeded into multi-well plates, and incubated at 37°C prior to addition of a test compound. To determine Gi/Gs agonism, media was aspirated from cells and replaced with 15 μL 2:1 HBSS/10mM HEPES:cAMP XS+Ab reagent. Concentrated (4X) test compound in assay buffer was added to cells and incubated at 37°C or room temperature for 30 or 60 minutes. For Gi agonist activation, cells were incubated with EC80 forskolin in addition to a test compound. Vehicle concentration was 1%.

[331] Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). For Gs agonist mode assays, percentage activity was calculated using the following formula:

[332] % Activity = $100\% \times (\text{mean RLU of test sample} - \text{mean RLU of vehicle control}) / (\text{mean RLU of MAX control} - \text{mean RLU of vehicle control})$.

[333] For Gi agonist mode assays, percentage activity was calculated using the following formula:

[334] % Activity = $100\% \times (1 - (\text{mean RLU of test sample} - \text{mean RLU of MAX control}) / (\text{mean RLU of vehicle control} - \text{mean RLU of MAX control}))$.

[335] Methods - Calcium Mobilization: GPCR activity of serotonin receptor 2B (HTR_{2B}), among others, was measured using the Calcium No Wash^{PLUS} assay, which monitors calcium mobilization in cell lines expressing Gq-coupled GPCRs by loading a calcium-sensitive dye into cells. Administration of a compound results in the release of calcium from intracellular stores and an increase in dye fluorescence that can be measured.

[336] Cell lines were expanded from freezer stocks and seeded into multi-well microplates. Then, the plates were incubated at 37°C for an appropriate amount of time and loaded with Dye Loading buffer. To determine compound agonist activity, cells were incubated with the sample to induce a response, and HBSS/20 mM Hepes was added using a FLIPR Tetra (MDS). Activity was measured on a FLIPR Tetra. Calcium mobilization was monitored for 2 minutes.

[337] To determine compound antagonist activity, cells were pre-incubated with the sample followed by an post-incubation administration of the compound with 3X EC₈₀ agonist using FLIPR. Compound antagonist activity was measured on a FLIPR Tetra (MDS) and calcium mobilization was monitored for 2 minutes.

[338] Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). For agonist mode assays, percentage activity was calculated using the following formula:

[339] $\% \text{ Activity} = 100\% \times (\text{mean RFU of test sample} - \text{mean RFU of vehicle control}) / (\text{mean MAX RFU control ligand} - \text{mean RFU of vehicle control})$.

[340] For antagonist mode assays, percentage inhibition was calculated using the following formula:

[341] $\% \text{ Inhibition} = 100\% \times (1 - (\text{mean RFU of test sample} - \text{mean RFU of vehicle control}) / (\text{mean RFU of EC}_{80} \text{ control} - \text{mean RFU of vehicle control}))$.

[342] Methods - Monoamine Transporter Assay: Neurotransmitter uptake via transporters was measured using the Neurotransmitter Transporter Uptake Assay Kit from Molecular Devices. Dopamine, norepinephrine or serotonin transporter activity in cells was detected using a homogeneous fluorescence based assay. Increased intracellular fluorescence intensity following uptake of biogenic amine neurotransmitters via transporters is measured and can be run in a kinetic or endpoint mode.

[343] To determine percentage inhibition of neurotransmitter uptake via transporter, cell lines were expanded from freezer stocks, seeded into a multi-well microplate, and incubated at 37°C. Then, the compound was administered and the mix was incubated again. Following compound incubation, dye was added to the wells and the plate was re-incubated. Microplates were then transferred to a PerkinElmer EnvisionTM instrument for fluorescence signal detection.

[344] Compound activity was analyzed using CBIS data analysis (ChemInnovation, CA). For blocker mode assays, percentage inhibition was calculated using the following formula:

[345] $\% \text{ Inhibition} = 100\% \times (1 - (\text{mean RLU of test sample} - \text{mean RLU of vehicle control}) / (\text{mean RLU of$

positive control - mean RLU of vehicle control)).

[346] Methods - Ion Channel Assay: Membrane potential changes were measured using the FLIPR® Membrane potential Assay Kit. A fluorescent indicator dye in combination with a quencher is used to reflect real-time membrane potential changes associated with ion channel activation and ion transporter proteins.

[347] To determine agonist and antagonist activity, cell lines were expanded from freezer stocks, seeded into multi-well microplates, and incubated at 37°C. Cells were then loaded with dye and incubated again.

[348] For agonist determination, cells were incubated with the sample at different dilutions to induce a response. For antagonist determination, cells were pre-incubated with the sample at different dilutions. Following dye administration, the sample was added to the cells in the presence of EC₈₀ agonist and then re-incubated at room temperature in the dark.

[349] Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). For agonist mode assays, percentage activity was calculated using the following formula:

[350] % Activity = 100% x (mean RLU of test sample - mean RLU of vehicle control) / (mean MAX control ligand - mean RLU of vehicle control).

[351] For antagonist mode assays, percentage inhibition was calculated using the following formula:

[352] % Inhibition = 100% x (1 - (mean RLU of test sample - mean RLU of vehicle control) / (mean RLU of EC₈₀ control - mean RLU of vehicle control)).

[353] Results & Significance: **TABLE 3** shows *in vitro* EC₅₀ values for ASR2001 at various receptors. **TABLE 4** shows *in vitro* IC₅₀ values for ASR2001 at various other targets, including transporters, ion channels, kinases, and enzymes. In each case the activity of positive controls was also known.

TABLE 3. Receptor binding data for ASR2001 (^a Results expressed as IC₅₀ and pIC₅₀)

Target	Assay Type	EC ₅₀ (μM)	pEC ₅₀
5-HT _{1A}	cAMP	9.9701	5.0013
5-HT _{1B}	cAMP	0.0031	8.5086
5-HT _{2A}	DOI competition	0.0036 ^a	8.4437 ^a
5-HT _{2A}	Ca ⁺⁺ flux	0.0424	7.3731
5-HT _{2A}	β-arrestin 2	0.0487	7.3123
5-HT _{2B}	Ca ⁺⁺ flux	3.9717	5.4010
5-HT ₃	Ca ⁺⁺ flux	> 10	< 5.00
5-HT _{5A}	β-arrestin 2	> 10	< 5.00

5-HT ₆	β -arrestin 2	> 10	< 5.00
5-HT ₇	cAMP	> 10	< 5.00
D ₁	cAMP	> 10	< 5.00
D _{2S}	cAMP	> 10	< 5.00
ET _A	Ca ⁺⁺ flux	> 10	< 5.00
mGlu2	cAMP	> 10	< 5.00
H ₁	Ca ⁺⁺ flux	> 10	< 5.00
H ₂	cAMP	> 10	< 5.00
M ₁	Ca ⁺⁺ flux	> 10	< 5.00
M ₂	cAMP	> 10	< 5.00
M ₃	Ca ⁺⁺ flux	> 10	< 5.00
DOR	cAMP	> 10	< 5.00
KOR	cAMP	> 10	< 5.00
MOR	cAMP	> 10	< 5.00
V _{1A}	Ca ⁺⁺ flux	> 10	< 5.00

Table 4. Binding data for ASR2001 at other targets

Target	Assay Type	IC ₅₀ (μ M)	pIC ₅₀
DAT	Substrate surrogate	N.D.	N/A
NET	Substrate surrogate	N.D.	N/A
SERT	Substrate surrogate	5.2195	5.2824
nACh ($\alpha_4\beta_2$)	Ca ⁺⁺ flux	5.3378	5.2726
Cav1.2	Ca ⁺⁺ flux	> 10	< 5.00
GABA _A	Membrane potential	> 10	< 5.00
hERG	TI ⁺ flux	> 10	< 5.00
KvLQT1	TI ⁺ flux	> 10	< 5.00
Nav1.5	Membrane potential	5.9708	5.2240

NMDA	Ca ⁺⁺ flux	> 10	< 5.00
TK LCK	Inhibition of kinase binding	> 10	< 5.00
TK INSR	Inhibition of kinase binding	> 10	< 5.00
TK VEGF2	Inhibition of kinase binding	> 10	< 5.00
AGC ROCK1	Inhibition of kinase binding	> 10	< 5.00
AR	Nuclear hormone receptor translocation	> 10	< 5.00
GR	Nuclear hormone receptor translocation	> 10	< 5.00
COX ₁	Enzyme inhibition	> 10	< 5.00
COX ₂	Enzyme inhibition	> 10	< 5.00
AChE	Enzyme inhibition	> 10	< 5.00
MAO-A	Enzyme inhibition	7.8067	5.1075

Example 3: In Vivo PK of 2-(4-bromo-5-propoxy-2-methoxyphenyl)ethan-1-amine (ASR2001)

[354] **Purpose:** The aim of this experiment was to evaluate the in vivo pharmacokinetics (PK) of ASR2001 and psilocybin dosed once orally in male C57BL6 mice. Terminal blood samples and brains were collected at 8 timepoints over the duration of the study.

[355] **Methods:** Seventy-eight male C57BL6/j (72 study, 6 blanks) were ordered from Charles River UK (Margate, Kent UK). Mice were housed in groups of up to 3 upon arrival in the animal facility of Nottingham University under a normal phase 12 h light-dark cycle (lights on 07:00). Relative humidity was typically 55 ± 15% with prolonged periods below 40% RH or above 70% RH avoided as detailed in the UK Code of Practice. The mice were housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzlenest and nestlet. Animals had free access to standard maintenance diet (Envigo Teklad 2018) and tap water ad libitum. Animals were given wet mash on arrival (powdered standard diet mixed with water) to aid recovery. Wet mash was removed the following day. Body weights were recorded upon arrival (Thursday), the following day (Friday) and on Monday. Animals were acclimatized to the facility for approximately 4 days prior to procedures.

[356] **Day 1:** all mice were weighed, tail marked, and returned to their home cages. Mice were dosed to a timed schedule. Dosing commenced at approximately 08:30.

[357] **Blood Sampling:** Following a single dose, mice were terminally bled by cardiac puncture to a timed schedule (n=3 mice per group, per timepoint).

[358] **Blood sample handling:** Terminal blood samples (approx. 0.5 mL) were placed into K3EDTA-coated tubes (e.g. Greiner Bio Paediatric tubes -459036) following cardiac puncture and spun within 30 minutes of

collection in a cooled centrifuge. Samples were held on wet ice prior to centrifugation. Plasma samples were aliquoted into two 50 μ L samples and stored on duplicate plates. Plasma samples from psilocybin-treated animals had 50 mM DTT added at a ratio of 10:1 (plasma:DTT) to aid stabilization of psilocin within the sample: 5 μ L of 50mM DTT was added to each plasma sample. Samples were stored frozen in 96-well plates (initially on dry ice and then transferred to a freezer at approx. -20 °C or -80 °C).

[359] *Brain collection and handling:* Whole brains were removed from all mice, rinsed briefly with saline and blot dried. The left and right frontal cortices (~25-30 mg each frontal cortex) were dissected separately from the brain, weighed, frozen on dry ice, wrapped in aluminum foil, placed in individual bags and stored at 20 °C (for subsequent ex vivo binding; see Example 4). The remaining brain tissue was weighed, frozen on dry ice, and placed into a 7mL Precellys tube prior to transferring (on dry ice) to Sygnature DMPK with the plasma samples. Carcasses were disposed of at the end of the in vivo phase.

[360] *Results:* Results are shown below in **TABLE 5** and **FIGS. 1-6**.

TABLE 5. Pharmacokinetic properties of ASR2001 and psilocybin (by measurement of psilocin) dosed once orally in male C57BL6 mice

Parameter	ASR2001 3 mg/kg PO in Male Mouse (C57BL/6) Plasma Group A (Formulation: Saline)	ASR2001 3 mg/kg PO in Male Mouse (C57BL/6) Brain Group A (Formulation: Saline)	Psilocin (after administration of Psilocybin at 10 mg/kg PO) in Male Mouse (C57BL/6) Plasma Group C (Formulation: Saline)	Psilocin (after administration of Psilocybin at 10 mg/kg PO) in Male Mouse (C57BL/6) Brain Group C (Formulation: Saline)
Tmax (h)	0.5	1	0.25	0.5
Cmax (ng/mL)	130.00	1850.00	878.00	1340.00
Half-Life (h)	1.44	1.29	1.70	4.47
AUClast (ng/mL.h)	284.00	6480.00	1060.00	3600.00
AUCinf (ng/mL.h)	291.00	6680.00	1140.00	4420.00
MRTlast (h)	2.11	2.86	1.80	2.34
MRTinf (h)	2.28	3.07	2.40	4.59
AUC % Extrapolation to Inf	2.23	3.02	7.02	18.60
CL/F (mL/min/kg)	172.00	-	-	-
Vz/F (L/kg)	21.50	-	-	-

Example 4: Ex Vivo Receptor Binding Studies

[361] Purpose: To determine receptor occupancy of test compounds in mouse frontal cortex 5-HT_{2A} receptors.

[362] Methods: Frontal cortices were homogenized in ice-cold assay buffer using a glass/Teflon homogenizer (12 strokes, 800 rpm) at a tissue concentration equivalent to 3.75 mg wet weight of tissue/mL. Membranes (400 μ L; equivalent to 1.5 mg tissue/tube) were immediately incubated with 50 μ L of 0.75 nM [³H]Cimbi-36 and either 50 μ L of assay buffer (total binding) or 50 μ L of 1 μ M 25CN-NBOH (non-specific binding) at 25 °C for 30 mins. There were 2 total and 2 non-specifics for each animal.

[363] Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/A filters, presoaked in 0.5% polyethylenimine (PEI) using a Skatron cell harvester. Filters were rapidly washed with ice-cold wash buffer (wash setting 9,9,0) and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator). Assay buffer consisted of 50 mM TrisH, pH 7.4 and 4 mM CaCl₂, wash buffer consisted of 50 mM Tris, pH 7.4.

[364] Data was processed as disintegrations per minute (dpm). Specific binding was defined as total binding minus non-specific binding for each sample. Data was square root transformed and analyzed by one-way ANOVA followed by an appropriate post-hoc test.

[365] Results: Results are shown in **TABLE 6** and **FIGS. 7-9**, expressed as mean specific binding (dpm), percentage of control, and percentage receptor occupancy.

TABLE 6. Summary of ASR2001 mean specific binding data

Compound (3 mg/kg)	Timepoint (mins)	n	Mean	SEM	%	p
Naïve	0	4	1182	43		
ASR2001	15	3	1070	31	91	0.395
ASR2001	30	3	973	56	82	0.018*
ASR2001	45	3	1057	28	89	0.284
ASR2001	60	3	984	155	83	0.027*
ASR2001	120	3	1033	53	87	0.146
ASR2001	240	3	1027	38	87	0.119
ASR2001	360	3	1041	15	88	0.184
ASR2001	480	3	1126	41	95	0.940

Data was square root transformed and analyzed by robust regression, followed by Dunnett's test to compare each timepoint to the naïve group. *p<0.05

Example 5: Metabolic Stability of Test Compounds in Liver Microsomes of Different Species

[366] Purpose: To determine whether the disclosed compounds are metabolized in a liver microsome assay. Human, rat, mouse, and dog microsomes were used in this experiment, as described in **TABLE 7**.

TABLE 7. Liver Microsomes Used in this Experiment

Species	Cat. No.	Lot No.	Sponsor	Strain & Gender
Human	452117	38297	Corning	Pooled, Male & Female
Rat	452501	1300002	Corning	Pooled, Male Sprague-Dawley
Mouse	452701	1104001	Corning	Pooled, Male CD-1
Dog	452601	9350001	Corning	Pooled, Male Beagle

[367] Methods: A master solution was prepared according to **TABLE 8**.

TABLE 8. Composition of Master Solution.

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 μ L	100 mM
Ultra-pure H ₂ O	-	66 μ L	-
MgCl ₂ solution	50 mM	40 μ L	5 mM
Alamethicin	5 mg/mL	2 μ L	25 μ g/mL
Microsomes	20 mg/mL	10 μ L	10 μ L

[368] 40 μ L of 10 mM NADPH solution and 40 μ L of 20 mM UDPGA solution were added to each well. The final concentrations of NADPH and UDPGA were 1 mM and 2 mM. The mixture was pre-warmed at 37 °C for 5 mins. Negative control samples were prepared by replacing cofactors (NADPH and UDPGA) solution with 80 μ L of ultra-pure H₂O. The negative control was used to exclude the misleading factor that resulted from instability of chemical itself. Samples with cofactors were prepared in duplicate. Negative controls were prepared in singlet.

[369] Reactions were started with the addition of 2 μ L of 200 μ M control compound or test compound solutions. Diclofenac was used as positive control in this study. The final concentration of test compound or control compound was 1 μ M.

[370] Aliquots of 50 μ L were taken from the reaction solution at 0, 15, 30, 45 and 60 minutes. The reaction was stopped by the addition of 4 volumes of cold acetonitrile with IS (100 nM alprazolam, 200 nM imipramine, 200 nM labetalol and 2 μ M ketoprofen). Samples were centrifuged at 3, 220 g for 40 minutes. Aliquot of 90 μ L

of the supernatant was mixed with 90 μL of ultra-pure H_2O and then used for LC-MS/MS analysis. Chromatography and mass spectrometry parameters are described in **TABLES 9** and **10**, respectively.

TABLE 9. Chromatographic Conditions

LC system: Shimadzu; MS analysis: QTRAP® 4500 from AB Inc (Canada) with an ESI interface						
Column temperature: 40 °C; Injection volume: 3 μL						
Column: XSelect Hss T3 2.5 μm (2.1x50 mm) Column XP coupled with preguard column						
Mobile phase: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)						
Time (min)	0	0.1	0.5	0.8	0.81	1.0
% B	5	5	100	100	5	5
Elution rate: 1.0 mL/min						

TABLE 10. MS Parameters

Ion source: Turbo spray; Ionization model: ESI; Scan type: MRM						
Curtain gas: 30 L/min; Nebulize gas: 50 L/min; Auxiliary gas: 50 L/min						
Temperature: 500°C; Ionspray voltage: +5500 v (positive MRM)						
Compound ID	Q1 (m/z)	Q3 (m/z)	DP (v)	EP (v)	CE (v)	CXP (v)
ASR2001	288.2	214.2	80	10	30	15

[371] For data analysis, all calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. The slope value, k , was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve. The *in vitro* half-life (*in vitro* $t_{1/2}$) was determined from the slope value: *in vitro* $t_{1/2} = -(0.693/k)$. Conversion of the *in vitro* $t_{1/2}$ (min) into the *in vitro* intrinsic clearance (*in vitro* CL_{int} , in $\mu\text{L}/\text{min}/\text{mg}$ protein) was done using the following equation (mean of duplicate determinations):

$$\text{in vitro } \text{CL}_{\text{int}} = \frac{0.693}{t_{1/2}} \times \frac{\text{volume of incubation } (\mu\text{L})}{\text{amount of proteins } (\text{mg})}$$

[372] Results & Significance: Results for metabolic stability are presented in **TABLE 11** as *in vitro* half-life, $T_{1/2}$, and *in vitro* intrinsic clearance, CL_{int} .

TABLE 11. Metabolic Stability of Test Compounds in Liver Microsomes

Compound ID	Species	$T_{1/2}$ (min)	CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$ protein)
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ASR2001	Human	434.40	3.19
	Rat	31.96	43.37
	Mouse	99.72	13.9
	Dog	63.58	21.80

Example 6: Metabolic Stability of Test Compounds in Different Species of Hepatocytes

[373] Purpose: To determine the metabolic stability of test compounds in different species of hepatocytes. Human, rat, mouse, and dog hepatocytes were utilized, as described in **TABLE 12**.

TABLE 12. Hepatocyte Information

Species	Vendor	Cat. No.	Lot No.	Strain & Gender
Human	BioIVT	X008001	QZW	10-Donor, Pooled
Rat	BioIVT	M00005	GFU	Pooled, Male Sprague-Dawley
Mouse	BioIVT	M005052	TDD	Pooled, Male CD-1
Dog	BioIVT	M00205	APJ	Pooled, Male Beagle

[374] Methods: 10 mM Stock solutions of test compound and positive control were prepared in DMSO. Thawing medium and supplement incubation medium (serum-free) were placed in a 37°C water bath for at least 15 minutes prior to use. Stock solutions were diluted to 100 µM by combining 198 µL of 50% acetonitrile/50% water and 2 µL of 10 mM stock solution. Verapamil was used as positive control in the assay.

[375] Vials of cryopreserved hepatocytes were removed from storage, ensuring that vials remain at cryogenic temperatures. The pressure was removed by loosening and re-tightening the cap. The vials were thawed in a 37°C water bath with gentle shaking. Vials remained in the water bath until all ice crystals had dissolved and were no longer visible. Vials were sprayed with 70% ethanol before being transferred to a biosafety cabinet. And then the contents were poured into the 50 mL thawing medium conical tube. Vials were centrifuged at 100 g for 10 minutes at room temperature. Thawing medium was aspirated and hepatocytes were re-suspended with serum-free incubation medium to yield $\sim 1.5 \times 10^6$ cells/mL. Cell viability and density were counted using AO/PI fluorescence staining, and then cells were diluted with serum-free incubation medium to a working cell density of 0.5×10^6 viable cells/mL. A portion of the hepatocytes at 0.5×10^6 viable cells/mL was boiled for 5 min prior to adding to the plate as negative control to eliminate the enzymatic activity so that little or no substrate turnover should be observed. The boiled hepatocytes were used to prepare negative samples, which used to exclude the misleading factor that resulted from instability of the chemical

itself.

[376] Aliquots of 198 μ L hepatocytes were dispensed into each well of a 96-well non-coated plate. The plate was placed in the incubator for approximately 10 minutes. Aliquots of 2 μ L of the 100 μ M test compound and positive control were added into respective wells of the non-coated 96-well plate to start the reaction. The final concentration of the test compound is 1 μ M. This assay was performed in duplicate. The plate was incubated in the incubator for the designed time points.

[377] 25 μ L of contents were transferred and mixed with 6 volumes (150 μ L) of cold acetonitrile with IS (100 nM alprazolam, 200 nM labetalol, 200 nM caffeine and 200 nM diclofenac) to terminate the reaction at time points of 0, 15, 30, 60, 90 and 120 minutes. Samples were centrifuges for 45 minutes at 3,220 g and an aliquot of 100 μ L of the supernatant was diluted by 100 μ L ultra-pure H₂O, and the mixture was used for LC/MS/MS analysis. Chromatography and mass spectrometry parameters are described in **TABLE 13** and **TABLE 14**.

TABLE 13. Chromatographic Conditions

LC system: Shimadzu						
MS analysis: API 4000 and 6500+ instrument from AB Inc (Canada) with an ESI interface						
Column temperature: 40 °C						
Gradient and flow, G-1.0min: 0-0.1min, 3%B; 0.1-0.5min,3- 100%B; 0.5-0.8min, 100%B; 0.8-0.81min,100-3%B;0.81-1.0min,3%B. Injection volume: 10 μ L. Elution rate: 1.0 mL/min.						
Gradient and flow, G-1.0min-1: 0-0.1min, 5%B; 0.1-0.5min,5- 95%B; 0.5-0.8min, 95%B; 0.8-0.81min,95-5%B;0.81-1.0min,5%B. Injection volume: 1 μ L. Elution rate: 1.0 mL/min.						
Column: T3: Waters XSelect HSS T3, 2.5 μ m, 2.1 x 50mm. Hydro-RP: Phenomenex Synergi 4 μ m Hydro-RP 80Å (30x2.0 mm)						
Mobile phase: MP-FA, Phase A: water(0.1% FA); Phase B: ACN(0.1% FA)						
Time (min)	0	0.1	0.5	0.8	0.81	1.0
% B	5	5	100	100	5	5
Elution rate: 1.0 mL/min						

TABLE 14. MS Parameters

Ion source: Turbo spray; Ionization model: ESI; Scan type: MRM
Collision gas: 6 L/min; Curtain gas: 30 L/min; Nebulize gas: 50 L/min; Auxiliary gas: 50 L/min

Temperature: 500°C; Ionspray voltage: +5500 v (positive MRM) / -4500 v (negative MRM)										
Compound ID	Species	Q1 (m/z)	Q3 (m/z)	DP (v)	EP (v)	CE (v)	CXP (v)	Gradient and Flow	Mobile Phase	Column
ASR2001	Human	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP
	Rat	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP
	Mouse	288.2	271.3	80	10	30	10	G-1.0min-1	MP-FA	T3
	Dog	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP

[378] All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. Determine the *in vitro* half-life ($t_{1/2}$) of the parent compound by regression analysis of the percent parent disappearance vs. time curve. The *in vitro* half-life (*in vitro* $t_{1/2}$) was determined from the slope value: $\ln t_{1/2} = - (0.693 / k)$. Conversion of the *in vitro* $t_{1/2}$ (in min) into the *in vitro* intrinsic clearance (*in vitro* CL_{int} , in $\mu\text{L}/\text{min}/10^6$ cells) is done using the following equation (mean of duplicate determinations): *in vitro* $CL_{int} = kV/N$, wherein V is equal to the incubation volume (0.2 mL) and N is equal to the number of hepatocytes per well (0.1×10^6 cells). Scaled-up CL_{int} was also calculated using the following equation: $CL_{int} = kV/N'$ scaling factor, wherein V is equal to the incubation volume (0.2 mL) and N is equal to the number of hepatocytes per well (0.1×10^6 cells). Scaling factors for *in vivo* intrinsic clearance prediction and Liver blood flow (Q) for different species are described in **TABLE 15**.

TABLE 15. Scaling Factors for Intrinsic Clearance Prediction in Hepatocytes

Compound ID	Species	Q1 (m/z)	Q3 (m/z)	DP (v)	EP (v)	CE (v)	CXP (v)	Gradient and Flow	Mobile Phase	Column
ASR2001	Human	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP
	Rat	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP
	Mouse	288.2	271.3	80	10	30	10	G-1.0min-1	MP-FA	T3
	Dog	288.2	271.3	80	10	30	12	G-1.0min	MP-FA	Hydro-RP

[379] Results & Significance: Results for metabolic stability are displayed in **TABLE 16** as *in vitro* half-life, $T_{1/2}$, *in vitro* intrinsic clearance, CL_{int} , and scale-up CL_{int} .

TABLE 16. Metabolic Stability of Test Compounds in Hepatocytes.

Compound ID	Species	$T_{1/2}$ (min)	$CL_{int}(\mu\text{L}/\text{min}/10^6 \text{ cells})$	Scale-up $CL_{int}(\text{mL}/\text{min}/\text{kg})$
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ASR2001	Human	253.87	5.46	13.89
	Rat	6.51	212.75	995.67
	Mouse	70.68	19.61	231.63
	Dog	325.74	4.25	29.27

Example 7: In Vitro CYP Enzyme Inhibition

[380] Purpose: To assess the interactions between disclosed compounds and cytochrome P450 (CYP450) enzymes. Such interactions will provide insight into metabolism-mediated drug-drug interactions, which can occur when a compound affects the pharmacokinetics, such as the absorption, distribution, metabolism, and excretion, of simultaneously administered drugs by altering the activities of drug metabolizing enzymes and/or drug transporters.

[381] Methods: An in vitro study is conducted to assess the inhibitory effect of the disclosed compound on recombinant human CYP450 isoenzymes. Recombinant human CYP450 isoenzymes are used to metabolize pro-fluorescent probe substrates to fluorescent products. Inhibition of human P450 isoforms is measured by reduced fluorescence following treatment with the disclosed compound at various concentrations.

[382] Briefly, the disclosed compound is incubated in different concentrations in a mix containing buffer, enzymes, and substrate. Then, fluorescence is measured using a plate reader and percentage inhibition may be extrapolated out from the readings. Alternatively, the inhibitory effects of the disclosed compound on CYP enzymes may be assessed using high-performance liquid chromatography. Inhibition is evaluated using the Michaelis-Menten method. CYP enzyme inhibition may be conducted according to the methods described in Lin et al., J Pharm Sci. 2007 Sep;96(9):2485-95 and Wójcikowski et al., Pharmacol Rep. 2020 Jun;72(3):612-621.

[383] Results & Significance: Metabolizing enzymes in the liver, such as CYP450 enzymes, are responsible for the majority of drug metabolism that occurs in the body. Six CYP450 class enzymes metabolize 90 percent of drugs, and two of the most significant metabolizers are CYP3A4 and CYP2D6 (Lynch & Price, Am Fam Physician. 2007;76(3):391-6). Compounds can interact with such enzymes by inhibiting their enzymatic activity (CYP inhibition) or by inducing their gene expression (CYP induction).

Example 8: In vitro evaluation of membrane permeability and interactions with P-glycoprotein (P-gp) in MDCKII MDR1 cells

[384] Purpose: To assess the permeability and transport liability of disclosed compounds. Permeability is assessed using MDCK (Madin-Darby canine kidney) cells, and the effects of P-glycoprotein (P-gp) are evaluated to determine drug transport.

[385] Methods: A bidirectional permeability study (apical to basolateral [AB] and basolateral to apical [BA]) is

conducted to evaluate the apparent permeability of the disclosed compound. Further, an evaluation to determine if the disclosed compound acts as a P-gp substrate in MDCKII-MDR1 and mock MDCKII cell lines is performed.

[386] Briefly, the disclosed compound and reference compounds are evaluated in two directions in the absence and presence of a P-gp inhibitor. The MDCKII and MDCKII-MDR1 cells are incubated in a transport buffer on both apical [A] and basolateral [B] sides. Then, the disclosed compound is added to each side of the cells and incubated. The rate of transport of the disclosed compound is determined in the absence or presence of a P-gp inhibitor. Following incubation, where the disclosed compound will permeate the cells in both AB and BA directions, the permeability of the cells is measured using a LC MS/MS system. The efflux ratio of the disclosed compound is calculated to determine if it is a P-gp substrate.

[387] Results & Significance: This screening provides insight into the movement of the disclosed compound in a biological system. Compounds are classified as follows (Cambridge MedChem Consulting, ADME, 2019):

Papp (nm/s)	Classification
>150	High Permeability
50-150	Medium Permeability
<50	Low Permeability

[388] Mass balance as a percentage (%) is calculated using the following equation:

$$\% \text{Recovery} = 100 \times (\text{CD}(t) + \text{CR}(t)) / C_0$$

[389] Where CD(t) is the measured concentration in the donor well at time t (expressed as IS ratio), CR(t) is the measured concentration in the receiver well at time t (expressed as IS ratio), C_0 is the initial concentration in the donor solution (expressed as IS ratio).

[390] The percentage of cell integrity is calculated using the following equation:

$$\% \text{Integrity} = 100 \times [1 - \text{RFU}_{\text{basolateral}} / \text{RFU}_{\text{apical}}]$$

[391] LY RFU values are normalized by background mean values. A test item is considered to be a P-gp substrate when the efflux ratio in the absence of the inhibitor is >2 and if the ratio is significantly reduced in the presence of a P-gp inhibitor.

Example 9: In Vitro Activity at Trace Amine-Associated Receptor 1 (TAAR1)

[392] Purpose: To assess the activity of disclosed compounds at trace amine-associated receptor 1, a target of psychoactive substances. See, e.g., Rickli et al., Neuropsychopharmacology, 2016;26(8), 1327–1337, Simmler et al., Br J Pharmacol. 2013 Jan; 168(2): 458–470, and Simmler et al., Journal of Pharmacology and Experimental Therapeutics, 2016;357(1):134-144.

[393] Methods: A radioligand binding assay is performed according to previously described methods, for

example, by Rickli et al., *Neuropsychopharmacology*, 2016;26(8), 1327–1337, using [3H] RO5166017 as a radiolabel and RO5166017 as a competitor. Briefly, membrane preparations of human embryonic kidney (HEK) 293 cells that overexpress TAAR1 receptors, for example, of human origin (Revel et al., *PNAS*, 2011;108:8485–8490) are incubated with the radiolabeled selective ligand at concentrations equal to K_d . Ligand displacement by the compounds is then measured. Specific binding of the radioligand to the target receptor is defined as the difference between the total binding and nonspecific binding that is determined in the presence of selected competitors in excess.

[394] Results & Significance: Activation of TAAR1 has been shown to modulate monoaminergic neurotransmission. See, e.g., Revel et al., *PNAS*. 2011;108(20):8485–8490. TAAR1 may be a promising target for the treatment of neuropsychiatric disorders. For example, the effects of TAAR1 activation on dopaminergic neurotransmission may provide therapeutic benefit for addiction, such as substance use disorders (Liu & Li, *Front Pharmacol*. 2018;9:279).

Example 10: In Vivo Assessment Of The Behavioral Effects Of Disclosed Compounds Using HTR

[395] Purpose: The mouse head-twitch response (HTR) is a behavioral test that reflects 5-HT_{2A} receptor activation and can be predictive of psychedelic effects in humans (Halberstadt et al., *J Psychopharmacol*. 2011; 25(11): 1548–1561). The HTR is widely used as a behavioral surrogate for human psychedelic effects for its ability to reliably distinguish psychedelic from non-psychedelic 5-HT_{2A} receptor agonists (Halberstadt & Geyer, *Psychopharmacol (Berl)*. 2013;227(4):727-3).

[396] Methods: An HTR assay is performed in accordance with the methods described in Klein et al., *Neuropharmacol*, 2018;142:231-239 to assess the effects of disclosed compounds in mice. Male C57BL/6 J mice (6-8 weeks old) are obtained and housed in a vivarium that meets all requirements for care and treatment of laboratory animals. Mice are housed up to four per cage in a climate-controlled room on a reverse-light cycle (lights on at 1900 h, off at 0700 h) and are provided with ad libitum access to food and water, except during behavioral testing. Testing is conducted between 1000 and 1800 h. All animal experiments are conducted in accordance with applicable guidelines and are approved by an appropriate animal care committee.

[397] A head-mounted magnet and a magnetometer detection coil is used to assess HTR, as previously described (Halberstadt & Geyer, *Psychopharmacol (Berl)*. 2013;227(4):727-3, Halberstadt & Geyer, *Neuropharmacol*, 2014;77:200-7; Nichols et al., *ACS Chem Neurosci*. 2015; 6(7): 1165–1175). Briefly, mice are anesthetized and a small neodymium magnet is attached to the dorsal surface of the cranium using dental cement. Following a two-week recovery period, HTR experiments are carried out in a well-lit room with at least 7 days between sessions to avoid carryover effects.

[398] Test compounds are dissolved in a suitable solvent, e.g., water containing 5% Tween 80, and administered IP at a volume of 5 or 10 mL/kg body weight immediately prior to testing. Different doses are tested to produce a dose-response curve. Mice are injected with drug or vehicle, and HTR activity is recorded in a glass cylinder surrounded by a magnetometer coil for 30 min. Coil voltage is low-pass filtered (2e10 kHz cutoff frequency), amplified, and digitized (20 kHz sampling rate) using a Powerlab/8SP with LabChart v 7.3.2 (ADInstruments, Colorado Springs, CO, USA), then filtered off-line (40e200 Hz band-pass).

[399] Head twitches are identified manually based on the following criteria: 1) sinusoidal wavelets; 2) evidence of at least two sequential head movements (usually exhibited as bipolar peaks) with frequency 40 Hz; 3) amplitude exceeding the level of background noise; 4) duration < 0.15 s; and 5) stable coil voltage immediately preceding and succeeding each response.

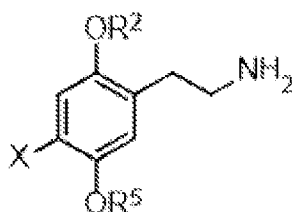
[400] Head twitch counts are analyzed using one-way analyses of variance (ANOVA). Post hoc pairwise comparisons between selected groups are performed using Tukey's studentized range method. The entire recordings are examined for head twitches. In some cases a shorter block of time is analyzed to accommodate compounds with a brief duration-of-action, as potency calculations can be confounded by extended periods of inactivity. ED₅₀ values and 95% confidence limits are calculated using nonlinear regression. Relationships between HTR potency and binding affinities are assessed using linear regression and ordinary least-squares regression. For all analyses, significance is demonstrated by surpassing an α -level of 0.05.

[401] Results & Significance: Results can show that certain disclosed compounds are unlikely to produce psychedelic effects in humans. When a psychedelic effect is produced, its magnitude is evaluated and compared amongst compounds. Results can be represented as ED₅₀ (mg/kg). Differences between the mouse HTR of disclosed compounds and suitable comparator compounds are also determined based on described methods.

J. Exemplary Aspects and Embodiments

[402] Among the various aspects and embodiments of the disclosure are the following, which will be understood to be exemplary and not limiting.

[403] In one exemplary aspect, provided is a compound of Formula (I),



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

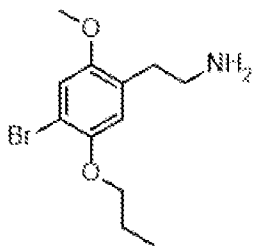
X is F, Cl, Br, I, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkylthio; and

one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl or C_3 - C_6 alkenyl; provided that when R^2 is methyl and R^5 is isopropyl, X is not Br.

[404] In some embodiments, R^2 is methyl and R^5 is C_3 - C_6 alkyl. In some embodiments, R^2 is methyl and R^5 is propyl. In some embodiments, R^5 is n-propyl. In some embodiments, R^5 is isopropyl. In some embodiments, R^2 is methyl and R^5 is butyl. In some embodiments, R^5 is n-butyl. In some embodiments, R^5 is isobutyl. In some embodiments, R^5 is sec-butyl. In some embodiments, R^5 is tert-butyl. In some embodiments, R^2 is methyl and R^5 is pentyl. In some embodiments, R^5 is n-pentyl. In some embodiments, R^5 is neo-pentyl.

[405] In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is CF_3 . In some embodiments, X is CH_3 . In some embodiments, X is SCH_3 .

[406] In some embodiments, the compound is selected from **TABLE 1** or **TABLE 2**.



[407] In some embodiments, the compound is , or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

[408] In some embodiments, provided is a pharmaceutical composition comprising a therapeutically effective amount of the compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the compound, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, is a pure or substantially pure individual enantiomer, or an enantiomerically enriched mixture having an optical purity of between 0-25%, between 25-50%, between 50-75%, between 75-90%, between 90-95%, or at least 95% enantiomeric excess.

[409] In some embodiments, the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration.

[410] In some embodiments, the composition is provided in unit dosage form. In some embodiments, the unit dosage form is an immediate release, controlled release, sustained release, extended release, or modified release formulation.

[411] In some embodiments, the compound or the prodrug in a total amount of between 0.1 and 100 mg, or between 1 and 10 mg. In some embodiments, the compound or the prodrug in a total amount of between 0.1 and 10 mg, or between 0.5 and 5 mg.

[412] In some embodiments, the pharmaceutical composition is further comprising a therapeutically effective

amount of an additional active compound, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof.

[413] In some embodiments, the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins.

[414] In some embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, or alter pharmacokinetics or pharmacodynamics. In some embodiments, the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.

[415] In some embodiments, provided is a compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments, for use in the treatment of a mental health disorder.

[416] In some embodiments, provided is the use of a compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments, for the manufacture of a medicament for the treatment of a mental health disorder patient according to the method of any of the following claims.

[417] In another exemplary aspect, provided is a method for modulating neurotransmission in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments.

[418] In some embodiments, modulating neurotransmission comprises activating one or more monoamine neurotransmitter receptor(s) and/or modulating the uptake activity of one or more monoamine transporter(s). In some embodiments, the one or more monoamine neurotransmitter receptor(s) is any of a serotonin receptor (HTR), a dopamine receptor, or a norepinephrine receptor; and the one or more monoamine transporter is a serotonin transporter (SERT). In some embodiments, the HTR is any one or more of HTR_{1A}, HTR_{1B}, HTR_{2A},

HTR_{2B}, and HTR₆. In some embodiments, modulating neurotransmission comprises agonizing HTR_{2A}.

[419] In another exemplary aspect, provided is a method of treating a medical condition in a mammal in need of such treatment, the method comprising administering to the mammal a therapeutically effective amount of the compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments.

[420] In some embodiments, the medical condition is a disorder linked to dysregulation or inadequate functioning of neurotransmission. In some embodiments, the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of monoaminergic neurotransmission. In some embodiments, the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of serotonergic neurotransmission.

[421] In some embodiments, the medical condition is a mental health disorder. In some embodiments, the mental health disorder is selected from the group consisting of: post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders, attachment disorders, and dissociative disorders.

[422] In some embodiments, the mammal has a genetic variation associated with drug metabolism, including a genetic variation relating to CYP2D6 or CYP3A4 enzymes; or associated with a mental health disorder, trauma or stressor related disorder, depression, or anxiety, and including a genetic variation in mGluR5 or FKBP5; or relating to a membrane transporter, such as SERT, DAT, NET, or VMAT. In some embodiments, the mammal has altered epigenetic regulation of a gene the expression of which is associated with a mental health condition or susceptibility to a mental health treatment, such as the SIGMAR1 gene for the non-opioid sigma-1 receptor. In some embodiments, the mammal is a human.

[423] In another exemplary aspect, provided is a method of reducing the symptoms of a mental health disorder in a human, the method comprising identifying a human in need of said reducing, and administering to the human the compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments.

[424] In a final exemplary aspect, provided is a method of improving mental health or functioning in a human, the method comprising identifying a human in need of said improving, and administering to the human the

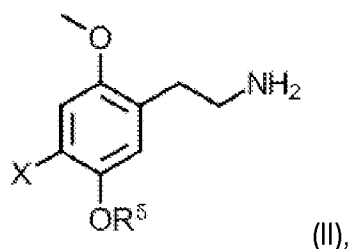
compound of any of the preceding embodiments, or a pharmaceutically acceptable salt, prodrug, hydrate, or solvate thereof, or the pharmaceutical composition of any of the preceding embodiments.

[425] The foregoing description, for purposes of explanation, uses specific nomenclature to provide a thorough understanding of the invention. However, it will be apparent to one skilled in the art that specific details are not required in order to practice the invention. Thus, the foregoing description of specific embodiments of the invention is presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise compositions, formulations, methods, or the like disclosed; many modifications and variations are possible in view of the above teachings. The embodiments were chosen and described in order to best explain the principles of the invention and its practical applications, through the elucidation of specific examples, and to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated, when such uses are beyond the specific examples disclosed. Accordingly, the scope of the invention shall be defined solely by the following claims and their equivalents.

CLAIMS

The invention claimed is:

1. A compound of Formula (II):

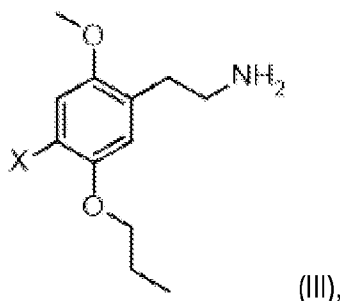


or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

X is Br, F, Cl, I, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkylthio; and

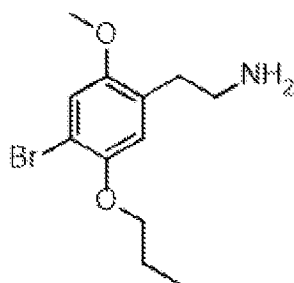
R⁵ is n-propyl, n-butyl, n-pentyl, n-hexyl, or C₃-C₆ alkenyl.

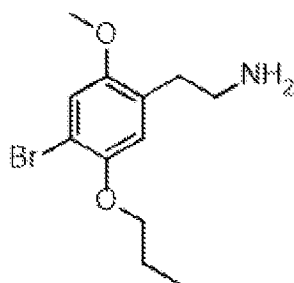
2. The compound of claim 1, wherein R⁵ is n-propyl, n-butyl, n-pentyl, or n-hexyl.
3. The compound of claim 2, wherein R⁵ is n-propyl.
4. The compound of claim 1, wherein X is Br.
5. The compound of claim 1, wherein the compound has the structure of Formula (III):

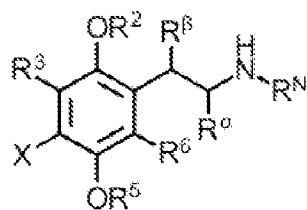


or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein X is Br, F, Cl, I, or CF₃.

6. The compound of claim 5, wherein X is Br.
7. A compound selected from **TABLE 1**, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.



8. A compound having the structure: , or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
9. A compound selected from **TABLE 2**, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
10. The compound of any one of claims 1-9, for use in the treatment of a medical condition.
11. The compound of any one of claims 1-10, or a compound having the structure of Formula (1),



(1),

or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein:

R^a is H or C_1 - C_6 alkyl;

R^b is H, OH, or C_1 - C_6 alkoxy;

X is Br, F, Cl, I, C_1 - C_6 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, nitro, or amino; wherein each C_1 - C_6 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, 3- to 6-membered cycloalkyl, 4- to 6-membered heterocycloalkyl, or amino is independently optionally substituted by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{OC}(\text{O})\text{H}$, $-\text{OSO}_2\text{OH}$, or $-\text{OC}(\text{O})\text{NH}_2$; and

one of R^2 and R^5 is methyl, and the other is C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_2 - C_8 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylene-3- to 6-membered cycloalkyl, C_1 - C_6 alkylene-4- to 6-membered heterocycloalkyl, or C_1 - C_6 alkylene-aryl, or C_1 - C_6 alkylene-heteroaryl; and R^3 and R^6 are both H; or R^2 and R^3 together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to

6-membered heteroaryl; R⁵ is C₃-C₆ alkyl, C₃-C₆ alkenyl, C₂-C₈ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkylene-3- to 6-membered cycloalkyl, C₁-C₆ alkylene-4- to 6-membered heterocycloalkyl, or C₁-C₆ alkylene-aryl, or C₁-C₆ alkylene-heteroaryl; and R⁶ is H; or

R⁵ and R⁶ together with the intervening atoms form a 4- to 6-membered heterocycloalkyl or 4- to 6-membered heteroaryl; R² is C₃-C₆ alkyl, C₃-C₆ alkenyl, C₂-C₈ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkylene-3- to 6-membered cycloalkyl, C₁-C₆ alkylene-4- to 6-membered heterocycloalkyl, or C₁-C₆ alkylene-aryl, or C₁-C₆ alkylene-heteroaryl; and R³ is H.

12. A pharmaceutical composition comprising the compound of any one of claims 1-9, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.
13. The pharmaceutical composition of claim 12, wherein the composition is suitable for oral, buccal, sublingual, intranasal, injectable, subcutaneous, intravenous, intraocular, topical, or transdermal administration.
14. The pharmaceutical composition of claim 12, wherein the composition is provided in unit dosage form.
15. The pharmaceutical composition of claim 14, comprising the compound in a total amount of between 1 and 200 mg, or between 5 and 100 mg.
16. The pharmaceutical composition of claim 15, comprising the compound in a total amount of between 10 and 75 mg, or between 20 and 50 mg.
17. The pharmaceutical composition of claim 14, wherein the unit dosage form is an immediate release, controlled release, sustained release, extended release, or modified release formulation.
18. The pharmaceutical composition of claim 12, further comprising a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
19. The pharmaceutical composition of claim 18, wherein the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathogens, psychedelics, monoamine oxidase inhibitors, tryptamines,

terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins.

20. The pharmaceutical composition of claim 18, wherein the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, or alter pharmacokinetics or pharmacodynamics.
21. The pharmaceutical composition of claim 20, wherein the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.
22. A method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-9, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
23. The method of claim 22, wherein the medical condition is a disorder linked to dysregulation or inadequate functioning of neurotransmission.
24. The method of claim 23, wherein the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of monoaminergic neurotransmission.
25. The method of claim 24, wherein the disorder linked to dysregulation or inadequate functioning of monoaminergic neurotransmission is that of serotonergic, dopaminergic, or noradrenergic neurotransmission.
26. The method of claim 22, wherein the medical condition is a mental health disorder.
27. The method of claim 26, wherein the mental health disorder is selected from the group consisting of post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders,

attachment disorders, and dissociative disorders.

28. The method of claim 27, wherein depression is major depressive disorder (MDD) or treatment-resistant depression (TRD).
29. The method of claim 27, wherein anxiety is generalized anxiety disorder (GAD).
30. The method of claim 27, wherein the mental health disorder is PTSD.
31. The method of claim 27, wherein the substance use disorder is alcohol use disorder (AUD), nicotine dependence or tobacco use disorder, opioid use disorder (OUD), stimulant use disorder, or sedative, hypnotic, or anxiolytic use disorder.
32. The method of claim 22, wherein the medical condition is a neurodegenerative disorder, pain or a pain disorder, or inflammation or an inflammatory disorder.
33. The method of claim 22, wherein the medical condition is an ischemic injury.
34. The method of claim 33, wherein the ischemic injury is a stroke or an ischemia-reperfusion injury.
35. The method of claim 22, wherein the compound is administered together with one or more sessions of psychotherapy or psychological support.
36. A method of modulating neurotransmission in a subject, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-9, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
37. The method of claim 36, wherein modulating neurotransmission comprises activating a monoamine neurotransmitter receptor and/or modulating the uptake activity of a monoamine transporter.
38. The method of claim 37, wherein the monoamine neurotransmitter receptor is any of a serotonin receptor, a dopamine receptor, and a norepinephrine receptor.
39. The method of claim 38, wherein the serotonin receptor is the 5-HT_{2A} receptor.
40. The method of claim 37, wherein the monoamine transporter is a serotonin transporter (SERT).
41. Use of the compound of any one of claims 1-9, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, for the manufacture of a medicament for the treatment of a medical condition.

42. A method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the pharmaceutical composition of claim 12.
43. A method of modulating neurotransmission in a subject, comprising administering to the subject the pharmaceutical composition of claim 12.
44. The pharmaceutical composition of claim 12, for use in treating a medical condition.
45. Use of the pharmaceutical composition of claim 12 for the manufacture of a medicament for treating a medical condition.
46. A method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the compound of claim 11, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
47. A method of modulating neurotransmission in a subject, comprising administering to the subject the compound of claim 11, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof.
48. The compound of claim 11, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, for use in treating a medical condition.
49. Use of the compound of claim 11, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, for the manufacture of a medicament for the treatment of a medical condition.

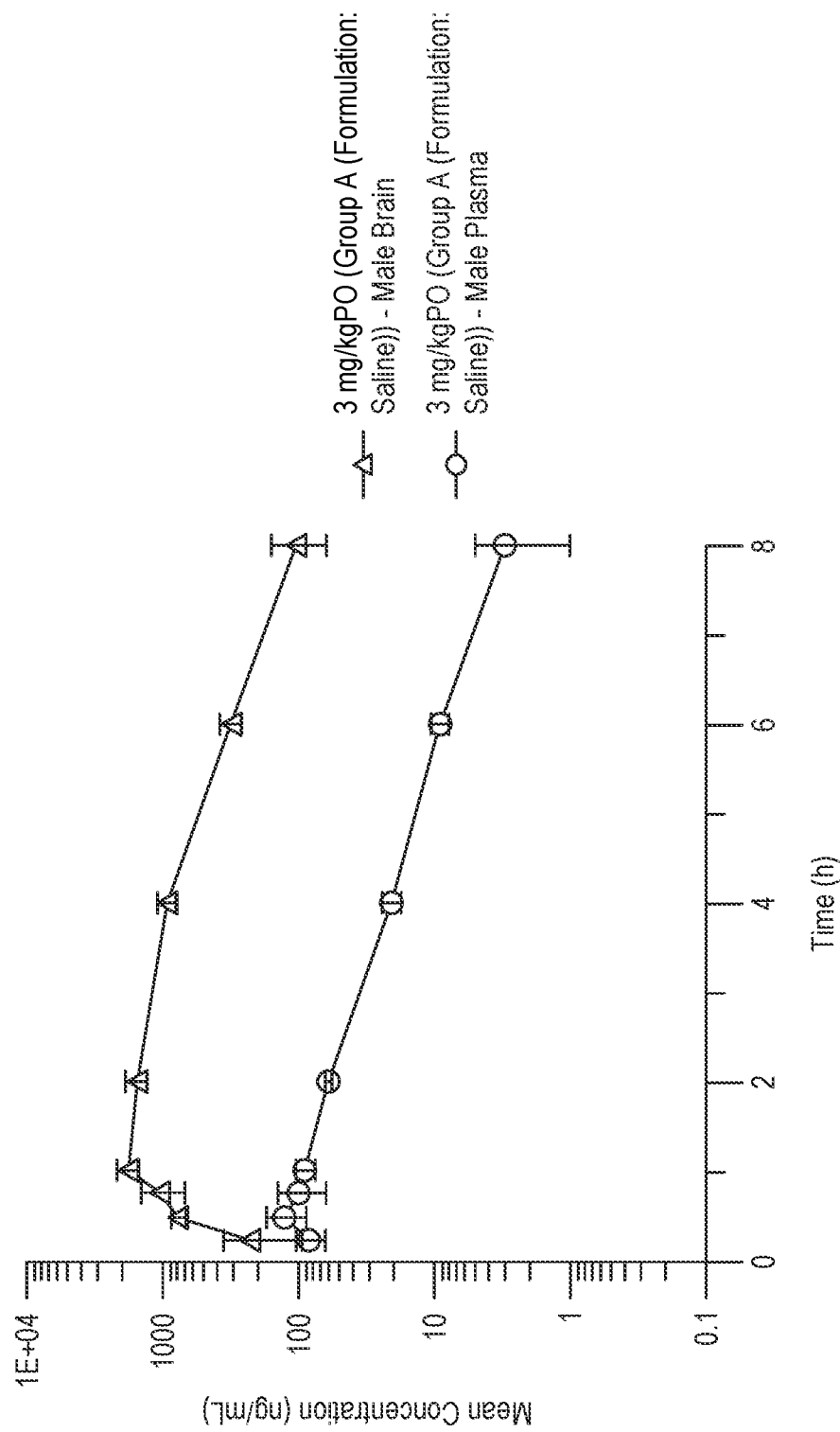


FIG. 1

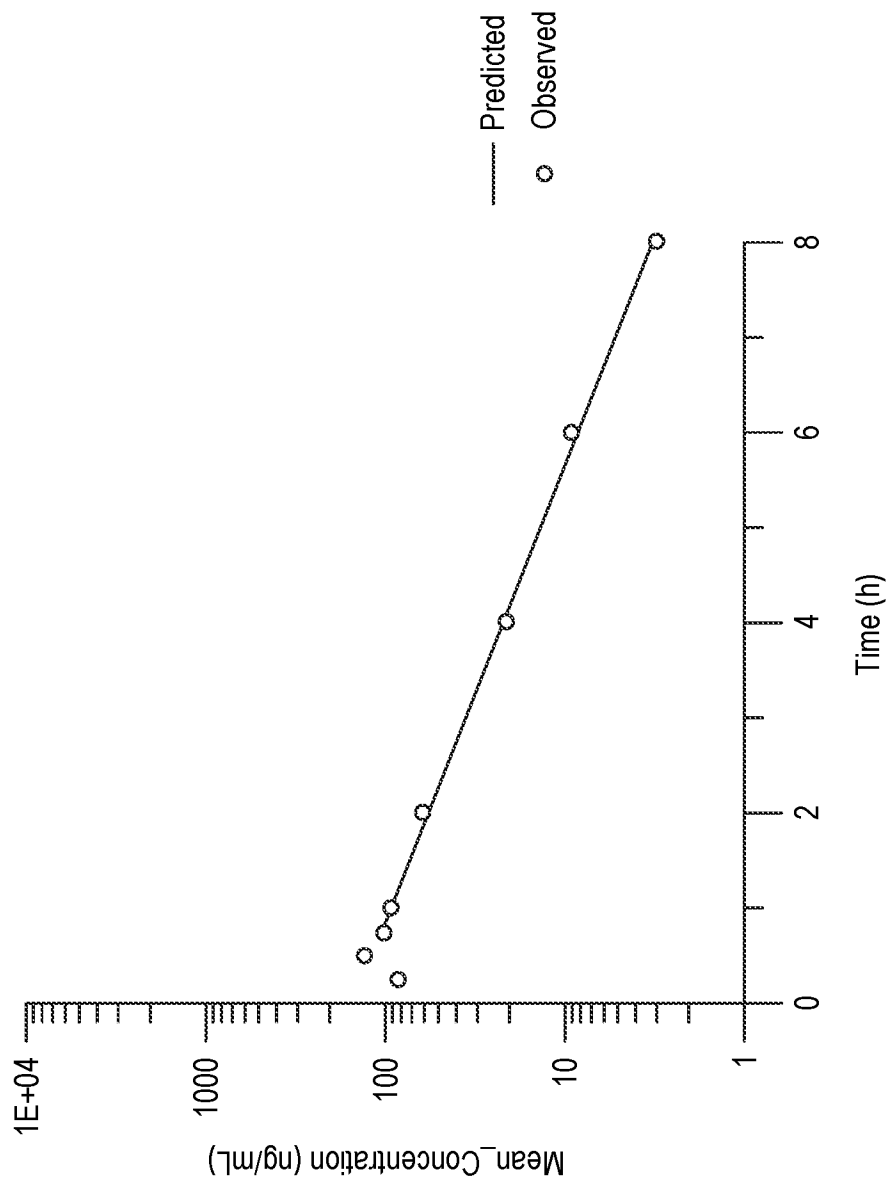


FIG. 2

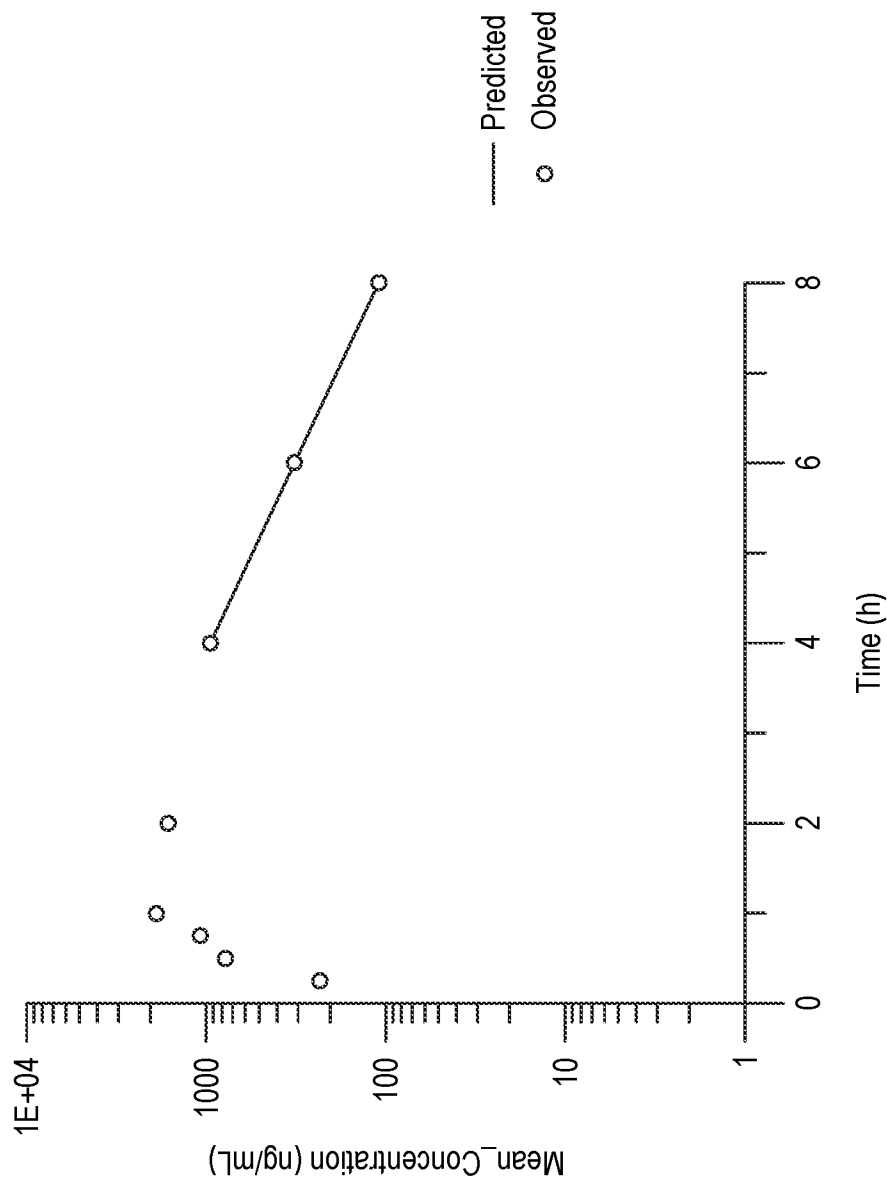


FIG. 3

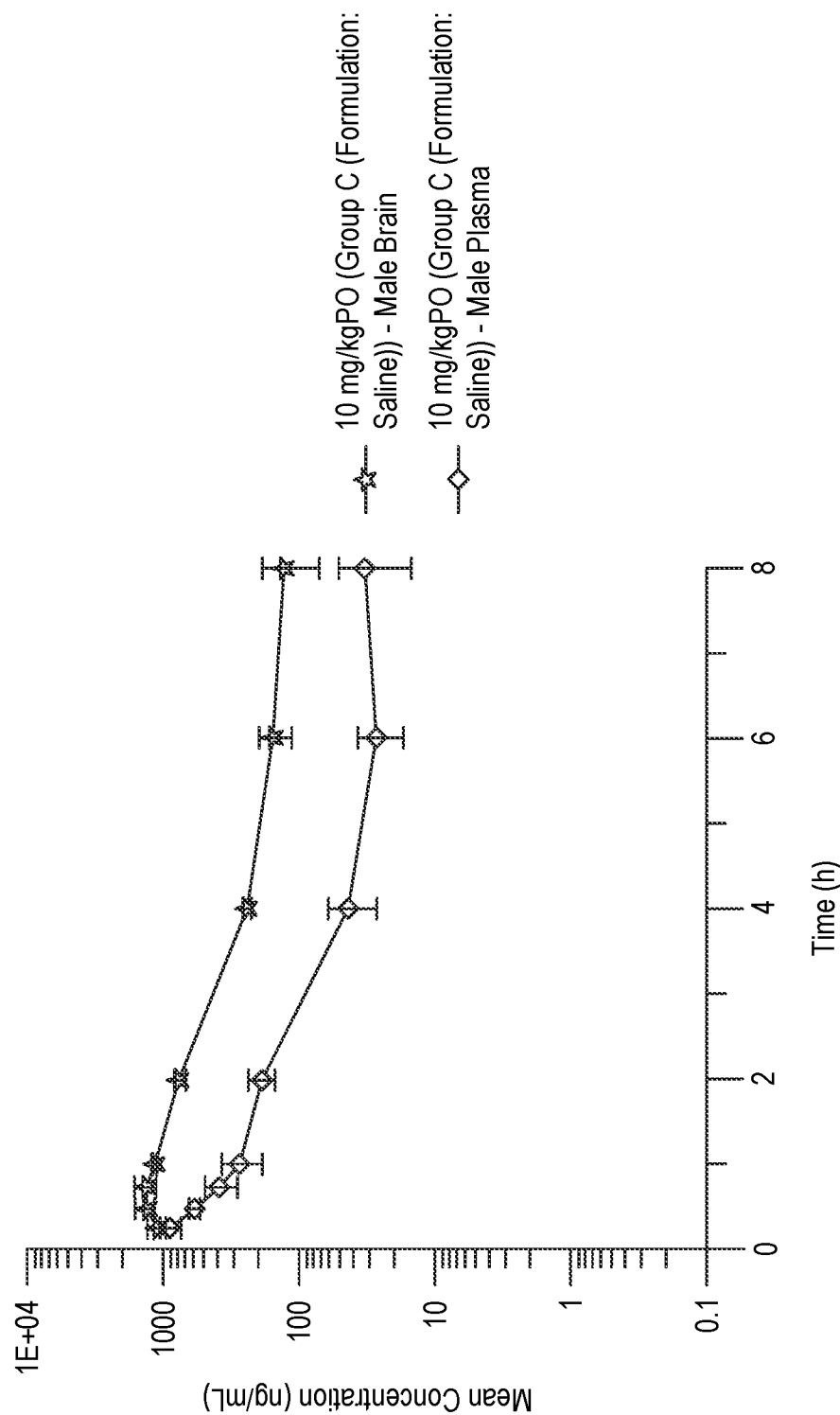


FIG. 4

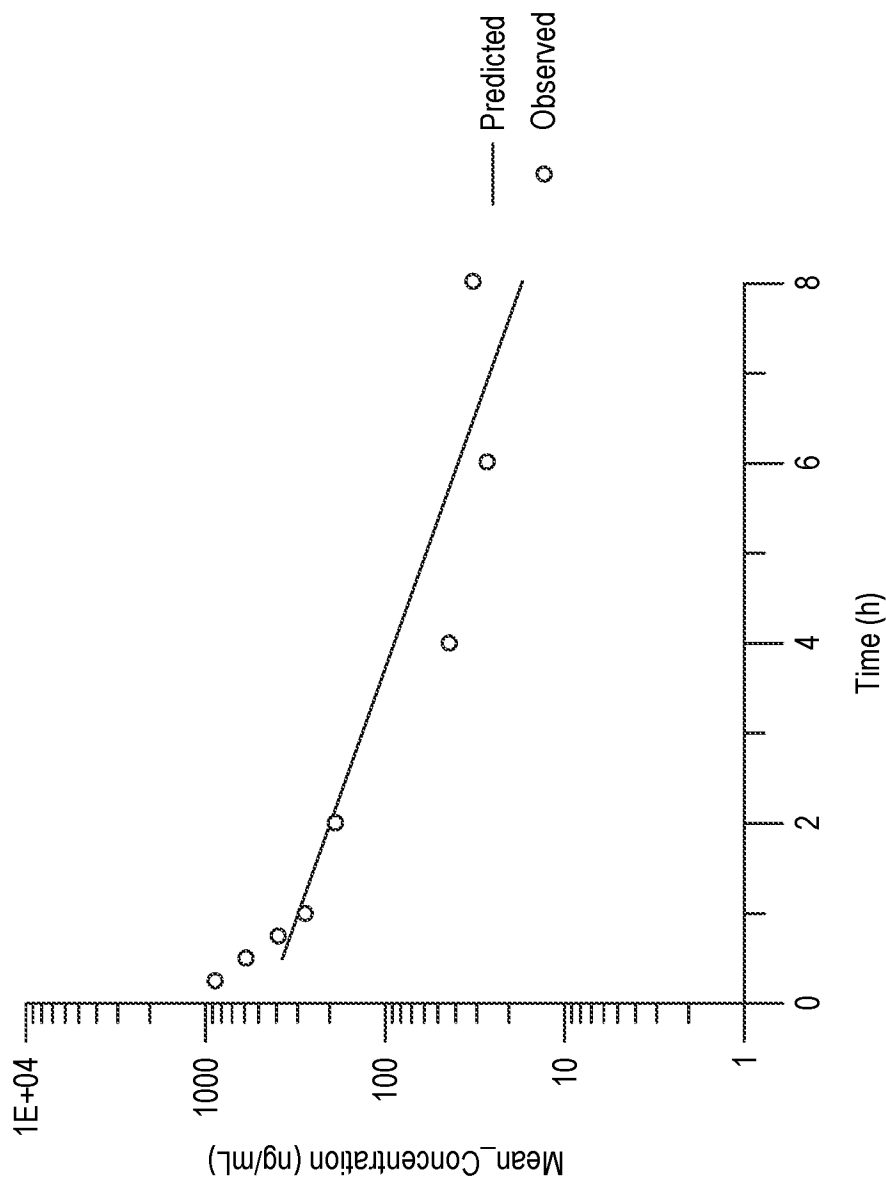


FIG. 5

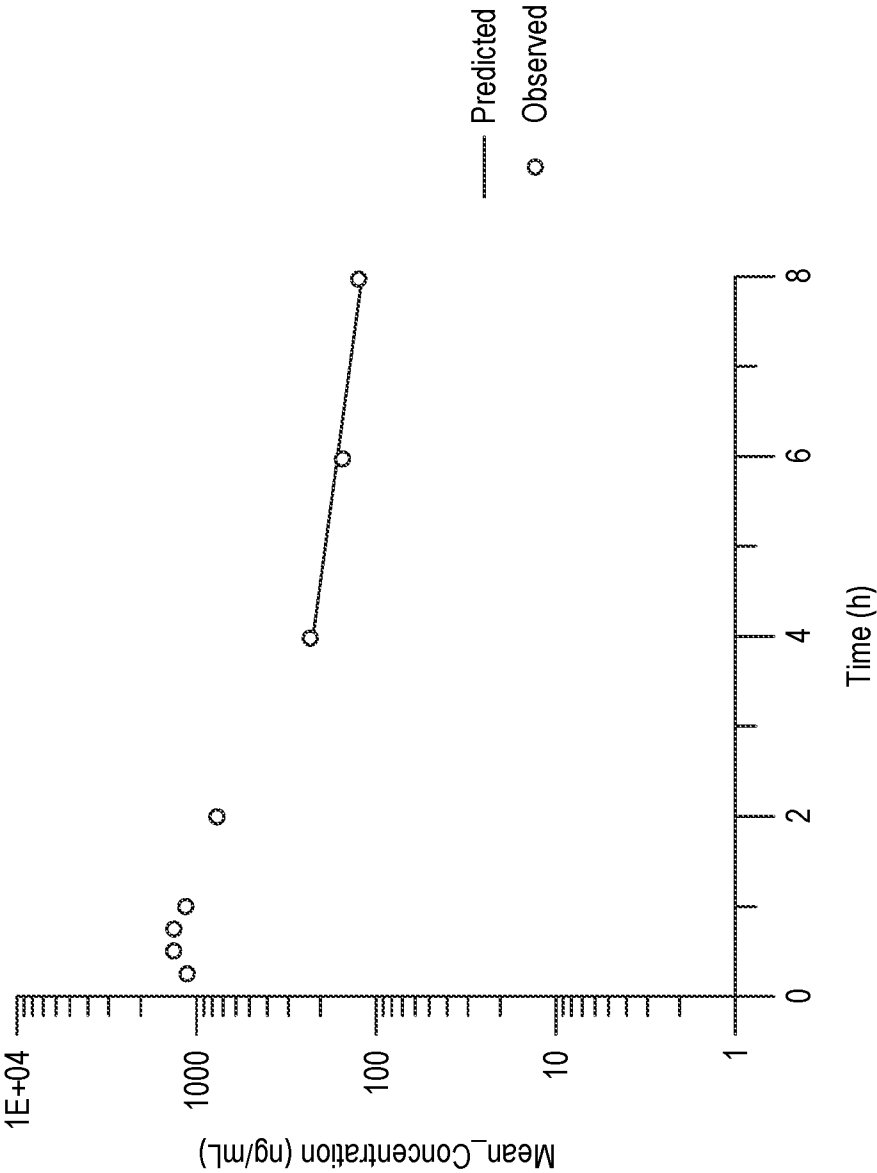


FIG. 6

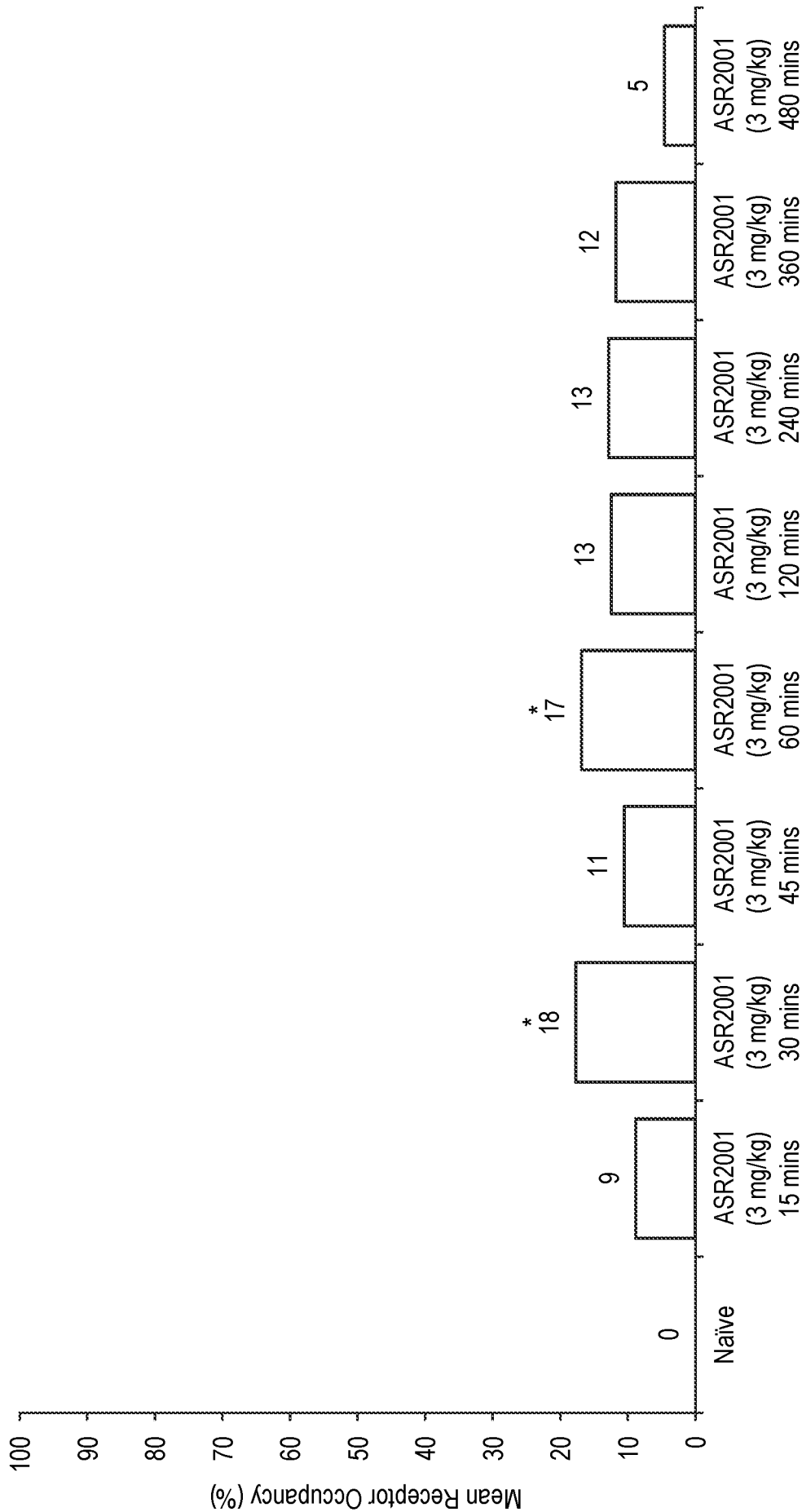


FIG. 7

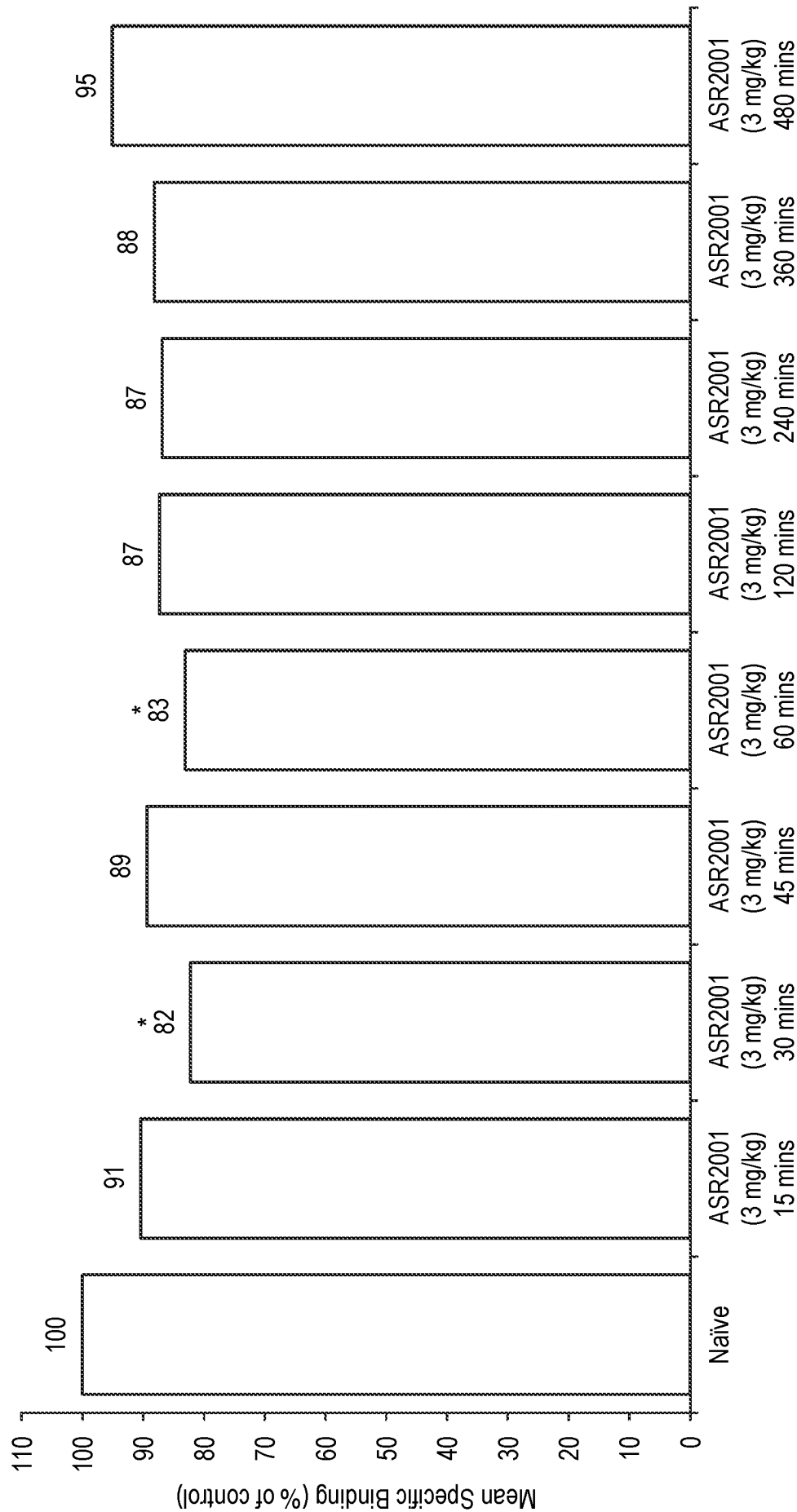


FIG. 8

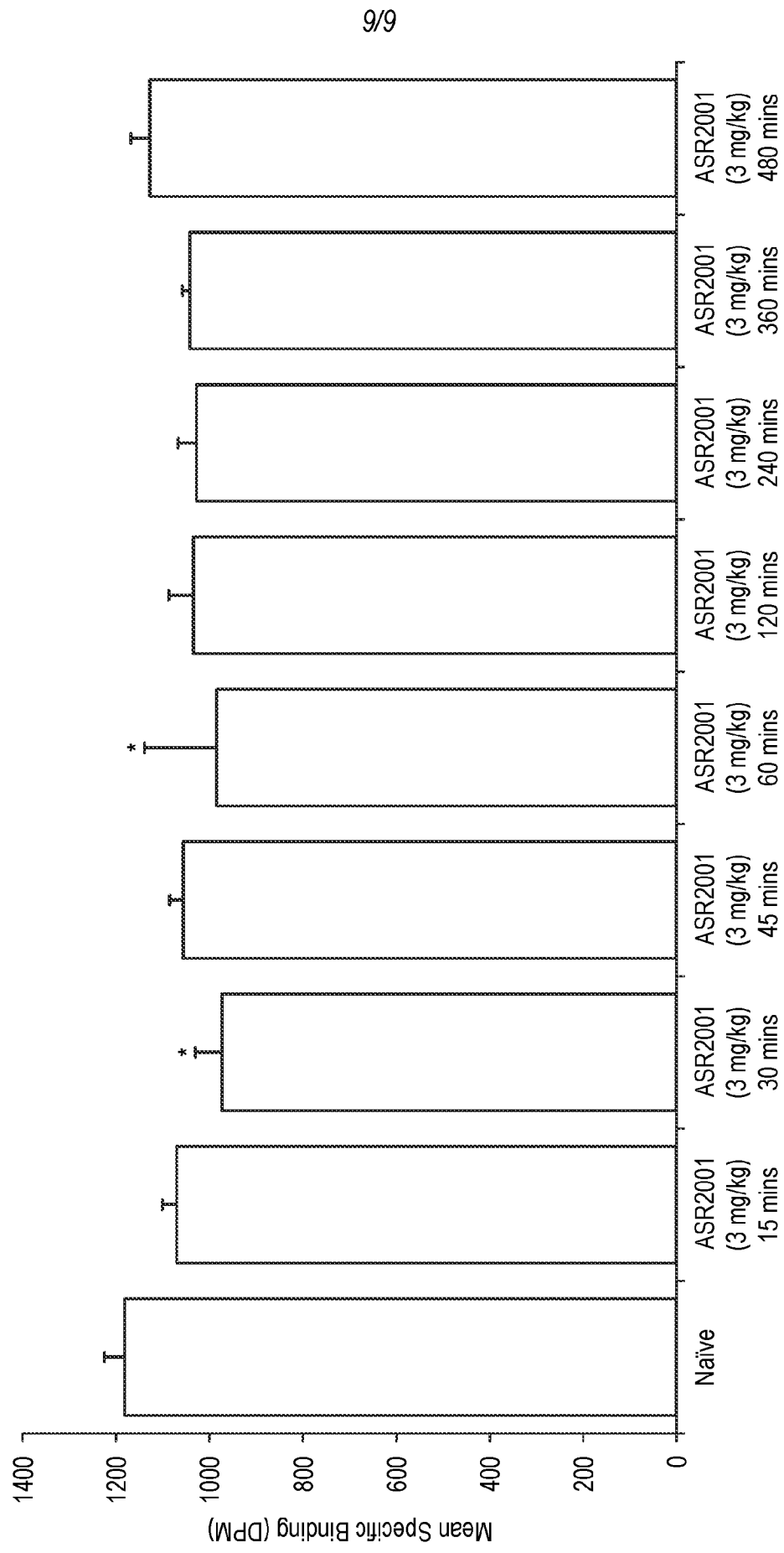


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/031312

A. CLASSIFICATION OF SUBJECT MATTERIPC: **C07C 217/82** (2024.01); **A61P 25/00** (2024.01)CPC: **C07C 217/82; A61P 25/00**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2022/006186 A1 (GILGAMESH PHARMACEUTICALS INC) 06 January 2022 (06.01.2022) entire document	1-8, 10, 12-45
A	WO 2023/049480 A1 (ALEXANDER SHULGIN RESEARCH INSTITUTE) 30 March 2023 (30.03.2023) entire document	1-8, 10, 12-45
A	US 4,034,113 A (SHULGIN) 05 July 1977 (05.07.1977) entire document	1-8, 10, 12-45

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

17 July 2024 (17.07.2024)

Date of mailing of the international search report

09 September 2024 (09.09.2024)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Authorized officer

MATOS

TAINA

Facsimile No. 571-273-8300

Telephone No. 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/031312

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 11, 46-49
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:

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

Group I+: claims 1-10 and 12-45 are drawn to compounds of Formula (II): or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, compounds, pharmaceutical compositions thereof, methods of treating thereof, methods of modulating thereof, uses and thereof.

The first invention of Group I+ is restricted to a compound of Formula (II): or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein: X is Br; and R5 is n-propyl; a compound; pharmaceutical compositions thereof, methods of treating thereof, methods of modulating thereof, uses and thereof. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (X, R5 – claim 1). It is believed that claims 1-8, 10, and 12-45 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula (II): or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof, wherein: X is F; and R5 is n-propyl; a compound; pharmaceutical compositions thereof, methods of treating thereof, methods of modulating thereof, uses and thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

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

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X and R5 and accordingly these groups lack unity a priori.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/031312

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

Additionally, even if Groups I+ were considered to share the technical features of a compound of core Formula (II); or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof; a compound, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof; a pharmaceutical composition thereof; a method of treating a medical condition in a subject in need of such treatment thereof; a method of modulating neurotransmission in a subject thereof; and a use thereof, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2022/006186 A1 to Gilgamesh Pharmaceuticals, Inc.

WO 2022/006186 A1 to Gilgamesh Pharmaceuticals, Inc. teaches a compound of core Formula (II); or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof (Pg. 2, Compound 1, see shown structure); a compound, or a pharmaceutically acceptable salt, hydrate, solvate, or isotopic derivative thereof (Pg. 2, Compound 1, see shown structure); a pharmaceutical composition thereof (Pg. 4, Ln. 15, pharmaceutical composition); a method of treating a medical condition in a subject in need of such treatment thereof (Pg. 4, Lns. 17-19, method of treating depression ... in a subject in need thereof); a method of modulating neurotransmission in a subject thereof (Pg. 4, Lns. 17-19, method of treating ... in a subject in need thereof; Pg. 22, Lns. 24-25, modulating glutamate or GABA levels or signaling; Pg. 1, Lns. 21-22, modulators of monoamine transporters); and a use thereof (Pg. 8, Lns. 25-26, compositions may be used to treat a mood disorder).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-8, 10, 12-45**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.